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ABSTRACTS

Presidential Lecture

PL

Systemic Lupus Erythematosus - Past and Future

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Conflict of interest: Yes

The number of patients with systemic lupus erythematosus (SLE) in Japan is approximately over 60,000 to 70,000, and 90% of the patients are female, age in between 20 to 40, childbearing years. In these 40 years, prognosis of patients with SLE has improved, and 10-year survival now becomes approximately over 95%. This may be due to a combination of earlier disease diagnosis and diagnosis of milder disease, due in part to availability of multiple serological tests for SLE. Among immune disorders that can be seen in lupus patients, autoantibodies such as antinuclear antibodies (ANA) are very useful for the diagnosis of SLE. Since LE cell had been found in bone mallow of lupus patients, LE cell test was commonly used for diagnosis of SLE. But after indirect immunofluorescence method (IF) was introduced, the detection of ANAs became a lot easier, defining different staining patterns that are directly associated with the targeted antigens. Then, ANAs have been divided into specific subtypes based on the nuclear or cytoplasmic components that they attack, and it was found that autoantibodies such as anti-dsDNA and anti-Sm are quite specific for SLE, and have been utilized as items in the diagnostic criteria for lupus. Then, such a criteria contributed to the early diagnosis, and to obtain lupus patients the better prognosis. Although the prognosis of SLE itself improved a lot, still the potential for significant morbidity and mortality remains in the group of patients with partially responsive or treatment resistant disease such as type IV lupus nephritis and CNS involvement, etc. To overcome these problems, various therapeutic approaches have been developed, and the introduction of cyclophosphamide pulse therapy achieved the higher rate of remission in patients with lupus nephritis comparing with the steroid pulse therapy alone. However, 15-20% of patients develop sever renal insufficiency. Therefore, the newer therapeutic approaches for SLE have been needed to rescue the patients from such intractable organ involvements. We present the clinical features of intractable disorders in our lupus patients, and will discuss novel therapies that have been developed based on the understanding of molecular mechanisms involved in the pathogenesis of SLE, offering possible alternatives to this patient cohort.

Representative Session

RS

Future basic and clinical needs in the treatment of rheumatic diseases

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Conflict of interest: None

Insights into pathogenetic pathways, optimization of outcomes assessments and the consequential successful evaluation of many novel therapies, particularly targeted therapeutics, have allowed for dramatic advancements in the treatment of several rheumatic diseases, such as rheumatoid arthritis (RA), ankylosing spondylitis (AS) and psoriatic arthritis (PsA), but also other chronic inflammatory conditions, such as psoriasis (PsO) and inflammatory bowel disease (IBD). Nevertheless, the respective fields still lack important pieces of information and progress in order to achieve ultimate therapeutic success, namely cure, in all inflammatory disease areas currently afflicted with chronicity, organ damage and enhanced mortality. (i) We still do not know the cause (s) of any of these chronic inflammatory disorders; (ii) we still do not understand sufficiently, why one chronic disease appears driven by a particular cytokine, or a particular set thereof, while others are mediated mainly by other messenger molecules, with some commonalities among them; (iii) we still are dealing with many disease entities or syndromes for which we neither have sufficiently useful outcome measures nor effective targeted remedies available, such as systemic lupus erythematosus or systemic sclerosis; and (iv) among the diseases that can be treated well today, we still do not know how to distinguish patients who will respond well to one but not another therapy nor do we understand sufficiently, who will be a good and who a lesser responder; realization of such personalized medicine approach, however, would be important to allow for faster achievement of improvement or disease remission and more cost-effective treatment approaches. These tension fields will be addressed. Examples of how questions of yesterday were overcome for the benefit of today's patients will be discussed and relate primarily to RA, AS, PsA, PsO and IBD: some agents work well in all these diseases, such as anti-TNF therapy, but others do not, such as IL-6- or some IL-17-inhibitors; however, even when a disease is regarded responsive, many patients do not attain the desired outcome state. These observations elicit questions of today that need to find pathogenetic insights and therapeutic solutions tomorrow. Thoughts to overcome the respective barriers will be presented, although for some of these areas more questions than potential answers or solutions will be posed. *"If you don't ask the right questions, you don't get the right answers." (Edward Hodnett)*

Symposium

S1-1

Roles of Toll-like receptors in autoimmunity

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Conflict of interest: Yes

TLR ectodomains consist of the tandem repeats of LRM, which is typically 24 amino acids in length [23]. The LRM adopts a loop structure, beginning with a short b-strand followed by a b-turn. Tandem repeats of LRM form a solenoid structure with parallel b-sheets. Consecutive b-sheets and b-turns form a continuous hydrogen-bonded, packed structure, generating a curved solenoid with the b-sheets on the concave side. TLR ectodomains are stabilised by their interior hydrophobic cores and hydrogen bonds between adjacent b-sheets [23]. The LRRs of the TLR ectodomains, especially those of TLR7, 8, and 9, are longer than 24 amino acids. The extra residues form a loop that protrudes from the convex or planar side of the LRR solenoid. A tentative loop is thought to be located between LRR14 and LRR15 in the TLR9 ectodomain and is predicted to be cleaved[15]. Consistent with this prediction, the present study showed that TLR9C begins at the C-terminal end of the loop. Considering that the protruding loop does not contribute to either the inner hydrophobic bonds or the hydrogen bonds between b-sheets, the proteolysis of the loop is not likely to influence the basic solenoid structure. The association between TLR9N and TLR9C is likely to be mediated by the hydrogen bonds between the b-sheets of LRR14 and LRR15, not by the loop between LRR14 and LRR15. This hypothesis is supported by the behaviours of the TLR9N mutants. A TLR9N construct lacking the loop (N440) was able to confer DNA-responsiveness to TLR9C, but TLR9N lacking LRR14 (N414) was not. J15A7 staining of TLR9N was amplified by TLR9C coexpression, suggesting that J15A7 preferentially binds to TLR9N+C over TLR9N alone. Amplification induced by TLR9C coexpression was observed for N440 but not N414, indicating that N414 failed to associate with TLR9C. Therefore, LRR14 is required for the interaction of TLR9N with TLR9C.

S1-2

Phenotype conversion from rheumatoid arthritis to systemic lupus erythematosus by introduction of Yaa mutation into FcγRIIB-deficient C57BL16 mice

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Conflict of interest: None

FcγRIIB negatively regulates BCR-mediated activation signals. We previously established an FcγRIIB-deficient B6-congenic mouse strain (KO1) by gene targeting in 129-derived embryonic stem cells followed by backcrossing to B6 mice. Intriguingly, KO1 spontaneously developed rheumatoid arthritis (RA), but not systemic lupus erythematosus (SLE). In the present study, we found that, in the KO1 strain into which Y chromosome-linked autoimmune acceleration (*Yaa*) mutation was introduced (KO1.*Yaa*), the incidence and severity of RA were markedly reduced, but instead severe SLE developed early in life. Irrespective of this phenotype conversion, KO1.*Yaa* showed a marked increase in serum levels of both lupus-related and RA-related autoantibodies, compared with findings in KO1 and B6.*Yaa* mice. It was noted that splenomegaly with germinal center (GC) formation and T follicular helper (T_{FH}) cell generation was evident early in the life of KO1.*Yaa*, but not KO1 and B6.*Yaa*, mice. Furthermore, IL-21 and IL-10 expression levels were significantly increased in the spleen of KO1.*Yaa* mice. Our data show that the strong epistatic interaction of FcgRIIB deficiency and *Yaa* mutation in KO1 genetic background induces not only B cell activation to produce large amounts of autoantibodies but also augmented T_{FH} cell generation associated with the increase in IL-21 and subsequent IL-10 expression early in life. This aberrant cytokine milieu may be responsible for the disease phenotype shift from RA to SLE in the KO1 mice carrying genetic predisposition to both RA and SLE.

S1-3

STING, Innate Immune Signaling and Self DNA-Activated Inflammatory Disease

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Conflict of interest: None

We have recently reported that STING (stimulator of interferon genes) is essential for controlling Toll-Like Receptor (TLR)-independent, cytosolic DNA-mediated innate immune signaling. Accordingly, STING appears essential for protecting the host against lethal disease following infection by pathogens such as HSV1. Such cellular DNA sensors may also play a key role in triggering inflammation aggravated autoimmune diseases. Autoimmune diseases such as systemic lupus erythematosus (SLE) affect millions worldwide. For example, SLE and diseases such as Aicardi-Goutieres syndrome (AGS) are characterized by the overproduction of cytokines such as type I interferon (IFN) suggesting that stimulation of host innate immune responses, speculatively by chronic infection or self nucleic acids, play a role in the manifestation of these diseases. It is known that mice lacking DNAse II die during embryonic development through comparable inflammatory disease since phagocytosed DNA from apoptotic cells cannot be adequately digested and intracellular host DNA sensors are activated resulting in the production of a variety of cytokines including type I IFN. However, we have found that STING complexes with phagocytosed undigested DNA and controls innate immune signaling events that facilitate such events. DNase II-dependent autoimmune embryonic lethality was rescued by loss of STING function and polyarthritis completely prevented since cytosolic DNA failed to robustly trigger cytokine production through STING controlled signaling pathways. Consequently, loss of STING expression similarly alleviated Trex1-dependent lethal inflammatory myocarditis in mice, a model for AGS, speculatively caused by endogenous self DNA. Our data provides molecular insight into the causes of DNA-mediated inflammation-dependent autoimmune disorders and affords a new target that could plausibly be therapeutically controlled, to help prevent such diseases.

S1-4

Neutrophils in the pathogenesis and manifestations of SLE

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Conflict of interest: None

Significant abnormalities in both innate and adaptive immunity are well documented to play an important role in the pathogenesis of systemic lupus erythematosus (SLE). However, the role of neutrophils--the most abundant immune cell type--in the pathology of SLE has been less well characterized. Over the past decade, compelling evidence has emerged implicating granulocytes in the development and perpetuation of SLE as well as in the organ damage and vascular complications frequently diagnosed in lupus patients. The description of an aberrant subset of neutrophils in SLE- (low-density granulocytes (LDGs)) has implicated these cells in the induction of vascular damage, synthesis of type I interferons and enhanced extracellular trap (NET) formation. This presentation will highlight the role of neutrophils in the pathogenesis of SLE, with a particular focus on the putative deleterious effects of LDGs and neutrophil extracellular trap formation.

S1-5

TLR Antagonism, a Novel Approach to the Treatment of Autoimmune and Inflammatory Diseases: From Bench to Bedside

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Conflict of interest: None

Toll-like receptors (TLRs) play a crucial role in the detection of pathogen-associated molecular patterns (PAMPs) and in the subsequent activation of immune responses. In autoimmune diseases, endosomal TLRs recognize damage-associated molecular patterns (DAMPs) and induce pro-inflammatory Th1, Th17, and inflammasome signaling cascades, which exacerbate the disease. We have designed synthetic oligonucleotide-based antagonists[1] of the endosomal TLRs 7, 8, and 9 that block TLR recognition of DAMPs and have shown activity in preclinical models of psoriasis[2], lupus[3], and other autoimmune and inflammatory diseases. Clinical proof of concept of TLR antagonism was established in a Phase 2 randomized, double-blind, placebo controlled trial in 44 patients with moderate to severe plaque psoriasis[4]. Placebo or IMO-3100 monotherapy (0.16 or 0.32 mg/kg) was administered subcutaneously weekly for four weeks. IMO-3100 is an antagonist of TLRs 7 and 9. Treatment was well tolerated and led to significant improvements in Psoriasis Area and Severity Index (PASI) scores, dermal thickness, and immunological markers in the psoriatic lesions. PASI improvements were correlated with down-regulation of IL-17. Preclinical studies established that inhibition of TLRs 7, 8, and 9 had a greater improvement on psoriasis-associated gene expression than did inhibition of TLRs 7 and 9 only. Based on these observations, IMO-8400, an antagonist of TLRs 7, 8, and 9, has been advanced into clinical development and a Phase 1 trial in healthy subjects was completed. A Phase 2 trial in psoriasis patients with a 12-week treatment period is in progress. Since endosomal DAMPS are implicated in diverse autoimmune and inflammatory diseases, TLR antagonism provides a novel therapeutic approach by blocking the induction of pro-inflammatory cytokines and immune signaling cascades. [1]J. Med. Chem. 2009, 52, 551–558; [2] JID, 2013, 133: 1777–1784; [3]Autoimmunity, 2013, 46 (7): 419–428; [4] IID 2013 Abstract #156

S2-1

Rheumatic diseases and infections ~overview~

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Conflict of interest: Yes

Many rheumatic diseases are closely associated with infection because of the sharing of “immune response” in their pathophysiology. First, the immune response to pathogenic microorganisms may cross-react to the self-antigen. Second, the activation of innate immunity elicited by infectious diseases may amplify the immune response to autoantigens up to the clinically overt level. Third, the modification of autoantigens following the cellular and tissue damage due to infectious diseases may lead to the autoimmunity. Thus, infection is likely to be a trigger of the onset or the exacerbation factor of rheumatic diseases, although infectious diseases may occasionally ameliorate, contrarily, rheumatic diseases by the favorable deviation of helper T-cell subsets. On the other hand, the immune disorder of rheumatic diseases, and the subsequent tissue damage may enhance the risk for infection. However, rheumatic diseases themselves do not usually increase the infectious risk, because of the upregulated interferon production and inflammation may contribute against infectious diseases. Consequently, infectious complications in patients with rheumatic diseases are likely to develop 1-2 months after the commencement of immunosuppressive treatment such as glucocorticoids, rather than before the treatment. Future therapeutic agents include those against cytokines, B cells and various kinases, which raise the importance of the management of infectious diseases, leading to the establishment of the well-organized infection survey and control, including vaccines. Interestingly, a recent report suggested that patients taking antimalarials were 16 times less likely to suffer a major infection. Because hydroxychloroquine is not available in Japan, we should regard hydroxychloroquine as an important agent used in combination with other immunosuppressive agents.

S2-2

Management of *Pneumocystis jirovecii* infection during immunosuppressive therapy for rheumatoid arthritis

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Conflict of interest: Yes

Early use of methotrexate and the emergence of innovative biological agents have altered the course of rheumatoid arthritis (RA) and improved patient and social outcomes. However, accompanying the increased use of these drugs, RA patients have been exposed to an increased risk of *P. jirovecii* infection, which causes acute fulminant *P. jirovecii* pneumonia (PCP) with severe oxygenation impairment, diffuse alveolar damage, and respiratory failure. By contrast, PCP occurring in HIV-positive individuals presents as a subacute disease course. Such differences in clinical presentation are attributed to differences in inflammatory responses of the lungs. High numbers of fatal PCP cases during biologic and non-biologic therapy for RA have been reported by pharmaceutical companies in Japan. Since PCP in RA patients, especially in elderly individuals, are likely to cause fulminant respiratory failure within the first several days, rheumatologists should follow up the patients for signs and symptoms of PCP development, even slight changes of the physical condition, with a high index of suspicion. Patient education is also important for early diagnosis of PCP. Outbreaks of *P. jirovecii* infection can occur through person-to-person transmission in outpatient facilities, and RA patients with asymptomatic carriage participate in the transmission cycle as infectious reservoirs. Measures to eradicate *P. jirovecii* from asymptomatic carriers should be taken, but guidelines for administration of prophylactic antibiotics nevertheless remain less clear. Universal routine prophylaxis during anti-RA therapy is impractical. In addition, severe adverse effects of prophylactic agents such as TMP-SMX should be considered. Through my experience with an outbreak among RA outpatients, I have learned that short-term prophylaxis with TMP-SMX is effective in controlling of *P. jirovecii* infection and prevention of future outbreaks of PCP.

S2-3

Tuberculosis and Non tuberculous Mycobacteriosis

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Conflict of interest: None

Biologics for RA brought innovative changes in RA treatment, but have the aspect of infection increases as a double-edged sword. TB requires close attention with a strong infectious behavior to others. In Japan, the TB developing risk in RA patients from 2003 to 2010 shows 4.34 times higher than in general population. The high prevalence of TB in the introductory period of biologics was reduced shortly, because all concerned efforts seem to be reflected. Today, accurate epidemiological data have not been obtained about non tuberculous mycobacteriosis (NTM), Japanese NTM lung disease prevalence is estimated over 8. In particular, the increase of nodular bronchiectasis (NB) type of *Mycobacterium avium* complex (MAC) disease has noted in Japan and US. NB type of MAC are more common in mature woman, this group is also a predilection population of RA onset. Unlike TB, NTM composed from over one hundred species, and clinical picture or chemotherapy is different for each species. Pulmonary *Mycobacterium kansasii* is curable almost with triple anti-TB drugs. Pulmonary *Mycobacterium szulgai* and *Mycobacterium fortuitum* are also respond relatively well to combination chemotherapy, respectively. In early case of MAC lung disease, negative conversion rate can be achieved about 80% with the guideline recommended protocol, but recurrence rate is high. The severe cases at the first visit are very intractable. Optimal chemotherapy for *Mycobacterium abscessus* lung disease has not been established and the treatment is most difficult. For the differences due to bacterial species, the trend of above mentioned seems to be paralleled under RA biologics treatment circumstances. There is also a view that TNF inhibitors enhance effectively mycobacterial chemotherapy, but we have only less effective agents for NTM than for TB, therefor, close attentions are needed for NTM treatment under biologics.

S2-4

Viral reactivation (mainly herpesvirus)

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Conflict of interest: Yes

Herpesvirus is a DNA virus with a double-stranded DNA genome, capsid, and an envelope. Herpes zoster virus (HZV), herpes simplex virus (HSV), cytomegalovirus (CMV), and EB virus (EBV) are pathogenic for humans. There has been a recent increase of herpes zoster associated with HZV reactivation due to use of tofacitinib. The incidence of herpes zoster in the long-term Japanese study of tofacitinib was 11.5% (51/375 subjects), which is higher than with other biological products. CMV infections in patients on immunosuppressive therapy are caused by reactivation. The incidence of CMV infection in patients with rheumatoid arthritis (RA) using biologics was 0.02 - 0.05%. Although the reported incidence with tofacitinib was less than 0.1%, the CMV antigenemia-positive rate was 8.9% in patients admitted to our clinic last year receiving immunosuppressive therapy. When bone marrow transplantation is performed in a CMV carrier and specific cytotoxic T lymphocytes (CTL) targeting CMV do not recover, the risk of opportunistic infection is high. Thus, specific CTL activity influences CMV reactivation. EBV reactivation may be involved in the onset of RA. We detected EBER and LMP-1 in the synovium of RA patients and cloned the signaling lymphocytic-activation molecule (SLAM) associated protein (SAP) gene, which activates CTL for EBV. One reason for reduced protection against EBV in RA patients is abnormal SAP function. Expression of LMP-1 on synovial cells suppresses SAP, activates EBV, and induces synovitis in RA patients. EBV reactivation and persistent infection cause MTX-associated lymphoproliferative disorder (MTX-LPD), which not only includes immunopathy associated with autoimmune diseases such as RA but also LPD due to EBV reactivation and persistent infection subsequent to immunosuppression by MTX, as well as impaired processing of atypical infected cells. Reactivation of herpesvirus and changes in pathology should be monitored carefully during immunosuppressive therapy.

S3-1

Genetics is a fundamental of epigenetics in autoimmune diseases

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Conflict of interest: None

Autoimmune diseases are caused by multiple factors including genes and environmental factors. Several HLA loci have been reported to be associated with respective autoimmune diseases. In addition, recent development of genome-wide association studies (GWASs) revealed a number of susceptibility loci and genes in each autoimmune disorder. Interestingly, although some susceptible single nucleotide polymorphisms (SNPs) affect an alteration of amino acid residues in the protein, majority of autoimmune associated SNPs were found to work as expression quantitative trait loci (eQTLs). An eQTL is a genomic locus that regulates the expression level of mRNA or protein. On the other hand, epigenetics are chemical changes that affect gene expression without altering the DNA code. In fact, our genome-wide association study meta-analysis of rheumatoid arthritis (RA) in a total of >100,000 subjects of European and Asian ancestries revealed 98 biological candidate genes which should contribute to RA pathogenesis. These RA risk polymorphisms are significantly enriched in overlap with H3K4me3, which is an epigenetic promoter-specific histone modification associated with active transcription. However, we now know that there is plasticity of epigenetic marks. Thus, a piece of epigenetic information does not necessarily indicate that the finding is a causative event. On the other hand, genetic information such as SNPs in common diseases are inherited prior to disease onset, therefore, genetic studies provide evidence that the pathway of susceptible genes is essential or causative in the pathogenesis. Thus, combination of genetic and epigenetic studies will make our understanding of autoimmune diseases more robustly. In this symposium, we will present recent development of genetic study of autoimmune diseases and discuss representative interactions between genetics and epigenetics in the pathogenesis.

S3-2

Suppression of Lupus Development by Manipulating MicroRNA Activity

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Conflict of interest: None

It has been well established that microRNAs maintain normal physiology and modulating contribute to disease pathophysiology through transcription and epigenetic pathways. Targeting miRNA has been considered as a promising therapeutic approach for the diseases of immunological origin. We have shown that miRNAs singly or synergistically activate abnormal immune and inflammatory pathways, leading to pathological lupus autoimmune responses including hyperactivation of type I IFN pathway, inflammatory chemokine RANTES overproduction, IL-2 secretion defect, T cell DNA hypomethylation and local tissue inflammation. More importantly, Inhibiting or reducing these abnormal miRNAs restores normal immune function in in vitro cell culture. We thus hypothesize that in vivo manipulation of these miRNAs expression could regulate major inflammatory signaling pathways linked to lupus tissue damage and the approach to correct these dysregulated miRNAs should reverse lupus major phenotypes. Recently we have been evaluating the capacity of selective miRNA inhibition to cure lupus in murine models (spontaneous lupus prone mouse and pristane-induced lupus), as preparatory experiments before advocating human trials using this approach. We have applied gene knockout, transgenic and bone marrow chimeric mice, as well as chemically synthesized miRNA mimics and inhibitors, to study the role of miRNAs in inducing lupus-related pathological tissue damage. We also determined the potential for reversing disease and evaluate efficacy, while also elucidating the miRNA-related molecular mechanisms of lupus pathogenesis. We believe the results of these experiments would prepare our community of lupus investigators and pharmaceutical scientists to exploit this exciting new technology toward ending the suffering caused by lupus.

S3-3

Epigenetics in the pathogenesis of RA

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Conflict of interest: None

Epigenetics of rheumatic diseases has moved over the past decade into the center of interest in the development of novel diagnostics and new therapeutic strategies. Since it is emerging that epigenetic modulations are pivotal regulators of gene expression, our laboratory has been focussing on the epigenetic modulation of synovial cells in rheumatoid arthritis (RA) and related inflammatory disorders. After early studies by Bruce Richardson in Ann Arbor MI documenting ciculating CD4 T cells are hyopmethylated in RA, fellows in our laboratory could show that synovial fibroblasts (SF) in RA are globally hypomethylated, hyperacetylated and modulated by sumoylation and thereby responsible for the activated phenotype of RASF. We felt that it is important to characterize all these epigenetic modifications in RA simultaneously. For review (1). Since the epigenetic modifications of RASF, also include characteristic pattern in the expression of non-coding RNAs (ncRNA), such as miRNA and lncRNAs, we have studied thereby the regulation of TNFa (2) and IL-6, as well as the association of circulating miRs in response to therapy (3). Most recently we reported at the past ACR on the profiling of RASF for the expression and potential function of lncRNA. In this context targetting of specific miRs is on the horizon for the treatment of RA. 1) Gay S and Wilson AG. The emerging role of epigenetics in rheumatic diseases. Rheumatology 2013, Sep 11 (Epub ahead of print) 2) Trenckmann M et al. The TNFa induced miR18a activates RASF through a feedback loop in NF-kB signalling. Arthr Rheum 65:916-27, 2013 3) Filkova M et al. Association of circulating miR-223 and miR-16 with disease activity in patients with early RA. Ann Rheum Dis 2013, Jul 29 (Epub ahead of print)

S3-4

microRNA in joint destruction and repair

Tomoyuki Nakasa, Mitsuo Ochi
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Conflict of interest: None

Systemic joint destruction by chronic synovial inflammation is a major problem in rheumatoid arthritis (RA), and inflammatory cytokines play a crucial role in joint destruction. MicroRNAs (miRNAs) are a class of non-coding RNAs that regulate gene expression by binding the 3'-UTR of their target mRNAs leading to translational repression or mRNA degradation and have been reported to be associated with human diseases including RA. MiRNA (miR)-146 was reported to be strongly expressed in RA synovium induced by inflammatory cytokines. MiR-146 has the function of negative regulator of inflammatory response through the negative feedback by targeting TRAF6 and IRAK4. Over expression of miR-146 could decrease the catabolic factors and osteoclast differentiation *in vitro*. Systemic injection of miR-146 mimic could prevent joint destruction in collagen induced arthritis mice, suggesting that targeting of miRNA could prevent joint destruction in RA. However, the repair tissues which have been already destructed in RA are also important problem to solve. Cartilage, bone, ligament, and meniscus are destructed in RA joint and to restore these tissues should be considered to improve the joint function. Angiogenesis play an important role in tissue repair, especially bone, ligament, and meniscus. MiR-210 has a potent capability of induction of angiogenesis. Anterior cruciate ligament injury and medial meniscus injury model of rat were created, and intra-articular injection of miR-210 mimic into knee joint was performed to each model. In both model, intra-articular injection of miR-210 could enhance ligament and meniscus healing via angiogenesis with matrix production through up regulation of VEGF and FGF2. Local injection of miR-210 into medial collateral ligament injury and fracture of femur in rat model could also promote healing. Targeting miRNA will develop a novel therapeutic strategy to prevent the destruction and promote the tissue repair in RA joint.

S3-5

Epigenomic regulation in the plasticity of T helper cells

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Conflict of interest: None

$CD4^+$ T helper cells play critical roles for host defense and immune-mediated disease by their ability to differentiate into specialized subsets such as Th1, Th2, Th17, and Tfh cells. These subsets attain restricted patterns of cytokine secretion and specific expression of master transcription factors. Classically, the various T helper cell subsets have been viewed as terminally differentiated lineages with limited flexibility. However, following the recognition of new subsets, there is increased recognition of plasticity. In fact, T helper cells can express more than one master regulator. In experimental autoimmune encephalomyelitis, T-bet^+ RORγt^+ Th1/Th17 like cells are highly pathogenic. We also found that flexible T-bet^+ $Bcl6^+$ Th1/Tfh like cells might be involved in the pathogenesis of SLE. Using deep sequencing technology coupled to chromatin immunoprecipitation, we identified the genome-wide mapping of histone epigenetic modifications in T helper subsets and supported the idea that elements of both terminal differentiation (e.g. cytokine genes) and plasticity (e.g. master regulators genes) can coexist within the same subset. Recent studies have also shown that various types of miRNAs control phenotypic change of T helper cells. These findings argue that the epigenomic regulation of T helper cells is a key event for the development of autoimmune diseases. Thus, better understanding of the extrinsic and intrinsic signals that control stability and plasticity of T helper cells will have important therapeutic applications to control autoimmunity. In this symposium, we would like to highlight recent advances that pertain to this topic and the mechanisms that contribute to T helper cell differentiation and plasticity in the pathogenesis of autoimmune diseases. Collaborator: Dr. John J. O'Shea (National Institute of Arthritis and Musculoskeletal Diseases, NIH)

S4-1

Clinical significance of anti-citrullinated protein antibody (ACPA)

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Conflict of interest: None

Anti-citrullinated protein antibody (ACPA) is well known as a high specific marker for rheumatoid arthritis (RA) and it was added the new ACR/EULAR classification criteria for RA in 2010. In this presentation, we'll show the clinical significance of ACPA in daily practice using data of NinJa (National Database of Rheumatic Disease by iR-net in Japan) 2012 as follows; 1. Clinical importance of ACPA in diagnosis of RA 2. Prediction of future onset of RA by ACPA 3. Prediction of joint damage in RA by ACPA 4. Prediction of the efficacy of DMARDs/biologics in RA by ACPA 5. Is ACPA useful to judge the therapeutic effects in RA? 6. ACPA in the pathogenesis of RA 7. Clinical significance of ACPA in non-RA diseases 8. Is ACPA-positive RA different from ACPA-negative RA?

S4-2

Development and regulatory functions of anti-citrullinated protein antibodies

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Conflict of interest: None

Anti-citrullinated protein antibodies (ACPA) are widely used as the early diagnostic and prognostic markers for rheumatoid arthritis (RA). In addition, ACPAs can be detected in patient sera before the onset of initial RA symptoms and are known to exhibit arthritogenic activity in several mouse models; however, the development pathways and regulatory functions on joint inflammation *in vivo* remain largely unknown. During the antibody response against protein antigens, germinal centers provide the unique environment for somatic diversification of antibody repertoires, which not only generates high-affinity B cells but may also elicits autoreactive B cells accidentally. Indeed, Malmström's group has recently generated anti-citrullinated protein monoclonal antibodies from synovial IgG^+ B cells of active RA patients and confirmed the requirement of somatic hypermutations on the binding capacity to citrullinated proteins. Moreover, the extensive analysis of SLE mouse models has revealed the indispensable roles of somatic hypermutations on the acquisition of autorectivity, along with the identification of distinct B cell pathways leading to the production of autoreactive antibodies. During IgG^+ B cell development, terminal sialic acids are attached to Fc glycans on IgG Asn297; however, it has been observed that ACPAs are more desialylated by unknown mechanisms. The possible impacts of sialylated /desialylated ACPA on the arthritogenic activity have been investigated by using a model of collagen antibody-induced arthritis, revealing their modulatory functions on joint inflammation. We will discuss the possible regulatory functions of ACPA sialylation, which may play important roles on the initiation and suppression of joint inflammation.

S4-3

Anti-citrullinated GPI (glucose-6-phosphate isomerase) antibodies and disease activity in rheumatoid arthritis

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Conflict of interest: None

ACPA are elevated specifically in rheumatoid arthritis (RA) and several citrullinated autoantigens have been reported. Anti-CCP antibodies (Abs) test is widely used as clinical diagnostic marker. On the other hand, it is not used as monitoring of disease activity. We have studied GPI, an arthritogenic target in K/BxN arthritis mouse model. Immunization with whole protein or T cell epitope peptide of GPI was reported to provoke arthritis in the DBA/1 mouse. In humans, anti-GPI Abs were elevated specifically in RA. It is suggested GPI is involved in the pathogenesis of RA. We also reported that antibodies to citrullinated whole GPI using PAD existed in RA serum. Anti-CCG-2,-4 and-7 Abs were detected in 57.2% of the RA samples and its specificity was 97.1%. Anti-CCG Abs were associated with HLA-DRB1 shared epitope alleles. The levels of anti-CCG Abs were downregulated by six month treatment with TNF antagonists. So, we show the knowledge of association between anti-CCG Abs and disease activity and etiology of anti-CCG Abs. The levels of anti-CCG-2, 4, 7 and CEP-1 Abs were measured before and after 6 month treatment with TNF antagonists (n=58), tocilizumab (n=45) or abatacept (n=28). The change in the Abs was compared with disease activity. The levels of anti-CCG-7 Abs decreased significantly after TNF antagonists or tocilizumab treatment. The anti-CCG-2 Abs decreased after TNF antagonists and the anti-CCG-4 Abs decreased after tocilizumab treatment. The expression of citrullinated protein in RA and OA synovium was examined by immunochemical staining using anti-modified citrulline Abs. Citrullinated protein was detected in the surface layer of RA synovium. Anti-CCG-7 and CEP-1 Abs were purified from RA serum using peptide-affinity column. The deposition of anti-CCG-7 and CEP-1 Abs was examined by immunofluorescence staining. Anti-CCG-7 and CEP-1 Abs were deposited to RA synovium. It was suggested citrullination occurred and ACPA were deposited in rheumatoid synovium.

S4-4

Association between *PADI4* polymorphisms and radiographic joint damage in RA patients

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Conflict of interest: None

Rheumatoid arthritis (RA) is a systemic, chronic inflammatory disease influenced by both genetic and environmental factors, leading to joint destruction and functional impairment. Recently, a large-scaled GWAS meta-analysis using more than 100,000 samples were conducted and 101 RA susceptibility loci were identified 1. However, it is not clear whether these loci have significant impact on joint destruction or not. We focused on the 13 susceptible loci to investigate independent genetic risk factors for radiographic progression in the first five years from onset of RA. We found that the number of SE alleles and risk alleles of peptidyl arginine deiminase type IV gene (*PADI4*) had significant impact on progressive joint destruction, as well as following non-genetic factors: ACPA positive, female sex and younger age of onset 2. The results give important knowledge of the risks on progressive joint damage in RA patients. 1. Okada et al. Genetics of rheumatoid arthritis contributes to biology and drug discovery. Nature (e-pub ahead of print) 2. Suzuki et al. *PADI4* and HLA-DRB1 Are Genetic Risks for Radiographic Progression in RA Patients, Independent of ACPA Status: Results from the IORRA Cohort Study. PLoS One. 2013;8:e61045.

S4-5

Padi4 roles in mouse models of inflammatory arthritis

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Conflict of interest: None

Polymorphism in the locus of peptidylarginine deiminase type 4 (PADI4) was reported as a risk of rheumatoid arthritis (RA). PAD4 protein has a deiminase activity and plays a role in protein citrullination, that is, converting arginine residue to citrulline. Since anti-citrullinated peptide antibody (ACPA) is highly specific for RA diagnosis, autoantigen citrullination by PAD4 is closely investigated. However, PAD4 also plays roles in regulation of gene expression by the citrullination of nuclear proteins and cell proliferation and survival. PADI4 is mainly expressed in myeloid cells and monocytes, not lymphoid cells, however, PAD4 roles in immune systems remain unclear. Here, Padi4 knockout (KO) mice in DBA/1J background were prepared, and analyzed in glucose-6-phosphate isomerase (GPI)-induced arthritis model. Arthritis scores, histological scores, serum anti-GPI antibody, and serum IL-6 were significantly decreased in Padi4 KO mice. Notably, Th17 cells were decreased in the regional lynph nodes of Padi4 KO mice after immunization. On the other hand, Th17 cell differentiation and proliferation of Padi4 KO mice were not impaired in vitro. Next, myeloid cells and monocytes were analyzed because Padi4 was mainly expressed in these subsets. In naïve status, the numbers of myeloid cells and monocytes were not different between WT and KO mice in spleens. Notably, in GPI-arthritis mice, the numbers of myeloid cells and monocytes were significantly decreased in the spleens of Padi4 KO mice. In addition, in vitro survival of neutrophils was impaired in Padi4 KO mice. Taken together, we newly demonstrated that Padi4 has several direct and indirect effects on immune systems. Padi4 plays an important role in the pathogenesis of inflammatory arthritis, and will be a new target of RA therapy.

S4-6

Establishment of PADI4 determination system and clinical application

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Conflict of interest: None

Rheumatoid arthritis (RA) is a systemic inflammatory disease characterized by chronic and erosive polyarthritis. Results from recent studies of RA strongly suggested that the PADI4 gene and citrullinated proteins are major factors in the pathogenesis of RA. The modification of antigens by PADI4 in RA is highly likely to act as a trigger for the generation of autoantibodies. If so, determination of hPADI4 levels in the patients' peripheral blood has the potential for forming highly sensitive and specific diagnostic reagents to detect RA at its early stages and during its progression. The availability of an hPADI4 assay would be extremely helpful for resolving the mechanism of onset and subsequent development of RA. Therefore, we developed two novel methods for sandwich enzyme-linked immunosorbent assay (ELISA) for the determination of hPADI4 and the detection of hPADI4 autoantibodies in the peripheral blood (1). First, we prepared recombinant human (h)PADI1, 2, 3, and 4 proteins to develop mouse monoclonal antibodies specific to hPADI4. We then generated monoclonal antibodies against hPADI4 and developed two new sandwich ELISA methods for evaluating hPADI4 and PADI4 autoantibodies in the peripheral blood from 32 patients with RA, 10 patients with osteoarthrosis, and 20 healthy individuals. The distribution of hPADI4 in the patients' plasma was determined and identified two populations: one group with high hPADI4 levels and a second group with near zero levels. Most patients approximating zero hPADI4 levels had PADI4 autoantibodies. In contrast, most of those with higher plasma hPADI4 levels did not have detectable PADI4 autoantibodies. Therefore, the combined determination of hPADI4 level and the presence or absence of PADI4 autoantibodies might be a potentially useful criterion for diagnosing RA. (1) Ishigami et al., Two novel sandwich ELISAs identify PAD4 levels and PAD4 autoantibodies in patients with rheumatoid arthritis. Mod Rheumatol 23, 794-803 (2013)

S5-1

The impact of dysregulated transcription factors on the pathogenesis of systemic sclerosis

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Conflict of interest: None

Systemic sclerosis (SSc) is a multisystem connective tissue disease characterized by immune abnormalities, vasculopathy and resultant fibrosis of the skin and certain internal organs. It is generally accepted that this disease is caused by the complex interplay between hereditary and environmental factors, leading to the accumulation of predisposing factors and the subsequent activation of fibroblasts, endothelial cells and immune cells to variable degrees. Various combination of predisposing factors may explain disease heterogeneity and a variety of organ involvement in this disease. Skin sclerosis generally progresses within the first 5-6 years in diffuse cutaneous SSc, but spontaneously regresses thereafter. Furthermore, lesional dermal fibroblasts derived from early diffuse cutaneous SSc produce an excessive amount of type I collagen, but this pro-fibrotic phenotype is gradually lost along with passaging. Given that epigenetic regulation of gene expression is a dynamic and reversible process, these clinical and laboratory findings suggest that SSc dermal fibroblasts may be constitutively activated by a group of epigenetically regulated genes that links environmental exposure to disease onset. Based on this idea, we focused on two transcription factors, Friend leukemia virus integration 1 (Fli1) and Krüppel-like factor 5 (KLF5), that are epigenetically suppressed in SSc dermal fibroblasts and generated mice with double heterozygous deficiency of *Klf5* and *Fli1*. Notably, $Klf5^{+/-}$; $Fli1^{+/-}$ mice spontaneously recapitulate three cardinal features of SSc, such as aberrant immune activation, vasculopathy and fibrosis. This observation underscores the concept of epigenetic reprogramming underlying pathogenic changes in SSc and implicates the Fli1 and KLF5 pathways as central mediators linking its three features. In this symposium, I will present the detailed phenotype of this new SSc animal model and discuss a new therapeutic strategy for SSc based on this disease model.

S5-2

Vascular involvement in systemic sclerosis: current understanding and future perspectives

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Conflict of interest: Yes

Systemic sclerosis (SSc) is characterized by widespread vasculopathy and fibrosis of the skin and internal organs. Vascular involvement, such as pulmonary arterial hypertension, renal crisis, and digital ulcers, results in impaired activity of daily living and poor prognosis. Typical vascular histologies demonstrate obliteration of small arteries and venules with intimal fibrosis and loss of the vasculature. In nailfold capillaries, decreased vasculature and formation of giant capillaries usually precede clinical onset of skin sclerosis, followed by capillary loss and formation of ramified and bushy vessels. At autopsy, concentric intimal fibrosis of the vasculature is commonly found in virtually any organs, including lungs, heart, kidney, and gastrointestinal tract, irrespective of the presence or absence of corresponding clinical manifestations. Thus, interventions to vascular aspect of the disease, such as use of vasodilators, are necessary to all patients with SSc. It has been believed that vascular injuries and impairment of subsequent vascular repair process are a central mechanism for microvascular diseae in SSc. New blood vessel formation and endothelial rejuvenation is mediated through two distinct mechanisms: endothelial sprouting from preexisting endothelial cells (angiogenesis) and the peripheral recruitment of bone marrow-derived endothelial progenitor cells (vasculogenesis). These processes are deficient in SSc patients. This results in tissue hypoxia and recruitment of inflammatory cells and progenitors, leading to fibrosis of vascular wall as well as the surrounding tissue. Macrovascular disease that affects large vessels has also been described in SSc. The mechanism still remains unclear, but recent reports suggest SSc as an independent risk factor for accelerated atherosclerosis. Since vascular involvement plays a fundamental role in pathogenesis of SSc, early and continuous intervention to this process is necessary to improve longterm outcomes.

S5-3

The utility of biomarkers in systemic sclerosis

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Conflict of interest: None

Predicting disease progression is important for systemic sclerosis (SSc) patients. However, except for SSc-related autoantibodies there are no definitive serum biomarkers available to estimate disease progression. We sought to determine if baseline serum levels of chemokines and adhesion molecule could predict the progress of symptoms in early SSc patients. Ninety-two Japanese patients with early onset SSc presenting with diffuse skin sclerosis and/or interstitial lung disease were registered in a multicentre, observational study. Concentrations of CCL2, CCL5, CXCL8, CXCL9, and CXCL10 in serum samples were measured using cytometric beads array. Concentrations of ICAM-1, E-selectin, L-selectin, and P-selectin were measured by ELISA. Levels of chemokines and adhesion molecule were measured each year for four years. At their first visit, serum levels of CCL2, CCL5, CXCL8, CXCL9, and CXCL10 were significantly elevated in patients with SSc compared with healthy controls. The initial serum CXCL8 levels were significantly associated with the HAQ-DI at the fourth year. At their first visit, serum levels of ICAM-1, E-selection, P-selectin were significantly elevated and serum L-selectin levels were significantly reduced in patients with SSc compared with healthy controls. Overall, serum ICAM-1 levels at each time point were significantly inversely associated with the %VC of the same time and subsequent years. The initial serum ICAM-1 levels were significantly inversely associated with the %VC at the fourth year by multiple regression analysis. The initial serum P-selectin levels were significantly associated with the HAQ-DI at the fourth year by multiple regression analysis. Serum CXCL8 level may serve as a prognostic indicator of the physical dysfunction in SSc. Furthermore, serum levels of ICAM-1 and P-selectin may serve as prognostic indicators of respiratory dysfunction and physical disability, respectively.

S5-4

Up-to-date: Interstitial lung disease in patients with systemic sclerosis

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Conflict of interest: Yes

Systemic sclerosis (SSc) is one of connective tissue disease characterized by tissue fibrosis. Particularly, interstitial lung disease (ILD) is frequently complicated with SSc and is associated with mortality and morbidity in SSc. Cyclophosphamide is recommended as the treatment of ILD with SSc. In this session, I introduce several studies of randomized control trials for the treatment of ILD with SSc including our study.

S5-5

Hematopoietic stem cell transplantation in patients with systemic sclerosis

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Conflict of interest: Yes

Systemic sclerosis (SSc) is an autoimmune connective tissue disorder characterized by microvascular injury, skin fibrosis and distinctive visceral changes. Interstitial lung disease (ILD) is one of the most serious complications of SSc developing in more than 50% of SSc patients. The frequency of deaths due to ILD in SSc patients increased significantly over the 30-year time period, from 6% to 33% of SSc-related deaths. From late 1990s, hematopoietic stem-cell transplantation (HSCT) has been introduced as a treatment for autoimmune diseases such as multiple sclerosis, Crohn's disease and SSc. Phase III trial that examine the effect of HSCT as a treatment for patients with SSc is ongoing setting intravenous cyclophosphamide (IVCY) as a control treatment. In addition to the well-known effect of HSCT on the skin involvement, potency of HSCT has been reported to improve pulmonary function as well as CT findings in patients with SSc-related ILD. HSCT has been performed also in Japan, especially in Kyushu University and in our unit. We have performed

autologous peripheral blood stem cell transplantation (aPBSCT) in 13 SSc patients, resulting in improvement of skin score in 11. There was no treatment-related mortality. One patient experienced viral cystitis, one had severe cardiomyopathy and 2 developed systemic autoimmune diseases. There would be necessity for developing safer HSCT protocol as well as for selection of those patients who have poorer prognosis when treated with conventional therapies. In order to search a novel marker that is related to ILD in patients with SSc, we evaluated gene expression in the peripheral blood mononuclear cells. HLA-DR5 was highly expressed in patients with SSc-related ILD compared with those without ILD. Prevelence of *HLA-DRB5*01:05* was higher in SSc patients with ILD compared with those without ILD or healthy controls, suggesting that *HLA-DRB5*01:05* is a novel marker for developing ILD in patients with SSc.

S6-1

The cartilage degeneration -an attempt to develop the novel therapeutic drugs-

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Conflict of interest: Yes

Degradation of the cartilage extracellular matrix is a central feature of the osteoarthritis (OA) and thought to be mediated by proteinases that degrade structural components of the matrix, primarily aggrecan and collagen. OA can be considered as a very complex disease. This is one of reasons why the therapeutic drugs can't be developed to inhibit cartilage breakdown. The drug repositioning strategy, in which a panel of preapproved drugs is used to search for therapeutic modalities, was proposed. Off-label effects of several preapproved compounds have been reported, mostly for neurodegenerative diseases. In our research, we screened 1,040 FDA-approved drugs and picked up no less than twenty candidates in the first screening. And then, we go on to the second and third screening. Finally we decided two or three drugs as the final candidates that could have the therapeutic potential for specific disease. Here we report the results of our *SOX9* and wnt-beta catenin projects. *SOX9* expression decreases in cartilage in individuals with OA compared with age-matched controls. Experimentally, overexpression of *SOX9* in normal and OA articular cartilage stimulates ECM synthesis. Expression of ECM components could be restored in OA articular cartilage to levels similar to those in normal. These evidences support the idea of *SOX9* gene therapy in the treatment of OA. If these drugs really enhanced *SOX9* gene expressions by activating the promoter, we believe that they could be useful for the treatment of OA. We thought that wnt/b-catenin signaling could be another target, something novel, controversial and complicated. There are clearly various factors involving regulation of this pathway. We took notice one of the soluble antagonists of Wnt signaling, sFRP3, also called Frizzled related protein, FRZB was expected to function a inhibitor of Wnt signaling in chondrocytes. So we tried to identify a drug that induces *FRZB* gene expression and inhibits Wnt/β-catenin signaling.

S6-2

Scaffold-free tissue engineered construct derived from stem cells in osteochondral repair

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Conflict of interest: None

The objective was to in vitro generate a mesenchymal stem cell (MSC)-based tissue-engineered construct (TEC) to facilitate in vivo repair in a porcine chondral defect model. Porcine synovial MSCs were cultured in monolayer at high density and were subsequently detached from the substratum. The cell/matrix complex spontaneously contracted to develop a basic TEC. Immunohistochemical analysis showed that the basic TEC contained collagen I and III, fibronectin, and vitronectin. The basic TEC exhibited stable adhesion to the surface of a porcine cartilage matrix in an explant culture system. The TEC cultured in chondrogenic media exhibited elevated expression of glycosaminoglycan and chondrogenic marker genes. The TEC were implanted in vivo into chondral defects in the medial femoral condyle of 4-month-old pigs, followed by sacrifice after 6 months. Implantation of a TEC into chondral defects initiated repair with a chondrogenic-like tissue, as well as secure biological integration to the adjacent cartilage. Histologically, the repair tissue stained positively with Safranin O and for collagen II. Biomechanical evaluation revealed that repair tissue exhibited similar properties similar to those of normal porcine cartilage in static compression test but the TEC-repaired tissue had lower micro-friction properties than normal articular cartilage. We also conducted the same surgical model study using mature (12m-old-) pigs and there was no significant difference in the modified ICRS histological scoring and biomechanical properties except for lubrication properties. This technology could potentially be a unique and promising method for stem cell-based cartilage repair and early phase I/II clinical trial in cartilage repair has been started at Osaka University Hospital.

S6-3

Meniscus regeneration with synovial mesenchymal stem cells

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Conflict of interest: None

The meniscus is a wedge-shaped fibrocartilaginous structure and plays important roles in load distribution, shock-absorption, and knee joint stability. It has a poor healing potential due to its largely avascular nature, and loss of meniscal function leads to accelerated osteoarthritis. A new strategy to regenerate a meniscus is required for a massive meniscal defect. Synovial mesenchymal stem cells (MSCs) are an attractive cell source for meniscus regeneration due to their high proliferation and chondrogenic potentials. We examined the effect of repetitive intraarticular injections of synovial MSCs on meniscus regeneration in a massive meniscal defect of pigs. Two weeks before the injection, the anterior half of the medial menisci was resected in both knees of pigs. Fifty million allogeneic synovial MSCs were injected into the right knee at 0, 2, and 4 weeks and followed up by sequential MRI. The regenerated meniscus, adjacent articular cartilage, and subchondral bone were evaluated macroscopically, histologically, and by MRI at 16 weeks (n=7). DiI- and ferucarbotran- labeled MSCs were also evaluated periodically. Resected meniscus regenerated significantly better in the MSC group than in the control group based on histological and MRI analyses. Macroscopically, meniscal defect already appeared to be filled with synovial tissue at 2 weeks. DiI positive cells and ferucarbotran in the regenerated meniscus still appeared to be observed at 4 weeks. Articular cartilage and subchondral bone at medial femoral condyle were also more significantly preserved in the MSC group based on macroscopic, histological and MRI analyses. Intraarticular injections of allogeneic synovial MSCs promoted meniscus regeneration and protected articular cartilage in a pig massive meniscal defect model. It may lead to development of new treatment for meniscus regeneration in a clinical situation.

S6-4

Regenerative medicine for osteoarthritis and cartilage defects: The need for application

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Conflict of interest: None

Joint disease is a focus area of the medical care system because of the disabilities caused by these diseases and the rapidly aging population. Osteoarthritis (OA) occurs in patients with advanced age, and is predominantly characterized by gradual deterioration of cartilage. Current metal-based joint replacement is effective for terminal OA, to resurface and realign the joint. The technology of cell-based regenerative medicine, including tissue engineering, is available to treat cartilage defects particu-

larly in developed Western countries. In April 2013, autologous chondrocyte implantation (ACI) was approved as the first orthopedic cell therapy by the Japanese Ministry of Health, Labour and Welfare in Japan. Other options for cartilage repair besides ACI are available. Our clinical trial involves human bone marrow mesenchymal stem cell (hBMSC) implantation with arthroscopic surgery to treat cartilage defects. This therapy is simpler and less invasive than ACI, and can be used widely if adequately effective. This randomized controlled study includes 8 facilities in western Japan. The technical/financial difficulties involved in engineering cell-based alternatives to metal-based prostheses are yet to be resolved. Long-term follow-up clinical trials with high statistical power are needed to verify the efficacy of new cartilage joint therapy. We could elucidate the prognostic/risk factors for OA progression by determining the etiology and found that the younger individuals, who might be a good target for new therapy. Therefore, novel, cost-effective therapy with promising long-term outcomes using current medical resources is needed. We developed the automated robotized-cell processing expert system with Kawasaki Heavy Industries, by altering the conventional cell-processing center while establishing the consignment system for cells for medical infrastructure. We hope to achieve stable expansion and proliferation of hBMSCs to develop a cell sheet for cartilage repair.

S7-1

Molecular understanding of RA pathogenesis from clinical experiences with biological agents

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Conflict of interest: Yes

In addition to an animal model, synovial tissues form patients with Rheumatoid Arthritis (RA) by synovial biopsy and surgical operation have facilitated greatly our understanding of pathogenesis of RA. Molecular understanding even in individual patient is becoming possible through clinical experience with the use of biological agents targeted on the specific molecules, which are identified and developed by translational research. Such progress further raises substantial clinical questions, which are then reverse translational to bench. In this lecture, I will review the studies from the blood samples of RA patients treated with anti-TNFα such as infliximab, anti-IL-6 receptor, tocilizumab, and selective inhibitor on T cell co-stimulatory molecules, abatacept. In Keio First Bio cohort for RA patients treated with first biological agents, circulating cytokines measured by ultra-sensitive electro-chemiluminescent assay and blood immune cells by modern immune-phenotyping with eight color flow cytometer are analyzed along with clinical parameters such as DAS28, SDAI, CDAI and mTSS. Given the critical role of TNFα and IL-6 axis in RA, other inflammatory cytokines such as IL-1β, IL-17, and GM-CSF, regulatory factors including sIL-6R, IL-27, and Treg cells, as well as important molecules located up and down stream of TNFα and IL-6 axis are shown. Possible role of these molecules as biomarkers for disease activity or predicting response is discussed.

S7-2

Tailor-made targeted therapy by assessing peripheral lymphocyte subsets in patients with systemic autoimmune diseases

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Conflict of interest: Yes

Targeted therapy using biological agents has brought about paradigm shift for the treatment of systemic autoimmune diseases such as rheumatoid arthritis (RA). Biologics targeting T cells, B cells and their cell surface molecules have been emerging in which lymphocytes play a central role during pathological processes. We have assessed cell surface molecules on peripheral lymphocytes in patients with RA and systemic lupus eryhtemtosus (SLE) before and after the intervention with biologics using 8-color flow cytometry and have clarified the relevance of lymphocyte subsets/phenotypes to the heterogeneity of diseases as well as appropriate choice of the treatment strategy. For instance, $CD4^+CD28^+$ cells and $CD4^+CD28^-$ cells increased in RA patients and the majority of $CD4^+CD28^+$ cells are $CD45RA^-CCR7^+$ central memory T cell (Tcm) which consists of $CXCR5^+$ follicular helper T cells (Tfh) and $CD4^+CXCR3^+$ Th1 cells. Furthermore, Tcm bearing Tfh-phenotype decreased in patients who highly responded to CTLA4-Ig abatacept. In SLE patients, $CD19^+IgD^-CD27^+$ effector memory B cells (Bem) and $CD19^+CD27^+CD38^+$ plasma cells increased and among them the increase of $CXCR5^-CXCR3^+$ Bem was marked. However, Bem disappeared from the periphery for several years in SLE patients with clinical remission by anti-CD20 antibody rituximab therapy, but Bem increased just before the recurrence of SLE after the remission. The increase of Bem was not observed in patients with inadequate response to rituximab. Taken together, marked heterogeneity in subsets/phenotype of peripheral T cells and B cells was observed in patients with RA and SLE and its relevance to pathological processes, heterogeneity of diseases and differential responses to the targeted therapies using biologics has been discussed. Such approaches to subsets/phenotype of peripheral lymphocytes should lead to the development of differential tailor-made therapy in patients with RA and SLE revealing different clinical course.

S7-3

Tocilizumab treatment in autoimmune diseases of the central bervous system

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Conflict of interest: Yes

Neuromyelitis optica (NMO) is an autoimmune disease affecting the central nervous system, which is characterized by recurrent episodes of optic neuritis and myelitis. Although NMO woulld clinicaly resemble multiple sclerosis (MS) with regard to the clinical symptoms and relapsing-remitting course, differential diagnosis of NMO from MS is now possible by measuring serum autoantibodies against water channel protein aquaporin 4 (AQP4). Anti-AQP4 antibodies are able to cause destruction of astrocytes and therefore, their role in NMO pathogenesis looks ovbious. Notably, disease modifying drugs commonly prescribed for MS appear to augment the disease activity in NMO. We have found that plasmablasts producing anti-AQP4 antibodies are increased in the peripheral blood of NMO, and the ability of the plasmablasts to produce autoantibodies and their survival depend on the presence of IL-6, which led us to speculate the efficacy of drugs targeting IL-6 siganling in NMO (Chihara et al PNAS 2011). More recently, we have used tocilizumab for intractable cases of NMO, and found that the treatment is very effective in reducing the relapse rates as well as neurogenic pain and general fatigue associated with NMO (Araki et al. Neurol 2014). In this symposium, the results of our studies will be presented for deeper understanding of the pathogenesis of NMO and MS.

S7-4

Molecular mechanisms of dysregulated persistent production of IL-6 in immune-mediated diseases

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Conflict of interest: Yes

Since dysregulated continual production of IL-6 plays a pathological role in various immune-mediated diseases, a humanized anti-IL-6 receptor antibody, tocilizumab, was developed. Worldwide clinical trials proved the efficacy and tolerable safety of tocilizumab, leading to its current approval for the treatment of rheumatoid arthritis, juvenile idiopathic arthritis, and Castleman's disease. Moreover, favorable results of off-label use of tocilizumab suggest that it will be widely applicable for the treatment of other intractable immune-mediated diseases, particularly, systemic sclerosis, large-vessel vasculitis, neuromyelitis optica, adult-onset Still's disease, amyloid A amyloidosis, and polymyalgia rheumatica. The

success of tocilizumab has also accelerated the development of other IL-6 inhibitors. However, in order to achieve the broad application of IL-6 inhibitors for refractory diseases, further clinical evaluation and clarification of mechanism (s), through which IL-6 blockade strategy is efficacious for phenotypically different diseases, are essential. A transient expression of IL-6 contributes to host defense against infections and tissue injuries and then, the production ceases after stress is removed from the host. However, dysregulated persistent production of mostly unknown etiology is involved in the development of various diseases. IL-6 expression is tightly regulated by transcriptional and posttranscriptional mechanisms, to which several transcriptional factors, microRNAs, and RNA-binding proteins such as Arid5a and Regnase-1 contribute. Thus, detailed analyses of these proteins and microRNAs will facilitate to the identification of more specific target molecules and investigations into pathogenesis of specific diseases. In the symposium, I will present the current findings regarding these issues and discuss about future perspectives of IL-6 blockade strategy for various immune-mediated diseases.

S7-5

Pathological involvement of mitochondrial DNA in Behçet's Disease

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Conflict of interest: Yes

Behçet's disease (BD), which is characterized as an autoimmune disease, is an adult-onset chronic systemic inflammatory disorder. Although autoreactive lymphocytes are suggested to be involved in the pathogenesis of BD, the clinical properties and pathohistology of BD seem to resemble autoinflammatory diseases in terms of enhanced innate immune responses. Recently, mitochondrial DNA (mtDNA) has been shown to play crucial in activating the inflammatory response; however, the role of mtDNA in the pathogenesis of BD is yet to be clarified. We show here that serum mtDNA levels were significantly elevated in BD patients, therefore; high mtDNA levels can be seen as an important characteristic of BD. Interestingly, mtDNA was enveloped inside exosomes and dominantly released by monocytes. Additionally, BD-derived exosomes promoted sterile inflammation by enhancing neutrophil mobilization and cytokine production, in which Toll-like receptor 9 (TLR9) and NLR family, pyrin domain containing 3 (NLRP3) inflammasome were crucial, suggesting that mtDNA is the primary element in exosomes. Collectively, our findings indicate that mtDNA in exosomes is intrinsically involved in the pathogenesis of BD; therefore, provide a new diagnostic tool and therapeutic target for BD.

S8-1

NLRP3 inflammasome and inflammatory diseases

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Conflict of interest: Yes

NLRP3, a member of the Nod-like receptor family, forms the inflammasome with its adaptor protein ASC and mediates inflammatory immune responses. Clarification of the regulatory mechanism underlying NLRP3-inflammasome activation is an urgent research task, because excessive activation of the NLRP3-inflammasome often causes inflammatory diseases such as gout. Here we show that loss of nicotinamide adenine dinucleotide^{+}(NAD^{+}) caused by mitochondrial damage induces acetylated a-tubulin-driven spatial arrangement of mitochondria leading to the creation of sites for NLRP3-inflammasome activation. Chemical compound screening revealed that tubulin polymerization inhibitors including colchicine, a drug for gout, specifically suppress NLRP3-inflammasome activation. Microtubules mediate dynamic transport of mitochondria and subsequent proximity of ASC on mitochondria to NLRP3 on the endoplasmic reticulum at the perinuclear region. NLRP3-inflammasome inducers such as uric acid crystals cause aberrant mitochondrial homeostasis to reduce the NAD^{+} level, which in turn inactivates the NAD^{+}-dependent a-tubulin deacetylase SIRT2, resulting in accumulation of acetylated a-tubulin. Accumulated acetylated a-tubulin mediates mitochondria-endoplasmic reticulum contact to promote NLRP3-inflammasome formation. These findings indicate that, in addition to direct activation of NLRP3, the creation of optimal sites for signal transduction by microtubules is required for entire activation of the NLRP3-inflammasome. Thus, the microtubule system would be a promising therapeutic target for treatment of NLRP3-related inflammatory diseases.

S8-2

A novel inflammatory biomarker of autoimmune disease

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Conflict of interest: None

To identify novel serological biomarkers for inflammation, we took advantage of iTRAQ technology, a comprehensive and quantitative proteomic approach, and analyzed sera from RA patients before and after the treatment with anti-TNF-α antibody. As a result, we identified LRG (leucine rich alpha-2 glycoprotein), a glycoprotein of unknown function with a molecular weight of ~50kD, whose serum levels are high during active stage of arthritis and promptly decreased after anti-TNF-α therapy. Indeed, serum LRG levels correlated very well with the disease activity score (DAS28) in patients with RA. In addition to RA, serum LRG levels in patients with inflammatory bowel disease (IBD; CD and UC) are elevated during active stage and are reduced at remission. Moreover, LRG levels in patients with IBD correlated better with disease activity score and endoscopic score than CRP. Notably, LRG is not specific to autoimmune diseases, because high levels of LRG were detected in patients with pneumonia and tuberculosis. Unlike CRP, LRG was upregulated not only by IL-6, but also by the other inflammation-related cytokines such as TNF-α, IL-22 and IL-1β. These results collectively suggest that LRG is a promising biomarker for inflammation and infection and may be clinically useful as a surrogate marker of treatment response and adverse effects (infection) during IL-6 blockade therapy. Functional analyses of LRG demonstrated that LRG binds to TGF-β and induces angiogenesis by modulating TGF-β functions. Analyses on murine models of inflammatory diseases such as DSS-induced colitis indicated that inflammation in LRG knockout mice is less severe than WT mice and tissue repair in knockout mice tends to be accelerated. These results suggest that LRG is an important regulator of inflammatory response and subsequent tissue repair in the pathogenesis of inflammatory diseases.

S8-3

Regulation of autoimmunity by NKT cells

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Conflict of interest: None

Innate lymphocytes are important cells to brige acuquired and innate immunity. Innate lymphocytes include NKT cells, MAIT cells, gdT cells and innayte lymphoid cells (ILCs). In this session, we will demonstrate data on the role of NKT cells and MAIT cells in the regulation of animal models of autoimmune diseases. Moreover, we will show data on these cells in human autoimmune diseases.

S8-4

Regulation of the development of autoimmune arthritis by the transcription factors determining the differentiation of helper T cell subsets

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Conflict of interest: None

$CD4^{+}$T cells play a critical role in the generation of rheumatoid arthritis (RA). Recent studies reported the pathogenicity of IL-17 producing Th-17 cells in RA. However, the regulatory mechanism of $CD4^{+}$T

cell differentiation in the development of arthritis is not clarified. Collagen induced arthritis (CIA) was induced in T cell specific T-bet transgenic (T-bet Tg) mice, and significant suppression of CIA was observed in T-bet Tg mice compared with wild-type C57BL/6 (WT) mice. In vitro experiments revealed that IL-17 production from type II collagen (CII) reactive T cells was not detected in T-bet Tg mice, and that overexpression of T-bet and down-regulation of RORγt in CII reactive T cells in T-bet Tg mice. Although $CD4^+$T cells from naïve WT or T-bet Tg mice were cultured in the condition favoring Th-17 differentiation, IL-17 production and RORγt expression were inhibited in T-bet Tg mice. These results showed that overexpression of T-bet in T cells suppressed the development of autoimmune arthritis by the inhibition of CII reactive Th-17 differentiation. Next, we generated T cell specific RORγt transgenic (RORγt Tg) mice, and induced CIA. Unexpectedly, CIA was significantly suppressed in RORγt Tg mice compared with WT mice. IL-17 production from CII reactive T cells was elevated in RORγt Tg mice. Although no significant difference was observed in the expression of Foxp3 in $CD4^+$ T cells between WT and RORγt Tg mice, the expression of RORγt and chemokine receptor 6 were significantly elevated in Foxp3 Tregs in RORγt Tg mice. In vitro suppression assay reveled that $Foxp3^+$ Tregs in RORγt Tg mice maintained the suppressive function. Moreover, adoptive transfer of draining lymph node cells inhibited the development of CIA in recipient WT mice, suggesting the possibility that suppressor cell subset regulates autoimmune arthritis in RORγt Tg mice. In conclusion, the transcription factor T-bet and RORγt have a pivotal role in the generation of autoimmune arthritis.

S8-5

CD4+CD25-LAG3+Treg-mediated control of autoimmune diseases

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Conflict of interest: Yes

Tolerance inducing mechanisms for systemic autoimmune diseases have not been elucidated. Although there is evidence for the suppression of systemic autoimmunity by CD4+CD25+Foxp3+ regulatory T cells, the disease phenotype of Foxp3-mutated IPEX patients is quite different from that of SLE. Previously, we identified a CD4+CD25-Foxp3- regulatory T cells (Treg) population that expresses both lymphocyte activation gene-3 (LAG3) and early growth response gene-2 (Egr2). Here, we examined whether CD4+CD25-LAG3+ Treg play a role in the regulation of antibody production and systemic autoimmunity. In T cell specific Egr2-deficient mice, adoptive transfer of WT CD4+CD25-LAG3+ Treg reversed excessive development of follicular helper T cells (TFH) and germinal center B cells (GCB) in the spleen. In in vitro, CD4+CD25-LAG3+ Treg more efficiently induced B cell apoptosis and suppressed antibody production than CD4+CD25+ Treg. In lupus-prone MRL/lpr mice with Fas-mutation, adoptive transfer of CD4+CD25-LAG3+ Treg from MRL/+ mice significantly suppressed progression of nephritis and anti-dsDNA antibody production. Analysis of gene-targeted mice revealed that Fas and Egr2 were required for CD4+CD25-LAG3+ Treg-mediated B cell suppression. In addition to Egr2, Egr3 is also a transcription factor required for the induction of T cell anergy. It was reported that while CD2-Cre driven Egr2 deficient mice develop a lupus-like disease at 15 months, CD2-Cre driven Egr2/Egr3 double deficient mice develop the disease at as early as 2 months. When we generated CD4-Cre driven Egr2/Egr3 double deficient mice, the mice also developed the disease at 3 months. These results strongly suggest that Egr2/Egr3 on T cells control systemic autoimmunity, and the function of Egr2/Egr3–deficient LAG-3Treg is under investigation. Further examination of CD4+CD25-LAG3+ Treg may reveal the mechanisms for systemic autoimmunity.

S8-6

The role of regulatory B (Breg) cell in autoimmune diseases

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Conflict of interest: None

B cells are critically involved in the pathogenesis of autoimmune diseases including systemic lupus erythematosus and rheumatic arthritis. Indeed, B cell-targeting therapies including monoclonal antibodies against CD20, CD22, and BAFF in the treatment of these disorders have been drawing great attention, and some of them have been approved for clinical use after large clinical trials. However, the results of these clinical studies also elucidate the complexity of B cell functions. B cells play an essential role in humoral immunity by antibody production. However, recent studies have revealed that B cell is not just an antibody-producing cell but has more diverse functions in the immune system. These functions include antigen presentation and cytokine production. Moreover, recent studies have identified “regulatory B (Breg) cells”, which exert immunosuppressive functions via IL-10 production and thus is also called “B10 cells”. Murine Breg cell exhibit cell-surface phenotype of CD-1dhiCD5+ or CD21hiCD23hi and belong to marginal zone (MZ) B cells or T2-MZ precursor B cells. In humans, Breg cells have been reported as CD19+CD24hiCD38hi B cells or CD19+CD24hiCD38hi B cells. Various mouse autoimmune models have demonstrated the potent inhibitory functions of Breg cells, and their role in human diseases has also been implied. Thus collectively, the complexity of B cells in autoimmune diseases is due to this double-edged role of proinflammatory and anti-inflammatory functions. The recent advance in understanding the role of Breg cell in autoimmune diseases will be reviewed in this symposium.

S9-1

Evaluation of functional disability and activity limitation of daily living in rheumatoid arthritis patients with multi-joint damages

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Conflict of interest: None

To determine the priority of the surgical treatment for the multi-joint disorders of the rheumatoid arthritis (RA) patient, we inspected the associations between the level of limitation of activity in daily living (ADL) and function of individual joints. A comprehensive evaluation including difficulty in performing 44 activities in daily living (ADL), damaged joints, range of motion (ROM) of joints was conducted in RA patients hospitalized to Niigata Rheumatic Center during the term between July, 2011 and August 2012. The associations between them were analyzed. Total of 221 patients, mean age 64.6±11.2 year, disease duration 13.3±11.3 year, 85.1% women, participated in the study. The most frequently damaged joint was finger, lower limb, and wrist. Among 44 activities, 14 activities were claimed by 10% or more patients to have difficulty. Four leveled difficulties of these activities were factor analyzed and three components were identified. Stepwise regression analysis was performed to identify the independent variables which contribute to each factor scores. The first factor was associated with elbow, shoulder, and forearm damages. The second factor was associated with wrist and hand damages and DAS28 (ESR). The third factor was associated with damages of elbow, wrist, and lower limbs. Analysis of variance was conducted to examine the differences in ROM of joints by the level of ADL. Among 14 activity items, significant differences in ROM of all joints were observed by the activity levels of following three items; standing up from the floor, button and unbutton, shampooing. RA patients suffered from multifaceted limitation of ADL. Several joint damages collaborated and decided activity levels in complicated manners. Elbow and hand joint damages give broad range of daily activity limitation so that they may have priority to be treated.

S9-2

Modern THA and TKA improve function and quality of life in patients with rheumatoid arthritis

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Conflict of interest: Yes

BACKGROUNDS: Biologics and/or MTX treatment of patients with rheumatoid arthritis (RA) has improved markedly over the past 10 years in Japan. As the joint destruction in patients with RA becomes milder, the number of THA/TKA operations might decrease. On the other hand, with the trend toward milder disease, RA patients are demonstrating a strong desire to stay more active in activities of daily living, and even in athletics. One of the most successful treatment for painful joints is total joint arthroplasty, such as THA/TKA. OBJECTIVE: To investigate whether the number of THA and TKA, a long-term consequence of poorly controlled RA, have changed over 2000 to 2011, assess the severity of destruction of RA hips and knees over this period, investigate the number of multiple joint reconstructions and the effect on improvement of activities of daily living. METHODS: In a serial cross-sectional study of patients with RA in our hospital, trends in annual performances of THA and TKA from 2000 to 2011 were examined. RESULTS: The number of THA performed in 2005-2011 was 139, which is lower than 186 in 2000-2005. The number of THA with bonegraft for acetabular protrusion deformity in 2006 to 2011 was 10, which is lower than 27 in 2000 to 2005. The number of TKA performed in 2006-2011 was 329, which is a little bit lower than 371 in 2000-2005. The number of TKA with constrained system, augmentation, or stem extension for severe deformity in 2006 to 2011 was 14, which is lower than 26 in 2000 to 2005. The number of patients with 3 or 4 joints replacement in 2006-2011 was 7, which is lower than 38 in 2000-2005. CONCLUSIONS: Rates of THA and TKA in RA patients have declined and severity of joint destruction have lowered, suggesting that longterm outcomes of RA are improving. Improving the quality of life for patients could be obtained by combining the careful assessment of function and the modern THA/TKA technology.

S9-3

Rheumatoid foot - Foot deformity correction under understanding the relationship between hindfoot and forefoot -

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Conflict of interest: Yes

Since multiple joints are often affected in patients with rheumatoid arthritis (RA), both comprehensive evaluation of the damages occurred in multiple joints and precise evaluation of isolated damaged joint are required either to estimate the prognosis of joint damage progression or to indicate the surgical intervention. Hind, mid, and forefoot deformities are thought to be correlated mutually, however the intercorrelation is not well understood because of varieties in the distribution of affected joints and in the extent and pattern of damage of affected joint. So further understanding the pathology of rheumatoid foot is necessary for better strategy of surgical intervention. We have to know the influence of the change in alignment and restricted motion in affected joint on the adjacent joints and the progression patterns of rheumatoid foot. Our previous several observational studies of rheumatoid foot showed that rheumatoid valgus hindfoot had valgus and lateral shift displacements of the calcaneus and navicular bones relative to the talus without displacement of cuboid relative to both the calcaneus and navicular, that there were at least two patterns of flattening in rheumatoid hindfoot, and that rheumatoid foot had the difference of correlation between hind-mid-forefoot changes while grouping the existence of second MTP joint dislocation. Our previous case report showed that correction of severe valgus, calcaneal lateral offset, and pronated foot deformity instantly normalized hallux valgus deformities postoperatively. These findings provide us with useful information for selection of surgical procedures for rheumatoid foot and also make us to notice that there is room for improvement on present surgical procedures. Further studies provide a chance to progress to better surgical intervention due to deep understanding the rheumatoid foot pathology.

S9-4

Effects of total elbow arthroplasty in combination with biologic agents for rheumatoid arthritis

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Conflict of interest: Yes

The ARASHI study group developed a new scoring method for large joints that can evaluate progression of joint destruction as well as joint remodeling. The prospective SWEET study on 750 large joints of 75 patients before and after biologic therapy showed that joint destruction evaluated by total ARASHI change score was not changed in 44 cases (58.7%), progressed in 16 cases (21.3%), and improved in 15 cases (29.0%). Changes in the knee joints greatly affected both progression and improvement of total ARASHI score. In the elbow joint, ARASHI change score was not changed in 64 cases (85.3%), progressed in 4 cases (5.3%), and improved in 7 cases (9.3%). Bio can prevent the joint destruction of elbow joint, partly by induction of osteoarthritis-like remodeling in the damaged joint. In the review of 1289 records of orthopaedic surgery for RA performed in our institute between 2003 and 2013, the number of TKA and THA has decreased, but the number of TEA has not changed. We examined the pre- and post-operative data of 24 elbows without Bio (Bio (-) group) and 15 elbows with Bio (Bio (+) group). The disease activity evaluated by DAS28-CRP was significantly lower in Bio (+) group than Bio (-) group, and has been significantly improved by TEA both in Bio (-) and Bio (+) groups. DASH score also improved in both groups byTEA, but significant improvement was noted only in Bio (-) group. The elbow joint function evaluated by JOA elbow score significantly ($p<0.0001$) improved from 48 to 91points and 55 to 92 points in Bio (-) and Bio (+) group, respectively. The results suggested the better preoperative elbow condition can be achieved in RA patients under good disease control with Bio, and favorable effect of TEA can be expected for functional reconstruction of the elbow joint to compensate the limitation of Bio on bone and joint destruction.

S9-5

Grip power and surgical treatment of the rheumatoid wrist and hand

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Conflict of interest: None

Objectives: The objective of this study was to clarify the relationship among grip power, ADL, and functional disorder at the individual joint. **Patients and Methods:** During the period between July 2011 and Aug 2012, 218 hospitalized patients with RA were investigated about grip power, independent level (0~4), cause and site with problem in 14 items of ADL. **Results:** In all ADL items, significant difference was noted in grip power depending on the independent level ($p<0.001$). Based on the results of stepwise regression analysis, the first factor consisting of “hair dressing”, “washing one’s body”, “taking on and off one’s shoes”, “clipping nails”, “buttoning” etc. related to grip power, elbow, shoulder, and wrist problems. The second factor consisting of “opening plastic bottle”, “opening lids”, “squeezing towels” etc. related to grip power, wrist, and thumb problems. The third factor consisting of “getting in and out of bathtub”, “standing and sitting” etc. related to age, lower extremity, elbow, and wrist problems. No assistance in all items was required in 28% of the female and 48% of the male. In the ROC curve, grip power with the maximal Youden index was 136.5mmHg (ca 11.8kg) in the female and 152.5mmHg (ca 13.5kg) in the male. The explanatory variable of grip power in the female was age, disease duration, DAS28, fingers, thumb, and elbow problems. **Discussion:** Procedures of surgical reconstruction which could provide increased grip power to the severely deformed wrist and hand were partial or total wrist arthrodesis, fusion at the

MP or IP joint of the thumb, and fusion at the PIP joint of the fingers. Synovectomy for the painful joint with persistent synovitis could also provide pain relief and increased grip power. **Conclusion:** Grip power was one of the determinants of ADL in the patient with RA, and it was a useful objective index of ADL. Higher level of ADL could be achieved by a surgical hand reconstruction.

S9-6

A prospective cohort study to evaluate comprehensive joint reconstruction surgery and establish treatment guidelines for patients with rheumatoid arthritis with impairment in multiple joints: baseline analysis

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Conflict of interest: Yes

[Objectives] Now, treatment goal for rheumatoid arthritis is aggressively set to remission. Reconstruction surgery should be needed for further improvements of physical function for long-standing RA patient. The purposes of this study are to characterize functional impairment in surgical patients and to set the treatment goal of joint reconstruction surgery in conducting a multicenter study (the Ishiguro group from the Ministry of Health, Labour and Welfare). [Methods] With the baseline defined as presurgery, we collected data on age, sex, disease duration, drug therapies, and disease activity. Functional evaluations were made using the HAQ, DASH (upper limb function), and JSSF-RA (foot and ankle function), and patient subjective evaluations using the EQ-5D (comprehensive assessment of QOL) and BDI-II (depression). Joint range of motion was also measured as part of this evaluation. [Results] 347 surgical patients were registered. Mean values for age (65.2 years), disease duration (18 years), and sex (88% female) were recorded, in addition to median values for DAS28 (3.0) and CRP (0.33). Patients noted most remarkable ADL disabilities for the following items on the HAQ-DI: HAQ2 (shampoo hair), HAQ4 (arising), HAQ11 (tub bathing), and HAQ16 (opening and closing a wide mouth jar). As the level of disability increased, a concomitant decrease was observed in each joint's range of motion. Following ROMs of the joints which represented nearly non-existent levels of disability, are needed; wrist, flexion-extension as well as 150° pronation and supination, 130° elbow flexion, and 140° shoulder flexion, ankle flexion-extension of 55°, knee flexion-extension of 120°, hip flexion-extension of 120°. [Conclusions] Upper limb function in RA patients who required surgical procedures was significantly associated with many kinds of daily activity. Treatment goal could be set based on range of motion of not only the joint which is required surgical procedures but also other joints totally.

S10-1

Up-to-date therapeutic strategies for pulmonary arterial hypertension associated with connective tissue disease

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Conflict of interest: Yes

Recent introduction of molecular-targeting drugs, such as prostanoids, endothelin receptor antagonists, and phosphodiesterase-5 inhibitors, has improved functional capacity, hemodynamics, and survivals in patients with pulmonary arterial hypertension (PAH) associated with connective tissue disease (CTD). In our single center cohort, 3-year survival rate has been improved from 26% to 76% during the past 20 years, but long-term outcomes are still unsatisfactory. To further improve prognosis, it is imperative to practice personalized medical approach. Since a various forms of PH, including PAH, pulmonary veno-occlusive disease (PVOD), PH owing to left heart disease, PH owing to interstitial lung disease, and chronic pulmonary thromboembolism, can occur in patients with CTD, it is critical to identify underlying pathophysiologies before initiating treatment. In patients with PAH associated with systemic lupus erythematosus, mixed connective tissue disease, Sjögren's syndrome, upfront combination therapy with two or more PAH drugs should be initiated in combination with immunosuppressive treatment to achieve remission, which is normalization of exercise capacity and hemodynamics. In contrast, patients with systemic sclerosis and PAH often have concomitant PVOD, myocardial involvement (usually diastolic dysfunction), and interstitial lung disease. Aggressive treatment with PAH drugs sometimes results in pulmonary edema and worsening of oxygenation by increasing a ventilation-perfusion mismatch. Therefore, extreme caution is necessary upon initiation, increasing dosage, and addition of PAH drugs to prevent these unfavorable complications. Since introduction of new treatment modalities is less likely in the next few years, optimization of current therapeutic strategies based on multidisciplinary approach is required for this intractable condition.

S10-2

Treatment for gastrointestinal complications of collagen vascular diseases

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Conflict of interest: None

Collagen vascular diseases are known to present with a diverse array of gastrointestinal manifestations and even rheumatologists should cope with various digestive symptoms in daily clinical practice. In particular, gastrointestinal bleeding and peritonitis following perforation of the bowel are medical emergency to respond promptly. These can be classified as: 1) gastrointestinal damage due to the collagen vascular disease itself; 2) adverse events caused by pharmacotherapiessuch as anti-inflammatory drugs (NSAIDs) and glucocorticoids (GC); or 3) gastrointestinal infections following immunosuppression due to administration of GC or immunosuppressant. The first group includes lupus enteritis and protein-losing gastroenteropathy in systemic lupus erythematosus (SLE), reflux esophagitis and chronic intestinal pseudo-obstruction in systemic sclerosis (SSc), amyloidosis in rheumatoid arthritis (RA), bowel ulcer and bleeding in rheumatoid vasculitis, microscopic polyangiitis, and ileocecal ulcer in Behcet disease. IgG4-related disease includes autoimmune pancreatitis and sclerosing cholangitis. In addition, portal hypertension and esophageal varix caused by obstruction of splenic vein are reported as complication of IgG4-related disease. In particular, colonic ulcers associated with SLE, gastrointestinal motor abonormality in SSc, and bowel involvement in vasculitis are resistant to several treatments. On the other hand, introduction of biologics such as TNF-alfa and IL-6 antagonists have facilitated tight control of amyloidosis in RA and ileocecal ulcer in Behcet disease. The second group includes lesions in the small and large intestine due to NSAIDs and GC, in addition to peptic ulcers. The third group includes candidal esophagitis and cytomegalovirus (CMV) enteritis. Here I will mainly introduce the treatments for gastrointestinal involvement due to the collagen vascular disease including new therapeutic modality such as biologics.

S10-3

The treatment of intractable myositis-associated interstitial lung disease

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Conflict of interest: None

In patients with polymyositis (PM) and dermatomyositis (DM), inter-

stitial lung disease (ILD) is often complicated and determines prognosis. Myositis- specific autoantibodies (MSAs) are useful markers for PM/DM, which are correlated with certain clinical and pathophysiological conditions. Anti-aminoacyl-tRNA synthetases (ARS) and anti-MDA5 antibodies are most often detected (50-70%) in ILD patients complicated with DM/PM. The patients with anti-MDA5 Ab frequently develop rapidly progressive ILD resistant to treatment, then show poor outcome by the first 6 months from the onset. Therefore, aggressive therapy should be started as soon as possible after diagnosis. Age, hyperferritinaemia, high anti-MDA5 titer, and hypoxemia are thought to be poor prognostic factors. In the group who received the intensive treatment protocol combined with glucocorticosteroids, cyclosporine and intravenous cyclophosphamide pulse, the survival rate at the first 6 months was improved significantly when compared with the group who received the traditional step-up-therapy in accordance with exacerbation as a historic control (75.0% vs 28.6%). Furthermore, the patient who showed poor response to the intensive protocol was successfully treated with the plasma exchange with the improvement of a serum ferritin level and anti-MDA5 titer. The most cases of ILD with anti-ARS show chronic type and good response to the initial glucocorticoid treatment. However, since these ILD repeat exacerbation and the respiratory functions deteriorate gradually during the courses, the long term survival rate is not necessarily satisfied. Accordingly, the preservation of pulmonary functions over long duration should be considered as a treatment goal, and combined use of the immunosuppressants from the early period is recommended. Detection of the MSAs in the early stage of the disease is very useful in predicting the clinical course and prognosis, and determination of the treatments according to morbidity is needed.

S10-4

Treatment of refractory lupus nephritis

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Conflict of interest: Yes

Lupus nephritis is a common complication in systemic lupus erythematosus (SLE) and predicts a poor outcome. Although the use of aggressive immunosuppressive agents has improved patient survival and renal outcome over the past several decades, the optimal treatment of LN remains challenging. The major therapeutic agents for LN during the 20th century were steroids, azathioprine, and cyclophosphamide. Especially, intravenous cyclophosphamide has been widely used for the initial treatment of diffuse proliferative LN. However, cumulative adverse effects, particularly an increased risk of gonadal toxicity, have led clinicians to search for alternative therapies. Predictive factors for the prognosis of lupus nephritis have been reported, including age, sex, hypertension, serum creatinine, and renal histology. Previously, we reported that renal survival of class IV-G (A/C) of ISN/RPS2003 classification was significantly poorer than class IV-G (A) (Rheumatoloty 47:702, 2008). Later, we also found that class III/IV + V (mixed type) was associated with poor prognosis as compared with pure type of proliferative or membranous nephritis and is a strong predictive factor on the multivariate analysis (the 55th Annual meeting of JSN 2012). According to the renal biopsy registry of JSN, mixed type of lupus nephritis constitutes substantial proportion of registered cases. Mixed type should be regarded as refractory lupus nephritis. In 2008, Bao et al. proposed a combination therapy with tacrolimus, and micophenolate mofetil (multi-target therapy) for initial treatment of mixed type of lupus nephritis (JASN 19:2001). Very recently, we reported that multi-target therapy was effective as an initial treatment for active lupus nephritis to achieve complete remission earlier at a higher rate (Mod Rheum online on Oct., 2013). In this symposium, I introduce our above data and discuss on the therapy of refractory lupus nephritis.

S10-5

Efficacy and safety of abatacept for patients with secondary Sjögren's syndrome associated with rheumatoid arthritis

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Conflict of interest: None

<Objective> To clarify the efficacy and safety of abatacept for secondary Sjögren's syndrome (SS) associated with rheumatoid arthritis (RA). <Methods> We designed open-labeled, prospective, observational, and multicenter study (ROSE trial; Rheumatoid Arthritis with Orencia Trial Toward Sjögren's syndrome Endocrinopathy) for secondary SS (diagnosed by 1999 revised Japanese diagnostic criteria) associated with RA (diagnosed by 1987 ACR or 2010 ACR/EULAR criteria), who were over 20 years old and consented to this study. 1) Primary endpoint was frequency of Simplified Disease Activity Index (SDAI) remission at 52 weeks after initiation of abatacept. 2) Secondary endpoints included Saxson's test and Schirmer's test. 3) Adverse events during observational periods were also analyzed. <Results> Thirty five patients (all females) have been enrolled in this study. Interim analysis for 24 weeks included assessment for effectiveness in 17 patients and safety in 18 patients. 1) SDAI significantly decreased from 17.5±9.4 (0 week, baseline) to 10.4±9.8 (24 weeks) ($P<0.05$) after initiation of abatacept. Patients with clinical remission by SDAI increased from 0 patient (0 week) to 4 patients (23.5%) (24 weeks). 2) Saliva volume by Saxson's test increased slightly from 2330±1928 (0 week) to 2599±2081 (24 weeks) mg/2 min in 17 patients. In 9 patients with Greenspan grading 1 and 2 of labial salivary glands biopsy, saliva volume increased more largely from 3014±2212 (0 week) to 3469±2325 (24 weeks) mg/2 min ($P=0.05$). Tear volume by Schirmer's test significantly increased from 3.8±5.6 (0 week) to 5.0±6.6 (24 weeks) mm/5 min ($P<0.05$). 3) Five adverse events occurred in five patients out of 18 patients (27.8%), and three of them were infections. Although abatacept was interrupted in 3 patients, it has been restarted after recovery of the adverse events. <Conclusion> These results indicated that abatacept might be effective for both SS and RA involvements in secondary SS associated with RA.

S10-6

Standard treatment and clinical trial of biologics for refractory ANCA-associated vasculitis

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Conflict of interest: None

Systemic vasculitis is the encompassing term for the inflammation of all-sized blood vessels. In Chapel Hill Consensus Conference 2012, Systemic vasculitis classified into two types, one is large vessel vasculitis such as Takayasu arteritis and Giant cell arteritis, the other type is medium and small vessel vasculitis including Kawasaki disease, polyarteritis nodosa, ANCA associated vasculitis and immune complex vasculitis (1). Based on the evidence from previous clinical studies in Western countries, high dose corticosteroids with concomitant use of cyclophosphamide in the European League Against Rheumatism (EULAR) guideline for vasculitis. Although these standard protocols produce the initial remission in any forms of vasculitis, refractory cases are not rare. Recently rituximab for refractory ANCA associated vasculitis has been reported (2,3). And TNF inhibitors tried to be treated with refractory ANCA associated vasculitis. We had 131cases of vasculitis in our hospital between 1998 and 2013. ANCA associated disease was 103 cases in the 131 cases. In this session, the emerging new treatments for refractory vasculitis are presented based on our treatments and worldwide clinical studies and better standard practices for vasculitis are discussed based on the clinical investigations in Japan. 1. Jennette J, et al.: 2012 Revised International Chapel Hill Consensus Conference nomenclature of Vasculitides. Arthritis Rheum. 2012 2. Stone JH et al.: Rituximab versus cyclophosphamide for ANCA-associated vasculitis. N. Engl. J. Med. 363:221-232. 2010 3. Jones RB et al.: Rituximab versus cyclophosphamide in ANCA-associated renal vasculitis, N. Engl J Med. 363:211-220, 2010

S11-1

Evaluation of rheumatoid arthritis with MR imaging

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Conflict of interest: None

MRI aids in assessment of bone, cartilage and synovium, providing reliable information for early diagnosis, prognosis and therapeutic effect in rheumatoid arthritis (RA). Synovitis is the earliest pathological change in RA, which is best seen on contrast-enhanced fat-saturated TIWI. Synovitis can be quantitated using volume measurements, dynamic study or scoring methods. Dynamic study can assess the rate of early enhancement of synovium, which correlates with activity of synovitis. As a scoring method, Rheumatoid Arthritis Magnetic Resonance Imaging Score (RAMRIS) is most commonly used for the study. However, use of this system is limited by its time-consuming and tedious method. Bone changes can appear as erosion and bone marrow edema. Erosion on MRI is defined as a well-circumscribed area of abnormal signal with focal loss of cortical bone, which shows contrast enhancement. Bone marrow edema appears as a region of bone change without clear margins that shows high signal on STIR with enhancement effect on post contrast images. Both erosion and bone marrow edema represent bone marrow inflammation associated with osteoclast activation. Erosions on MRI can be seen in RA patients without evidence of erosions on radiographs and is sensitive for the therapeutic outcome. Bone marrow edema is a pre-erosive lesion and an important factor to predict future derangement and dysfunction of the joint. Synovitis and bone changes on MRI are nonspecific. However, diagnostic specificity can be increased by combination with serological markers. Our study showed that the three objective measures (anti-CCP antibody and/or IgM-RF, symmetric synovitis on MRI, bone marrow edema and/or bone erosion on MRI) significantly contribute diagnosis of early RA. The diagnostic performance was proved to be similar to that of 2010 ACR/RULAR classification criteria for RA. Furthermore, MRI findings, especially bone edema, can improve the diagnostic accuracy of 2010 RA criteria.

S11-2

Visualization and evaluation of joint structures by ultrasonography and magnetic resonance imaging

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Conflict of interest: None

Treatment for rheumatoid arthritis (RA) has remarkably changed since the advent of biologic agents and the treatment goals have greatly shifted to the achievement of clinical remission and prevention of joint destruction. For evaluation of response to the treatment, imaging studies are important in addition to clinical evaluation by composite measure such as the 28-joint Disease Activity Score (DAS28). Magnetic resonance (MR) imaging and ultrasonography (US) allow the visualization and evaluation of not only bone erosions but also bone marrow edema and synovitis, which are difficult to detect on plain radiographic images. Diagnostic accuracy is improved by devising the setting of the MRI and US. The quality of image is improved by High-field MRI and surface coil. At least two planes or three dimensional images are necessary for assessment of bone erosion. In assessment of synovitis, MIP image enhances the perspicuity. In addition, volume measurement from 3D images makes quantitative evaluation possible and E-rate from Dynamic MRI image improves qualitative assessment. Imaging position, sequence setting, and image creation can be implemented as routine. Thus, it is important to establish routine regimen for imaging of RA in cooperation with a radiologist. Image qualities of US vary depending on a device, probe and setting. Such device, setting and procedure can affect evaluation of joint pathology. Therefore, it is inevitable to standardize the procedures to establish the assessment system by ultrasonographers. We established hand and wrist assessment system by ultrasonographers. In addition to procedure standardization, shortening time of inspection, constructing recording system is important. Because required conditions for US assessment are different between physicians and ultrasonographers, it is essential to build an assessment structure according to each condition. In this symposium, we will summarize visualization and evaluation of MRI and US.

S11-3

Assessment for the diagnosis and treatment in rheumatoid arthritis by ultrasound; comparison with magnetic resonance imaging

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Conflict of interest: Yes

We previously reported MRI-proven bone marrow edema (BME) is a strong predictor toward the progression to RA from undifferentiated inflammatory arthritis (Arthritis Rheum 2009;61:772). We also reported moderate to severe power Doppler (PD) synovitis is important for early differentiation and diagnosis of RA (Mod Rheumatol 2013;23:36). In our study comparing hand-US findings and hand-plain MRI findings, the severity of US-proven synovitis highly correlated with that of MRI-proven BME ($r=0.6$-0.8, $p<0.0001$). Moreover, MRI-proven BME was frequently found in the joints presenting moderate to severe US-proven synovitis. These results suggest that moderate to severe US-proven synovitis is important to diagnose RA and predict further radiographic progression. As for the monitoring of treatment, US synovitis scores improve in parallel with clinical assessments at the group level. We have been assessing US synovitis scores over time in RA patients treated with biologic DMARDs. Regardless of the severity of synovitis at baseline, US synovitis scores improved during the treatment. So, it may be difficult to predict the therapeutic responsiveness only by US synovitis at baseline. However, therapeutic efficacy tended to be excellent in the patients US synovitis scores improving early. On the other hand, a standardized response mean (SRM), which shows therapeutic responsiveness, of US synovitis scores was lower than that of clinical composite measure. Therefore, despite early improvement of clinical disease activity achieved by biologic DMARDs, it may take time to improve synovitis activity actually. At the individual level, there was discrepancy between clinical disease activity and US-proven synovitis activity in some patients. It may be important to monitor these patients by US to avoid the undertreatment or overtreatment. We will discuss about the utility of US for the diagnosis and treatment in RA including a comparison with MRI in this symposium.

S11-4

Ultrasonographic assessment of synovitis improves the therapeutic outcome of rheumatoid arthritis

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Conflict of interest: Yes

The imaging techniques in rheumatoid arthritis (RA) have substantially advanced along with the improvement of modern therapeutic strategies. The utility of musculoskeletal ultrasound in the management of RA has been extensively studied since research revealed that ultrasound visualizes both synovitis and bone lesions. The direct assessment of synovitis with ultrasound, which is impossible with plain radiograph, caused a paradigm shift in the imaging for RA. Ultrasound enables more accurate assessment of inflammation in the synovial tissues than clinical examination does. Accurate assessment of synovial inflammation directly improves therapeutic outcome of RA by accurate diagnosis and accurate assessment of disease activity of RA, which enables earlier intervention and tighter control of disease activity and reduces unnecessary or inappropriate use of anti-rheumatic drugs. In addition, the visualization of synovitis can indirectly improve therapeutic outcome of RA by better understanding of the pathophysiology of RA and improved physical

assessment skills and communication between patients and physicians. On the other hand, the benefit of ultrasound should be balanced with its cost and the time spent. Particularly, the time for scanning can be the major obstacle for this technique to be performed in daily practice. In this presentation, optimal choice of the patients and joints to be scanned will be discussed.

S11-5

The promotion of the use of musculoskeletal ultraound in rheumatology clinical practice

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Conflict of interest: Yes

The role of musculoskeletal ultrasound (MSUS) in the management of rheumatic diseases has been established based on numerous reports in the literature. On the other hand, there are still some obstacles to integrate MSUS into standard rheumatology practice. The lack of knowledge about its usefulness, limitation of time to perform, economic reason and lack of opportunity of training can be listed. Its widespread adoption should be stimulated through scientific meetings and training courses. For this purpose, in addition to the introductory MSUS courses which have been introduced by JCR for years, the first advanced MSUS course was held in 2013. The need for standardization of MSUS has been pointed out. Standardization of image acquisition and image interpretation have been established through various guidelines and training courses. The standardization of the best practice of MSUS is urgently needed. There is no protocol concerning when, who, where, how many joints MSUS should be performed. The role of MSUS must be different between clinical trials and daily clinical practice. In addition to the importance of MSUS in the serial evaluation of disease activity in limited patients participating in clinical trials, it is also, and probably more important to perform MSUS as part of an overall clinical evaluation in a rheumatology office that would include a history and physical examination (i.e., point of care MSUS). The establishment of the best practice of MSUS in routine clinical practice should result in the improvement of prognosis of all of the patients with rheumatic diseases.

S11-6

Assessment of disease activity in patients with rheumatoid arthritis using FDG-PET/CT

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Conflict of interest: None

Whole body F-18 fluorodeoxyglucose positron emission tomography (FDG-PET) can evaluate the degree of synovial inflammation in rheumatoid arthritis (RA) patients. We report here; 1. The assessment of the disease activity in RA patients using FDG-PET/CT, 2. A comparison of the accumulation of FDG and clinical findings under biological (Bio) treatments, 3. The features of FDG-PET/CT and MRI images of the shoulder joints in RA patients, 4. The relationship between the progression of joint destruction and the FDG uptake in RA joints, and 5. The evaluation of a spondylarthritis (SpA) patient using FDG-PET/CT. [Methods] We performed whole-body FDG-PET/CT and measured the accumulation of 18 F-FDG. The standardized uptake value (SUV) was calculated for the semiquantitative analysis. We examined the relationship between the total SUV and conventional parameters of the disease activity. The delta SUV (ΔSUV) was calculated, and the values were compared with respect to differences in the disease activity. The existence of synovial inflammation in the shoulder joint was investigated on MRI and PET. In order to investigate the relationship between the progression of joint destruction and the FDG uptake, we compared the change in the Larsen grade of each joint and the SUV. [Results] The SUVmax values were correlated with the DAS28, DAS28-CRP, SDAI and CDAI value. The ΔSUV was correlated with the ΔDAS28, ΔDAS28-CRP, ΔSDAI and ΔCDAI. The degree of synovial inflammation in the shoulder MRI exhibited a correlation with the SUVmax of the shoulder joint. There were also correlations between the progression of joint destruction and the SUV value of the joints. The SUVmax value in the SpA patients decreased following the administration of biological therapy. [Conclusions] FDG-PET is a useful modality for evaluating of the disease activity, curative effect of treatment and degree of synovial inflammation of the joints, as well as predicting the progression of joint destruction in RA patients.

S12-1

Rheumatoid arthritis and related diseases can cause several lines of pain mechanisms

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Conflict of interest: Yes

There are three types of underlying mechanisms of pain: Nociceptive pain, neuropathic pain and psychogenic pain. Rheumatoid arthritis (RA) and related diseases are autoimmune diseases, and they induce inflammation in mainly joints and thereby patients with RA and related diseases usually complain of joint pain. The underlying mechanism of the joint pain is categorized into nociceptive pain. Nociceptors on the peripheral nerve endings, which innervate into every tissue, are stimulated by the inflammatory 'soup' and nociceptive information is recognized as pain in the brain. In the anesthesiology field, acute post-operative pain and cancer pain are most-commonly treated as nociceptive pain. Individual pain ratings to nociceptive inputs are very varied, and one of explanatory factors to this variation is obesity. Obesity is also known as a risk factor of low back pain and joint pain in osteoarthritis, and the mechanisms of pain worsening by obesity is mechanical load to the musculoskeletal system. However, obesity can increase migraine and post-operative pain, which are irrelevant to mechanical load. We now focus persistent systemic inflammatory state by obesity, known as the metabolic syndrome, and its-related cytokines (adipokines). Here, I present our attempt to reveal the relationship between nociceptive pain and akipokines. Further, RA and related diseases can cause neuropathic pain state, because 1) RA can destroy peripheral tissues including nerve fibers and 2) successive nociceptive inputs by persistent inflammation can induce hyper-activation of the spinal nociceptive neurons. Further, as a new concept of chronic pain, central dysfunctional pain is proposed. In this symposium, I explain the current understanding of the central dysfunctional pain, in relation to joint pain by RA and related diseases.

S12-2

Development and maintenance of chronic pain conditions

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Conflict of interest: Yes

A large number of populations are known to suffer by chronic pain condition and result to cause low ADL level. Various factors such as, continuous nociceptive stimulations, neuronal plastic changes, psychosocial factors, biomechanical factors, age related degeneration etc have a role in development and maintenance of chronic pain conditions. Continuous nociceptive inputs raised from peripheral tissue are known to produces axonal reflex and results neuronal inflammation which augments local cytokine associated inflammation. And these local changes cause sensitizations and plastic changes of central nervous systems secondarily. Blocking of these neuronal circuits is essential to inhibit development of chronic pain. In addition to local inflammation control with NSAIDs, channel blockers antidepressants, opioids are useful pharmacological tools for chronic pain control. Besides, influence of psycho-social factors are not negligible factors for maintenance of chronic pain. Depression, character disorder and disease associate gains are often exists in these situations and care these problems are essential to improve painful conditions. In addition, musculoskeletal exercises are most important approaches to achieve good QOL under chronic pain situations.

S12-3

Hand Pain and Neural Pain that Rheumatologists Should Also Recognize

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Conflict of interest: None

Accurate diagnosis and differential diagnosis of musculoskeletal pain disorders is an important issue for the Rheumatologist. However, musculoskeletal pain disorders in the upper extremity, especially in the finger joints, wrist, elbow and shoulder joints present with a wide array of disabilities, and when deformation of the joint is present such as in rheumatoid arthritis (RA), accurate diagnosis of the cause of pain is not easy. RA often presents with synovial hyperplasia which leads to entrapment neuropathies, and therefore, the diagnosis of "neuropathic pain disorders" is also important. In this lecture, we will present various disorders common in RA, such as rupture and dislocation of extensor tendons due to synovitis of the tendon sheath in finger and wrist joints, insufficiency fractures of the distal radius and other loci which are common in cases with osteoporosis, carpal tunnel syndrome, where the median nerve is compressed in the wrist area, Guyon's canal syndrome, where the ulnar nerve is compressed in the wrist area. It has been reported that neuropathic pain (mainly entrapment neuropathies) are seen in up to 10% of RA patients, and therefore, the differential diagnosis is important. During actual examination, it is important to consider pathophysiology from the point of innervation patterns. For example, it is important to remember the dermatomal distributions, with C4 on the lateral aspect of the shoulder, C5 on the lateral aspect of the arm, C6 on the radial aspect of the forearm. Furthermore, if one remembers the nerve pathways which innervate the painful area, one can determine where to examine the Tinel sign, which is useful for localizing the spinal segments of a peripheral neuropathy. One must also keep in mind the presence of "double-crush," which is where pathology affects multiple loci simultaneously. Therefore, when diagnosing upper extremity pain, one must also examine the cervical spine, the neck portion, and the chest wall.

S12-4

Pharmacotherapy for management of rheumatic disease pain

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Conflict of interest: Yes

A 16th century western writer described 'to cure sometimes, to relieve often, to comfort always' for the role of the physician in patient care. This may mean 'to perform interventional therapy sometimes, to do pharmacotherapy often, to listen attentively patients' pain always' for management of rheumatic disease pain. Therefore, the pharmacotherapy must be an important and necessary item to manage rheumatic disease pain. However, prescription of non-steroidal anti-inflammatory drugs (NSAIDs) had been extended over a long period of time, as the first analgesic for rheumatic disease pain in Japan. In patients with rheumatic disease, NSAIDs have some problems. One is side effects such as including peptic ulcer, renal dysfunction and inhibition of platelet, because of long use of NSAIDs. Another is patients' dissatisfaction because of insufficient management of pain. Recently, pharmacotherapy for chronic pain including rheumatic disease pain has been dramatically changed and improved, because of being socially interested in chronic pain, understanding mechanism of chronic pain, development of many types of analgesics such as adjuvants and opioids, and other factors. Then, it may be easy and safe to manage rheumatic disease pain with patients' satisfaction. In this symposium, the trend of pharmacotherapy for management of rheumatic disease pain in reference to some guidelines.

S12-5

The psychological characteristics of patients suffered from intractable chronic pain complicated with rheumatic diseases: from the view of psychosomatic medicine

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Conflict of interest: None

Some cases of chronic pain complicated with rheumatic diseases are intractable with standard therapies. We treat such patients that visited our Department of Psychosomatic Medicine after treatments in many health care services. We try to clarify the psychological mechanisms of intractable chronic pain and we perform the multidisciplinary graduated psychosomatic approach to those patients. They are often relieved from suffering and obtain elevated QOL. In those cases with rheumatic arthritis or fibromyalgia that has been derived from rheumatic diseases as the disease concept, common psychological mechanisms have been frequently observed independent of the severity of organic diseases. The following three characteristics were important as the therapeutic targets in psychosomatic medicine. 1) Lowered self-appraisal / Over-adaptation 2) Compulsiveness / Perfectionism 3) Alexithymia: Difficulty in identifying feelings, Difficulty in describing feelings, and Externally-oriented thinking The above psychological characteristics make patients to move their bodies excessively and to gain continuous strain on the musculoskeletal system. Moreover, they think compulsively and burn out to pain catastrophizing on chronic sufferings. They do not often regard the compulsiveness as harmful for them because they have obtained social accomplishments by it. I would like to raise the issues from the view of psychosomatic medicine because the biological treatment is often inhibited by those psychological characteristics.

S13-1

Why do we need small molecule kinase inhibitors for the treatment of RA?

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Conflict of interest: None

There have been remarkable advances in the treatment of rheumatoid arthritis in the last decade. We have learned much especially from the advent of biologic therapeutics - specifically we have established that there are 'vulnerable nodes' in the inflammatory cascade that when inhibited lead to a 'collapse' of the inflammatory response such that clinical benefit can ensure. In addition we have established that the safety profile of such agents is clinically acceptable. Moreover we are seeing improvements not only in primary RA disease activity but also in damage reduction and altered co-morbidity. These agents however remain expensive, associate with some toxicities and even with their aggressive use, we have not established sufficiently high levels of disease remission, and certainly not drug free remission. As such there remains unmet clinical need. As new knowledge emerges as to the signal pathways that subserve the cytokine and other immune cell signaling events that regulate the RA synovial response there is increasing interest in whether such pathways can be used as therapeutic targets. Intracelluar targeting offers potential convenience of oral therapeutics, dose flexibility and also could capture combinatorial cytokine targeting by manipulation of the specific intracellular kinases selected for targeting. This lecture will discuss these pathways in context of current pathogenesis understanding, the achievements of current therapeutics and will finally lay out the possible benefits in intracellular targeting, and also its potential for harm.

S13-2

Clinical concerns in tofacitinib therapy in RA

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Conflict of interest: Yes

Tofacitinib is a small molecule compound that targets Janus kinase (JAK), a tyrosine kinase that resides in the cytoplasm. While biological products target a single cytokine or a cell surface molecule, targeting JAK will result in inhibiting multiple cytokines or cell surface molecules affecting its biological activity or expression in a direct or indirect manner. This mode of action enables this oral compound to exert a prominent anti-rheumatic activity resembling biological products. Although clinical benefit can be observed from the early stage of treatment with sustained effect, there are some concerns. The most frequently observed adverse events are nasopharyngitis, herpes zoster, hyperlipidemia and hypertension. Tofacitinib is eliminated by the hepatic metabolism and renal excretion, therefore liver and renal dysfunction can be observed in 0.1~1%. Tofacitinib preferentially inhibits JAK1 and JAK3, however JAK2 can be inhibited with increased concentration leading to the inhibition of erythropoietin resulting in anemia. These observations indicate that the concentration of tofacitinib could increase in certain patients. Interestingly, incidence of herpes zoster is obviously increased especially in the Asian population. Moreover, it is noteworthy that the highest incidence rate was observed in japan. Therefore, subanalysis of the clinical trials and the results from the post-marketing study would be crucial to reveal the risk factors. During the clinical trial, increased incidence of malignancies was suggested although the latest results have shown that the incidence rate was 0.85/100 patient-year which was comparable to usual RA patient population. As a result, the safety of tofacitinib seems to be comparable with the pre-existing biologics although there are still some concerns that we have to overcome.

S13-3

Mode of action of Btk-inhibitors and their clinical development in RA

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Conflict of interest: None

Rheumatoid arthritis (RA) is considered a chronic, inflammatory autoimmune disorder characterized by circulating autoantibodies, synovial inflammation, pannus formation, and cartilage and bone destruction in affected joints. In RA, the dysregulation of T- and B-cells, which results in the production of autoantibody, is involved in the initiation of the disease. During the chronic inflammatory phase, the autoantibody and immune complexes activate effector cells such as monocytes/macrophages, dendritic cells, mast cells and neutrophils that infiltrate the synovium, produce inflammatory cytokines and pannus formation, leading to the bone destruction mediated by osteoclasts. Bruton tyrosine kinase (Btk) is expressed in B-cells and also in monocytes/macrophages, mast cells, neutrophils and osteoclasts, all of which are involved in RA pathogenesis. Inactivation of Btk blocks in B cell receptor signaling and antibody production in B-cells, TNF production in macrophages, FceR-dependent degranulation in mast cells and bone destruction by osteoclasts. Thus, Btk is an attractive target for multiple cell inhibition in RA. Recently a selective and irreversible inhibitor of Btk ibrutinib has been developed, and was shown to be efficacious in certain types of B cell lymphoma. In addition, it was also reported that ibrutinib has a therapeutic effect in RA models by targeting multiple effector cells. More recently it has been shown that this drug also suppresses formation and bone-resorbing activity of osteoclasts in mice. Thus, ibrutinib will be a promising drug for RA treatment in the future. In this talk, I will present a recent progression of ibrutinib.

S13-4

Small molecule kinase inhibitors in rheumatoid arthritis: past lessons and future directions

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Conflict of interest: None

The great successes achieved with biologic agents in rheumatoid arthritis (RA) has generated substantial interest in novel therapeutic approaches. Particular attention has been paid to small molecule inhibitors of intracellular molecules such as kinases that may replicate some of the benefit observed with various macromolecule agents. Potential advantages for such molecules would include oral availability and lower development costs. Much early work was focused on inhibition of p38MAP kinase, based upon exciting *in vitro* and animal data. However, in RA patients, several p38MAP kinase inhibitors failed, both for lack of efficacy as well as toxicity. Lack of efficacy may relate in part to the inherent balance of regulatory and counter-regulatory factors operative in the mammalian immune system. Toxicity may relate to a relative lack of specificity of the individual agents used rather than the target. Understanding the reasons for the lack of success may be informative as regards the targeting of other kinases. Since that time, there have been some successes in kinase inhibition, most notably inhibitors of the janus kinase (JAK) molecules and of phosphodiesterase-4 (PDE4). It is likely that further successes with these approaches will provide a foundation for further development in the area.

S13-5

Jak inhibitors beyond tofacitinib for the treatment of RA

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Conflict of interest: None

The JAK family of 4 tyrosine kinases: JAK 1, JAK 2, JAK 3 and Tyk2, are expressed ubiquitously and mediate signal transduction for a variety of cytokines involved in inflammatory conditions: IL-6 → JAK1/JAK2 or JAK1/TYK2; IL-23 → JAK2/TYK2; IL-12 → JAK2/TYK2; INF-γ → JAK1/JAK2 and INF-α/β → JAK1/TYK2. JAKs work in pairs of 2 different JAKs or pairs of identical JAKs such as Jak1/3, Jak 1/2, Jak1/Ty2, etc. JAK1 and JAK3 are required for γ-chain cytokine receptor signaling. Tofacitinib, an inhibitor of JAK 3/1/2, is effective as monotherapy, after MTX, other DMARDs and in TNF inhibitor failures. A study of tofacitinib as monotherapy in MTX naïve patients, compared to MTX, demonstrated clinical, functional and radiographic benefit of both 5 and 10 mg BID, compared to MTX 20 mg a week. Tofacitinib shares many of the safety concerns of bDMARDs but has also been associated with an increased incidence of transaminitis, lipid elevation, neutropenia, anemia, elevated creatinine and herpes zoster. Tofacitinib has been approved for clinical use in several countries, including the United States, Japan, Switzerland, Russia and Argentina. The common approved dose is 5 mg BID, either as monotherapy or in combination with csDMARDs. The approvals have not included an indication for radiographic progression. With the demonstration of the risk: benefit profile of tofacitinib, the question has arisen as to whether other compounds which inhibit the Jak pathway by affecting different JAKs other than 3/1, or being more specific for JAK3, could be at least as efficacious with an improved safety profile. Clinical trial results have been presented for baracitinib, a Jak1/2 inhibitor, INCB039110 and GLPG0634, selective JAK-1 inhibitors and VX-509 a selective Jak 3 inhibitor. This presentation will compare the efficacy and safety of these new inhibitors of the JAK pathway with tofacitinib to see if there is a difference in efficacy and/or safety.

S14-3

Genome-wide search for susceptibilty genes in rheumatoid arthritis

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Conflict of interest: None

Rheumatoid arthritis (RA) is a complex trait with both genetic and environmental factors contributing to susceptibility. The polymorphism of *HLA-DRB1* gene encoding a MHC class II molecule is the major genetic factor of RA, which is also associated with the appearance of anti-citrullinated-peptide antibodies. In the last decade, genome-wide association studies (GWAS), which utilize up to a million of single-nucleotide polymorphisms as genetic markers, have unraveled genetic background of many complex traits including RA. Through GWAS and its meta-analysis, we have identified more than a hundred of risk loci for RA so far. Several genetic aspects of RA have been clarified by these analyses: 1) Compared with the strong effect of *HLA-DRB1* polymorphism (per-allele

relative risk ranging 2~3), the effects of non-HLA loci are moderate (per-allele relative risk ranging 1.1~1.2). 2) Most of non-HLA loci are expression quantitative trait loci (eQTL), where the disease-associated variants cause the disease by affecting expression of neighboring genes. 3) While there exist several loci specific to RA, most of the risk loci are shared with other autoimmune diseases. 4) Some loci exhibit ethnic differences in their effects, where environmental factors may be involved. Meanwhile, evidence shows a substantial proportion of genetic predispositions remain undiscovered. This "missing heritability" may be explained by rare variants, which cannot be identified by the conventional GWAS. As the fast advancement of next generation sequencing technology has enabled us to re-sequence the exome or whole-genome of patients, we are now entering a new stage of research.

S14-4

Standardized protocol of human immune cells using 10 color flowcytometer in primary immunodeficiency diseases

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Conflict of interest: None

Primary immunodeficiency diseases (PID) are caused by the mutations of various genes. They are often complicated with autoimmune diseases. The investigation of PID is important to understand common autoimmune diseases of unknown cause as a disease model because the PIDs are monogenic diseases. We started PIDJ project in 2008, which is a collaboration project among 13 pediatric department of national medical universities, Riken and Kazusa DNA research institute. General physicians could consult to the PID specialized doctors when they see suspected cases of PID via Web. Consultation leads to the central registration of the patients. PID specialized doctors and research groups analyze immunologically and genetically which can result in the genetic diagnosis and improvement of quality of life. Our group receive the consultation of antibody deficiency patients with various degrees of the defects of T cell and B cell differentiation. Thus we analyze the multicolor FACS and TREC, KREC to see the defect of T and B cell neogenesis. Recently, standardization of the analysis in human immunological disorders are reported. It is important to establish the method of analysis using the samples from the monogenic disorders as PID. The standardization of the method of 10 color FACS to analyze the immunological disorders will be presented in this symposium.

S14-5

Dysregulated regulatory T cells in rheumatic diseases: their roles in pathogenesis

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Conflict of interest: None

CD4+ regulatory T cells (Tregs) directly suppress acquired immune responses in periphery and are essential regulators of self-tolerance. They are a heterogeneous population in terms of surface phenotypes, cytokine production profiles, and mechanisms of immune suppression. Naturally occurring Tregs derived from the thymus are characterized by CD4, CD25, and transcription factor forkhead box P3 (FoxP3) and are specialized for immune suppression. Another Treg subsets are adaptive Tregs that acquire regulatory properties in periphery. It has been proposed that impairment of Treg-mediated immune regulation plays a critical role in emergence of autoimmune diseases. In fact, reduced proportion and impaired function of FoxP3+ Tregs have been reported in patients with various organ-specific autoimmune diseases, including multiple sclerosis and immune thrombocytooenia (ITP). In contrast, results of Treg proportion and function in patients with systemic lupus erythematosus (SLE), rheumatoid arthritis, and scleroderma were inconsistent among studies; and some showed upregulated FoxP3+ Tregs in comparison with healthy individuals. In our recent analysis in SLE patients, proportion of FoxP3+ T cells in circulating CD4+ T cells was increased in patients with active disease and was correlated with disease activity index. FoxP3+ T cells expanded in SLE patients were confirmed to originate from naturally occurring Tregs based on hypomethylation of Treg-specific demethylation region of the FoxP3 gene. Interestingly, they were predominantly CD4+FoxP3+CD127+/CD49d+ cells capable of producing IL-17, which were scarcely detected in healthy individuals. Recently, plasticity of human FoxP3+ Tregs has been reported, and a balance between Treg and Th17 is critically involved in regulating autoimmune and inflammatory processes of systemic autoimmune diseases. Further analyses of mechanisms controlling Treg plasticity should be useful in clarifying pathogenesis of autoimmune diseases.

S14-6

Musculoskeletal aspects of autoinflammatory diseases - elucidation of pathophysiology of epiphyseal overgrowth in CINCA/NOMID

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Conflict of interest: None

The autoinflammatory diseases are genetic disorders that cause inflammation as a main clinical feature. It has been shown that the oligomerized proteins complex named inflammasome plays an important role in their inflammation, especially in cryopyrin-associated periodic syndrome (CAPS). On the other hand, very few has been elucidated regarding the pathophysiology of the disease-specific other organ disorders. In this talk, I pick up one of musculoskeletal features observed in autoinflammatory diseases, epiphyseal overgrowth of the long bones in NOMID (Neonatal-onset multisystem inflammatory disease), the severest form of CAPS, and will present our data on the mechanism of the epiphyseal overgrowth in NOMID by using iPS technology. NOMID is a dominantly inherited autoinflammatory disease caused by gain-of-function *NLRP3* mutations, which causes activation of the NLRP3 inflammasome that produces IL-1b. Anti-IL-1 therapy controls systemic inflammation in NOMID, which supports the importance of the NLRP3 inflammasome in NOMID. However, a disease-specific feature of NOMID, epiphyseal overgrowth of long bones, is resistant to anti-IL-1 therapy. It indicates that other mechanisms than NLRP3 inflammasome underlie epiphyseal overgrowth that is believed to be due to abnormal chondrocyte hyperplasia resulting in endochondral ossification disorders. We investigated the effect of mutated NLRP3 on chondrocytes differentiated from NOMID patient-derived iPS cells. Mutant iPS cells produced large chondrocyte masses owing to glycosaminoglycan overproduction, which correlated well with increased expression of the chondrocyte master regulator SOX9. In addition to cartilage hyperplasia, *in vivo* transplantation of immature cartilaginous pellets into immunodeficient mice recapitulated the disorganized ossification of NOMID. These data indicated that part of the reasons why the chondrocyte hyperplasia occurs in NOMID is intrinsic hyperplastic capacity of chondrocytes derived from NOMID.

S15-1

Recent findings on osteoporosis from basic research

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Conflict of interest: None

Bone volume is tightly regulated in a delicate balance between bone-resorbing osteoclasts and bone-forming osteoblasts. Inflammatory diseases such as rheumatoid arthritis or estrogen-deficiency due to menopause frequently promote osteoclast activation and subsequent joint destruction or bone loss, respectively, however, precise molecular mechanisms un-

derlying such osteoclast activation remain largely unknown. We found that pro-inflammatory cytokines, namely IL-6, TNFα and IL-1 induce expression of inflammatory cytokines, IL-6 family cytokines, in a positive feedback loop manner. Those inflammatory cytokines activate Stat3 either directly or indirectly, and induce RANKL, an essential cytokine for osteoclast differentiation via Stat3, and that the positive feedback loop of inflammatory cytokine and RANKL expression were all inhibited in Stat3-deficient cells. Then, we screened Stat3 inhibiting small compounds, and a Stat3 inhibitor significantly inhibited the positive feedback loop of inflammatory cytokine and RANKL expression. Arthritis and osteoclastogenesis in collagen-induced arthritis model mice were significantly blocked by a Stat3 inhibitor administration, and thus, Stat3 was considered as a therapeutic target for inflammation induced osteoporosis. We also found that HIF1α, a hypoxia responsive transcription factor, was detected under an estrogen-deficient condition in ovariectomized (OVX) mice, in osteoclasts. Osteoclast-specific HIF1α conditional knockout mice were resistant to OVX-induced bone loss. We further found that administration of HIF1α inhibitor to OVX mice completely abrogated estrogen-deficiency induced bone loss. Therefore, HIF1α, was considered a therapeutic target to prevent osteoclast activation and bone loss seen in post-menopausal women.

S15-2

The diagnostic criteria for primary osteoporosis 2012 edition

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Conflict of interest: None

The diagnostic criteria for primary osteoporosis were revised based on the 2000 edition in 2012. The Japanese criteria for primary osteoporosis have been consisting of differential diagnosis and evaluation of bone evaluation. The most important point in revising the guideline should be that the principle in diagnosing osteoporosis was reminded, that is the purpose of diagnosing the osteoporosis is to define the patients whose bone strength is weakened clinically. Bone mineral density (BMD) is the most valuable measure in assessing the bone strength, but it cannot explain all of the variation in bone strength. In this revision of the criteria, the importance of prevalent fractures was re-examined and emphasized. Because the risk increase by prevalent vertebral fractures or hip fractures remains significant after adjusting for BMD, the presence of these fractures was recognized enough to diagnose osteoporosis. On the other hand, other types of fragile fractures were combined with low bone mass (young adult mean, YAM, less than 80%) for the diagnosis of osteoporosis. In the absence of any fragile fractures, the cut-off value for BMD was less than 70% of YAM. In addition to "YAM", T score was adopted to describe BMD measured for lumbar spine and proximal femur.

S15-3

Osteoporosis in Japanese Patients with Rheumatoid Arthritis: Results from the IORRA Prospective Observational Cohort Study

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Conflict of interest: None

Patients with rheumatoid arthritis (RA) are at high risk of developing fractures. Utilizing data from our Institute of Rheumatology Rheumatoid Arthritis (IORRA) cohort study, we reported fractures and factors associated with the fractures in Japanese patients with RA. IORRA is a prospective observational cohort study of patients with RA at the Institute of Rheumatology, Tokyo Women's Medical University. Our results suggest that the causes of fractures may differ depending on anatomical site and that prevention of falls may be the most effective way to reduce upper and lower extremity fractures, especially in older patients with RA. (*1*) High J-HAQ disability score, advanced age, history of total knee replacement, and low BMI appear to be associated with the occurrence of hip fractures in Japanese RA patients (*2*). A reduction in the daily prednisolone dose, together with the prevention of falls in female patients of advanced age with RA and a high BMI may be important in preventing distal radius fractures (*3*). J-HAQ disability score, tender joint counts, and impaired general health appear to be associated with falls in Japanese patients with RA, as previously reported for patients of other ethnicities (*4*). A substantial gap exists between fracture risk and osteoporosis treatment in Japanese RA patients, as previously reported for patients of other ethnicities (*5*). Vitamin D deficiency appears to be common in Japanese patients with RA. Female gender, younger age, high HAQ disability score, low serum levels of total protein and total cholesterol, high serum ALP levels, and NSAID use appear to be associated with vitamin D deficiency in Japanese patients with RA (*6*). **References** 1) Ochi K, et al, Arch Osteoporos 8, 130 (2013), 2) Furuya T, et al. Osteoporos Int 24, 1257 (2013), 3) Ochi K, *et al, Clin Rheumatol,* in press, 4) Furuya T, *et al. Clin Rheumatol* 28, 1325 (2009), 5) Furuya T, *et al. Clin Rheumatol* 30, 1105 (2011), 6) Furuya T, *et al. Clin Rheumatol* 32, 1081 (2013).

S15-4

Secondary Fracture Prevention in Osteoporosis

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Conflict of interest: Yes

Prevalent fragility fracture increases risk of subsequent fractures. Risk of vertebral fractures is as high as 4 - 7 times in patients with vertebral fractures compared to those without fracture. The one-year incidence rate of hip fracture as determined in patients with their first hip fracture was 3.4% and the rate ratio among those with one hip fracture was as high as 18.6 times in the age group of 65-69 years compared to that in the general population (POSHIP study). Because of the high risk of sustaining fragility fracture in patients after their initial fracture, pharmacologic intervention is essential. However, previous reports from Europe and North America suggest that pharmacotherapy is not necessarily prescribed adequately, only 16.5% in men and 39.6% in women, in these populations. According to the POSHIP study, anti-osteoporosis pharmacotherapy was performed in only 19% while 53% received no treatment during the one-year observational period after first hip fracture in Japan. Recently developed anti-osteoporosis drugs are proved to prevent fragility fractures. Weekly or monthly oral bisphosphonates as well as intravenous administration are available. These drugs are useful for secondary fracture prevention. However, it is not easy for the orthopedic doctors to manage secondary fracture prevention in all patients with fragility fractures they treated. Then liaison service for secondary fracture prevention became available in Europe. In this symposium current status of osteoporosis treatment as well as liaison service to reduce the burden of fragility fracture will be discussed.

S15-5

Diagnosis and treatment of glucocorticoid-induced osteoporosis

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Conflict of interest: Yes

In the last decades, several guidelines for the management of glucocorticoid-induced osteoporosis from different countries have been developed. Unfortunately, these guidelines demonstrated relatively large differences regarding the thresholds of daily glucocorticoid dosage and of BMD values which are regarded as cutoff values for initiating anti-osteoporotic drugs in subgroups of glucocorticoid-treated patients. Recently, an update of the American College of Rheumatology recommendations for the prevention and treatment of glucocorticoid-induced osteoporosis was published. Patients are subcategorized into fracture risk categories using the FRAX tool or tables provided by the ACR. The FRAX calculator uses only bone density at the hip. Patients with glucocorticoid-induced osteoporosis frequently lose bone mass first in trabecular bone (the spine) which may lead to an underestimation of vertebral fracture risk. Also, many of the clinical risk factors in FRAX are dichotomous (yes/no) and do not take into account of dose response (for example, dose of glucocorticoid, number of previous fractures, etc). Current Japanese guidelines indicated that the treatment objectives are patients that are using or planning to use oral glucocorticoids for 3 months or longer with a fragility fracture, with less than 80% BMD of young adult mean, and with 5mg

predonisolone equivalent or higher doses per day. We are now working on the revision of Japanese guidelines. Current Japanese guidelines recommended bisphosphonates as first-line drugs and active vitamin D3 or vitamin K2 as second-line drugs. Now in Japan, alendronate or risedronate provide the front-line treatment option in the majority of patients with glucocorticoid-induced osteoporosis.

S16-1

Unmet Needs in the Treatment of Rheumatoid Arthritis

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Conflict of interest: Yes

RA is a chronic progressive inflammatory disease mainly affecting the synovial membrane of joints and is characterized by lymphocyte activation, synovial proliferation, and bone/cartilage destruction. In 2010, ACR/EULAR proposed new RA classification criteria to classify patients with progressive arthritis and introduce methotrexate-based therapy in early stage disease. Although the advent of biologic therapy has greatly improved RA management, there are still unmet needs. However, new and highly effective DMARDs have continued to emerge until the most recent years, in particular, biological agents which target tumor necrosis factor, the lL-6 receptor, and T cell co-stimulation. Nevertheless, only a small proportion of patients in clinical practice achieve remission as defined by DAS, SDAI, the new ACR/EULAR Boolean criteria. Therefore several other biologics and small molecules which targeting to new molecules (IL-17A, GMCSF-R, CX3CL1, BAFF, JAK, Syk, histamine receptor etc.) have been created and under clinical trials for RA treatment. With multiple biologic and non-biologic options, there is a need for strong predictive biomarkers to determine which drug is most likely to be effective, safe, and durable in a given individual. With the newer biologics and small molecular compounds, pooled analyses of clinical trial databases provide an initial step in assessing their safety, but additional long-term data are needed to adequately define their overall safety profiles. Also the management of the RA patients who have comorbidities (chronic infectious diseases such as non tuberculous mycobacteriosis, renal dysfunction, interstitial pneumonia, chronic hepatitis and with malignancy) should be established. However, we tend to focus on the management of early stage f RA, reconstruction of impaired joints in established RA using regeneration of bone and cartilage could be important issue to be overcome.

S16-2

Difficult systemic lupus erythematosus

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Conflict of interest: Yes

The prognosis of systemic lupus erythematosus (SLE) was dramatically improved due to the establishment of steroid treatment, in particular to steroid-pulse-therapy. Further, effective immunosuppressants such as cyclophosphamide, tacrolimus have contributed for the patients to have better outcome as well as anti-infection prophylaxis. However, some diseases related with SLE still remain difficult to be treated and affect the mortality and morbidity of the patients with SLE. Among them, neuropsychiatric lupus (NPSLE) will be focused. NPSLE has been classified into diffuse psychiatric syndrome, neuropsychological syndromes and peripheral nerve system disorder. However, most manifestations in patients with NPSLE are complex and it is sometimes difficult to induce the remission even by the steroid-pulse-therapy. What should we do for such patients to have better outcome? We conducted a retrospective study comprised 128 patients with SLE who did not present any neuropsychological manifestations on admission. One hundred and thirty patients with other autoimmune diseases were served as a control group. All patients were treated with high-dose corticosteroids (prednisolone ≧ 40mg/day) between April 2002 and December 2012. The prevalence and characteristics of PSNP were reviewed on medical records. Neuropsychiatric events were classified according to the American College of Rheumatology criteria for NPSLE (1999). The prevalence of PSNP was significantly higher in patients with SLE (25%, 32/128) than those with other autoimmune diseases (5%, 8/130) ($p<0.01$, OR 5.08, 95%CI [2.24-11.54]). Diffuse psychiatric / neuropsychological syndromes occurred in 30 patients, neurologic syndromes of the central nervous system in 5 patients. PSNP was more frequent in patients with SLE, thus could be classified as one of the features of NPSLE.

S16-3

Polymyositis and Dermatomyositis

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Conflict of interest: Yes

Diagnosis of polymyositis (PM) and dermatomyositis (DM) in Japan is based on diagnostic criteria established in 1992. It is not sensitive enough to make a diagnosis of amyopathic DM. It does not include the findings of modern imaging technology: MRI. Currently, international collaboration is under progress to establish new criteria based. According to the patient registry in Ministry of Health, Labour and Welfare (MHLW), Japan, 40% of the patients suffer from muscle weakness even after the treatment. This is possibly due to treatment failure, steroid-induced myopathy, and/or disuse-related myopathy. Treatment guideline is now being established by the study group of MHLW. Patients only with skin manifestations should be treated topically. If patients accompany acutely progressive interstitial pneumonitis (APIP) or have risk factors to develop APIP, they should be treated high-dose glucocorticoids together with immunosupressants. The risk factors are being hypomyopathic, positive anti-MDA5 antibody, negative anti- aminoacyl tRNA synthase antibody, and high serum ferritin. However, the only myositis-specific antibody approved is anti-Jo-1 antibody. Prediction by the above factors is not always correct. Some patients do not respond even to the aggressive treatment. Without APIP, the patients should be treated with high dose glucocorticoids or intermediate dose of glucocorticoids together with immunosuppressants. Not all of the immunosuppressants we use are approved by the government. Intravenous immunoglobulin can be used effectively before the therapeutic effects of immunosuppressants take place, but expensive. We have been concerned that no treatment addresses specific pathology of PM/DM. Antibodies against CD226, which is crucial molecule on cytotoxic CD8 T cells for their cytotoxic function, was delivered to a mouse PM model, and suppressed the myositis effectively. Treatments that suppress specific pathology should be developed in the future.

S16-4

The treatment of cutaneous manifestations in systemic sclerosis

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Conflict of interest: Yes

Systemic sclerosis (SSc), the focus of this lecture, is a generalized connective tissue disease that involves sclerotic changes in the skin and sometimes various other organ systems. Clinical outcomes have improved probably due to better management of the complications, but SSc is still considered to be incurable and diffuse cutaneous SSc carries high risk of fatality. In this lecture, I would like to talk about cutaneous manifestations and treatment of this disease.

S16-5

Hematopoietic stem cell transplantation in the treatment of systemic sclerosis

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Conflict of interest: None

Scleroderma is a systemic connective tissue disease characterized by skin sclerosis and vascular lesion. It involves skin, lung, heart, kidney, intestine and joints. Autoimmunity is thought to be involved in the pathogenesis because autoantibodies to topoisomerase I and centromere are detected and are associated with diffuse and limited cutaneous type, respectively. Five-year survival of severe diffuse scleroderma is reported to be 50-60% and there are unmet needs for effective treatment against these patients. In Europe and Unites states, hematopoietic stem cell transplantation (HSCT) was performed in more than 200 patients with scleroderma. Burt and his colleagues reported that autologous HSCT (auto-HSCT) was superior to conventional intravenous cyclophosphamide (CY) in the improvement of skin sclerosis and interstitial pneumonia in their phase II randomized trial. We performed auto-HSCT in the treatment of 19 severe scleroderma patients as a phase I/II study. Peripheral blood stem cells (PBSCs) were mobilized with 4 g/m^2 of CY and G-CSF. After collecting PBSCs by apheresis, they were cryopreserved until autographting. CD34+ cells were immunologically selected in 11 patients just after apheresis. All of the patients were treated with high-dose CY (200 mg/kg) and received auto-HSCT. In patients with scleroderma, skin sclerosis was markedly improved within 6 months and the improvement was sustained for 60 months after HSCT. Vital capacity was significantly increased at 48 months after HSCT and KL-6, a marker for IP, was significantly decreased during 12-60 months after HSCT. A titer of anti-Scl-70 was significantly decreased during 1-60 months after HSCT. As toxicity, there were a variety of infections such as adenoviral hemorrhagic cystitis, herpes zoster and cytomegaloviral antigenemia. Progression-free and overall 5-year survivals were 65% and 89%, respectively. In conclusion, auto-HSCT is effective and potentially improves the prognosis of severe scleroderma.

S16-6

Vasculitis syndrome

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Conflict of interest: None

Vasculitis Syndrome includes several types of systemic inflammatory diseases caused by vasculitis, which characterized by inflammation of blood vessel wall with immune system abnormality. It is well known that prevalence of subtypes of large vessel vasculitis (Takayasu arthritis and giant cell arthritis) and subtypes of ANCA associated vasculitis (AAV) (microscopic polyangiitis (MPA) and granulomatosis with polyangiitis (Wegener's) are different between Western and Eastern countries. Current standard treatments recommended by global clinical guidelines are based on the clinical trials performed in Western countries. Because the characteristics of AAV patients in these trials are differ to Japanese AAV patients, it is not unclear whether these evidence can apply to Japanese AAV patients. To describe the current treatment status and evaluate the effectiveness of these treatments for Japanese AAV patients, the Research Committee on Intractable Vasculitides, the Ministry of Health, Labour and Welfare of Japan conducted a nationwide prospective cohort study of remission induction therapy in Japanese patients with AAV (RemIT-JAV). In RemIT-JAV, we revealed that MPA dominance in Japanese AAV patients linked to the important characteristics such as older age and more deteriorated renal function. In addition, the high prevalence of interstitial lung disease is distinct characteristics of Japanese AAV. Previous clinical trials in Western countries excluded oldest-old population more than 80 years, therefore we need to validate whether these Western protocol has equivalent effectiveness and safety in Japanese AAV. Since the Japanese physicians may concern about the safety of the global standard treatments, the usage of corticosteroid concomitant with cyclophosphamide was less common in RemIT-JAV. We hold this symposium focusing on the effectiveness and the safety of the Japanese practice for AAV and clarifying the problems that cannot be solved in Western guidelines.

S17-1

Dendritic cells and SLE: Analysis of dendritic cell-specific SHP-1 knockout mice

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Conflict of interest: None

Dendritic cells (DCs) promote immune responses to foreign Ags, but also induce immune tolerance to self-Ags. Accumulating evidence from studies in human and experimental models demonstrated the involvement of DCs in the initiation of autoimmune diseases. In SLE, interferon-α (INF-α), which is mainly produced by DCs, was identified as a key cytokine in the development of SLE in studies of lupus patients and the clinical trials targeting INF-α are now underway. In animal models, constitutive depletion of DCs in MRL/lpr mice ameliorated tissue injury. In addition, DC-specific conditional knockout mice for cell-intrinsic negative regulators, such as BLIMP1, A20 and SHP-1, were reported to develop SLE-like disease. Among these mice models, CD11c-specific SHP-1 knockout mice were generated by Matozaki's lab (Kaneko-T et al. J Immunol, 2012). The CD11c-specific SHP-1 knockout mice showed splenomegaly, increased number and function of CD11c$^+$DCs, and increased number of Th1 cells. The mice also demonstrated activation of B cells: increased number of CD5$^+$CD19$^+$(B-1a) cells in the spleen and elevated levels of serum IgM and IgG2. Moreover, aged mice developed spontaneous pneumonitis and nephritis, together with anti-nuclear antibody and anti-ds DNA antibody in the serum. As for the renal pathological findings, lupus-like nephritis were observed: severe proliferative glomerulonephritis and glomerular deposition of IgG and C3. Immunohistochemical staining revealed that infiltration of CD11c$^+$DCs, T cells (Thy1.2$^+$) and B cells (B220$^+$) in the glomeruli. These cells were also detected in tubulointerstitium and periglomerular area. FACS analysis for determining the infiltrated cells in the kidney showed that marked increased number CD4$^+$T cells. Taken together, CD11c-specific SHP-1 knockout mice is considered to be a novel model of SLE with proliferative nephritis. This model would be useful to investigate the association of DCs and SLE or lupus nephritis.

S17-2

Prospective study of the prevalence of central neuropsychiatric lupus erythematosus (NPSLE) manifestation, the cytokines and chemokines and IgG anti-NR2 glutamate receptor antibodies (anti-NR2) in NPSLE

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Conflict of interest: None

1. Prospective study of the prevalence of central NPSLE manifestation among patients with SLE in Tochigi prefecture from April 2010 to March 2013: 719 SLE patients were enrolled at the first of study 2010 and finally 823 enrolled patients were confirmed at the end of study 2013. Prevalence of SLE patients was 0.041% in Tochigi Prefecture population. Twelve, 16 and 15 SLE patients were diagnosed to have NPSLE in 2010, 2011 and 2012, respectively. Over half numbers of NPSLE occurred in patients with new onset of SLE each year. About 70% of neuropsychiatric symptoms were diffuse psychiatric/neuropsychiatric syndromes. 2. The increased intrathecal production of IL-6, IL-8, IP-10, MCP-1 and G-CSF in patients with central NPSLE: Analyze of cytokines and chemokines using the CSF and serum samples obtained at the same time in SLE patients showed the possibility that the increased levels of IL-6, IL-8, IP-10, MCP-1 and G-CSF in the CSF might be associated with the pathogenesis and appearance of central NPSLE. The comparison with normal controls followed the upper possibility. Especially, the significant difference of CSF IL-6 concentrations was most largest. The measurement of these cytokines and chemokines, especially IL-6 might be useful for the diagnose of central NPSLE. 3. Anti-NR2: Purified IgG anti-NR2 bound to endothelial cell (EC) surface, up-regulated the expression of ELAM-1, VCAM-1 and ICAM-1 on the EC surface and increased the production of IL-6 and IL-8 by ECs. Purified IgG anti-NR2 also activated the degrada-

tion of cytoplasmic IκB in the ECs. These results suggest the possibility that EC activation through the NF-κB signaling pathway induced by IgG anti-NR2 in the CNS might lead to inflammation of the blood–brain barrier (BBB), initiating the pathogenesis of neuropsychiatric SLE. Furthermore, autoantibodies and immune complexes in the sera, which enter the CSF through the BBB damaged by this inflammation, might bind to neuronal cells and cause NPSLE.

S17-3

Innate Immunity in SLE pathogenesis

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Conflict of interest: None

Systemic lupus erythematosus (SLE) is characterized by the production of autoantibodies to self-DNA or RNA and results in chronic inflammation in multiple organs. Toll-like receptor (TLR) s are known as the patten recognition receptors which play essential roles in innate immunity. Intracellular TLRs (TLR-3, -7, -8 and -9) have been found to engage intracellular pathogen-derived products; TLR-3 against ds-RNA, TLR-7, -8 against ss-RNA and TLR-9 against unmethylated CpG-DNA. Whereas, type I IFNs, central to both innate and adaptive immunity, have received particular attention for their role in the development of autoimmune responses, and a preponderance of evidence supports their disease-promoting activity in SLE. In humans with active disease, levels of IFN-a are increased in serum and affected tissues. Peripheral blood lymphoid cells and kidneys express a so-called 'interferogenic signature'(in that IFN-controlled genes are upregulated), and IFN-α in lupus sera promotes monocyte maturation to antigen- presenting dendritic cells (DCs). In SLE, immune complexes containing self-DNA or -RNA can activate pDCs to release IFN-α through the engagement of TLR9 and TLR7 respectively. In recent years, neutrophil extracellular traps (NETs) was discovered. They are web-like structures composed of chromatin backbones and granular molecules. They are released by activated neutrophils. Based on the observation that expression of TLR7 is up-regulated in SLE patients, recent report showed that anti-ribonucleoprotein (RNP) immune complexes could activate neutrophils from SLE patients, but not those from healthy controls, to release NETs. This process requires FcRIIa internalization and TLR7 activation. These NETs could potently activate pDCs, leading to secretion of high levels of IFN-α. In this presentation, deregulations of components of innate immunity, including macrophages, dendritic cells and neutrophils in both murine and human lupus will be discussed.

S17-4

Multi-target therapy for lupus nephritis

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Conflict of interest: None

Survival rate of the patients who have untreated lupus nephritis is less than ten percent, and it is applied equally to present day. The combination therapy of steroid and immunosuppressant agent is actively done these day, and the development of biological agents is advanced for systemic lupus erythematosus (SLE) and lupus nephritis just lilke rheumatoid arthritis (RA). But it requires more time to use in clinical practice, more effective and less side effects are desired as both induction and maintenance from ealry lupus nephritis to steroid resistant lupus nephritis. Mycophenolate mofetil (MMF) and Intravenous cyclophosphamide (IVCY) have an established reputation for induction and maintenance therapy. But MMF is only approved for renal transplant in Japan, while it is preferable not to use IVCY for young women because of side effects like ovarian dysfunction or cancer. And these drug, using with steroid, have a problem of increasing the chance of infection. We studied about efficacy and safety of multi-target therapy for induction and maintenance therapy. Study population is active lupus nephritis patients or lupus nephritis patients in remission who is treated with multitarget therapy. Thirty patients (male:5) met the definition. When we initiated induction therapy, the mean value were UPCR 4.34 g/gCr, serum creatinine 0.74mg/dl, C3 47.4mg/dl, and C4 7.1mg/dl. The study also showed that we could decrease the dose of steroid from 59mg/day to 8mg/day at 6 month. There was one disease flare until 12 months. There was no adverse event requiring hospitalization at all. Multi-target therapy for lupus nephritis has a high degree of therapeutic efficacy and safety.

S17-5

CNS lupus and Its management

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Conflict of interest: None

CNS lupus, neuropsychiatric (NP) lupus is one of the serious organ involvements in lupus, which had varieties of clinical manifestations and a difficult challenge to physicians. Immune-inflammatory mechanisms are causes of severe psychiatric symptoms such as acute confusional state and psychosis. Impaired cerebral-circulation by endothelial cell activation and thrombotic events causes cerebrovascular diseases in lupus. These two mechanisms interact with each other. For entrance of pathogenic antibodies into brain, disturbance of blood-brain-barrier caused by endothelial injury is required. Therefore, intensive immunosuppressive therapy combined with anti-coagulant /platelet therapies is recommended for severe psychiatric symptoms or NP events in active SLE. During high dose glucocorticoid therapy for active SLE, a few patients newly developed NP symptoms. Newly developed NP symptoms are considered to be caused by uncontrolled SLE or by GC adverse effects; the latter is referred as "GC-induced psychosis. We found GC-induced psychosis is CNS lupus itself, because cerebral blood circulation was impaired in active SLE patients without NP symptoms; GC decreased cerebral blood flow and anticoagulant therapy with heparin stopped the decrease in blood flow and prevented new onset of psychosis during GC therapy. These results indicate that GC-induced psychosis is apparence of subclinical NP lupus by GC. In our institute, anticoagulant therapy is routinely applied for patients receiving high-dose GC to prevent GC-induced psychosis. When active patients developed NP symptoms or any patients showed severe psychosis, intensive immunosuppressive therapy with anti-coagulant therapies were applied. No clinical trials with evidence of high grade have not been conducted for management of CNS lupus. Such clinical trials are required.

S17-6

New Therapeutic approach in Systemic Lupus Erythmatosus (SLE): Biologics in SLE

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Conflict of interest: None

In recent years the use of biologic therapies in the management of SLE has tried, a number of clinical trials have increased. The anti-B-lymphocyte stimulator (anti-Blys) antibody belimumab demonstrated efficacy and safety in two large randomised trials and has been approved for the treatment of SLE after more than 50 years. Biologics are being developed which target the B cell and prevent their activation or modify abnormal B cell responses. Several reports showed that the off-labeled use of rituximub seemed promising in patients with refractory disease, but randomized trials with this agent failed. Biological agents are being evaluated which target CD20 positive lymphocytes (oclerizumab), CD22 positive cells (epratzumab) or the receptors of BLyS and APRIL (atacicept). Epalizumab obtained long-term and safety and efficacy data. The most effective dose of atacicept reduced the number of disease flares. Monoclonal antibodies targeting interferon alfa (INFα) and interleukin 6 and 10 (IL6 or IL-10) are being investigated for SLE. Anti INFα monoclonal antibodies (sifalizumab, rontalizmab) and anti INFα receptor monoclonal antibodies have been analyzed in several clinical trials. Tocilizumab is a humanized monoclonal antibody against IL-6 receptor. In a pilot study of

tocilizumab in SLE was observed significant reduction of anti-DNA antibody and clinical activities. Abatacept is a soluble fusion proten of the extracellular domain of CTLA4 linked to the Fc portion. RCT trial assessed effects of abatacept on disease flares in mild SLE The study failed to meet the primary endpoints. A study in lupus nephritis was terminated because of lack of efficacy. But the benefit was obtained in SLE patients with polyarthritis. Clinical trial of abatacept is currently doing in SLE. New biologics currently will lead to therapeutic changes in the role of biologics in SLE management overcoming years.

S18-1

Production and mode of action of ANCA: Association of a novel autoantibody against moesin in the serum of patients with MPO-ANCA-associated vasculitis

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Conflict of interest: Yes

ANCA (anti-neutrophil cytoplasmic antibody) has been used for a serological marker for ANCA-associated vasculitis (AAV). Moreover, MPO-ANCA (myeloperoxidase-ANCA) is good marker for MPO-ANCA associated vasculitis (MAAV), which is higher incidence in Japan than US-Europe. Other serum markers have been investigated because MPO-ANCA does not always correlate with disease activity. We detected autoantibodies against moesin (1), which was located on the surface of stimulated endothelial cells, in the serum of patients (2). Serum creatinine in the anti-moesin autoantibody-positive group was higher than that in the negative group. Additionally, interferon (IFN)-g, macrophage chemotactic peptide-1 (MCP-1), interleukin (IL)-2, IL-7, IL-12p70, IL-13, GM-CSF, and G-CSF were significantly higher in the positive group. Furthermore, IL-7 and IL-12p70 levels correlated with the anti-moesin autoantibody titer. Based on these findings and the binding of anti-moesin IgG to neutrophils and monocytes, we detected the secretion of IFN-g, MCP-1, and GM-CSF from these cells. The anti-moesin autoantibody existed in the serum of patients with MPO-AAV and was associated with the production of inflammatory cytokines/chemokines targeting neutrophils with a cytoplasmic profile. This suggests that the anti-moesin autoantibody has the possibility to be a novel autoantibody developing vasculitis via neutrophil and endothelial cell activation. This study has been performed under collaboration with Drs. Suzuki K, Tsukita S, Itabashi M, Hamano Y, Maruyama N, Yumura W, Kameoka Yand, Nakayama T (1) Nagao T, *et al*., Nephrol Dial Transplant. 2011; **26**:2752-2760. (2) Suzuki K, *et al*., Nephrol Dial Transplant. in press. (3) Ellen F. Carney. Nature Reviews Nephrology 2014; **10**:3.

S18-2

Pathogenesis of ANCA-associated vasculitis

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Conflict of interest: None

Transfer of MPO-ANCA into wild-type mice results in the development of ANCA-associated vasculitis (AAV); therefore, indicating the pathogenic role of MPO-ANCA in AAV. ANCA can activate neutrophils primed by proinflammatory cytokines, such as TNF-α, to release reactive oxygen species and proteolytic enzymes; thus, consequently injure small vessel endothelial cells. Such "ANCA-cytokine sequence" is considered to be involved in the pathogenesis of AAV. A unique cell death of neutrophils, which is characterized by the release of chromatin fibers and intracytoplasmic proteins, including MPO and PR3, to outside of the cells, has recently been discovered. Although this mode of cell death, neutrophil extracellular traps (NETs), is an essential innate defense mechanism, the disordered NETs could be related to autoimmune diseases, including AAV. Recently, we have demonstrated that the process of abnormal formation and impaired degradation of NETs induced by antithyroid drug propylthiouracil was involved in the generation of MPO-ANCA and subsequent development of AAV. On the other hand, IgG eluted from MPO-AAV sera demonstrated high ability for NETs induction, and the ability correlated to the disease activity and was parallel to the ANCA affinity to MPO. In addition, low ability of MPO-AAV serum for NETs degradation was determined. The ability was partially recovered by depletion of IgG from the sera; thus, the presence of serum factors that precluded NETs degradation besides IgG was suggested. Correspondingly, activity of DNase I, an important regulator of NETs, was generally low in MPO-AAV. Furthermore, the presence of anti-NETs antibodies, which could interfere with the DNase I activity, was demonstrated in some MPO-AAV sera. The collective findings suggest that a connected mechanism of "NETs-ANCA vicious cycle" and "ANCA-cytokine sequence" could be critically involved in the pathogenesis of AAV.

S18-3

International epidemiologic study of ANCA-associated vasculitis

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Conflict of interest: None

Geographical differences in the epidemiology of the vasculitis have been observed. As for ANCA-associated vasculitis (AAV) among primary vasculitis, the prevalence of P/MPO-ANCA positive, microscopic polyangiitis (MPA) is more common in Japanese patients, but C/PR3-ANCA positive, granulomatosis with polyangiitis (GPA) in European and US patients. However, the existing schemes, such as ACR classification, CHCC definitions and Japanese diagnostic criteria, were made in the 1990s and either was used for each. After the 2000s began, the experts of European League Against Rheumatism (EULAR) and ACR started to discuss and review about the disease concept and classification criteria. During this process, in 2007, Watts et al. developed a stepwise algorithm for epidemiological studies of primary systemic vasculitis (EMEA algorithm). On the other hand, in 2013, Jennette et al. reported "2012 Revised International CHCC Nomenclature of Vasculitides". International collaborative study (DCVAS), which Japanese team is also participating in, is in progress now. We conducted a population-based survey of AAV in Miyazaki Prefecture, Japan and Norfolk, UK, between 2005 and 2009 on the basis of the subclassification of EMEA algorithm. There was no major difference in AAV incidence between Japan and the UK (22.6 vs. 21.8/million/year), but this prospective study found MPA and MPO-ANCA (84%) to be more common in Japan and GPA and PR3-ANCA (58%) to be more common in the UK. Recently, an international comparative study has been performed to investigate whether there were differences in phenotype and outcome in MPA between Europe and Japan. Phenotypes and treatment in MPA patients were different between Europe and Japan, but the survival and renal survival were similar. A similar comparative study for GPA is in progress now. Under the same classification standard, it is hoped that the international comparative study of various vasculitides progresses in future.

S18-4

Microscopic polyangiitis (MPA): An update on diagnosis and treatment

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Conflict of interest: None

Microscopic polyangiitis (MPA) is an anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis. It is a major subtype of ANCA-associated vasculitis in Japan. The clinical characteristics of MPA are elderly onset (average onset: over 60 years), MPO-ANCA dominance and multiple organ involvement. It also demonstrates various levels of disease severity and a high rate of severe infection during immunosuppressive therapy. Early diagnosis, proper immunotherapy, prevention of relapse, and treatment for complications during treatment are the most important factors for improving the prognosis of MPA. Recent advances in the di-

agnosis and treatment of MPA have led to improvement in the methods of ANCA measurement and greater awareness of the entity of ANCA-associated vasculitis among physicians. Nationwide studies, conducted by the Research Committee on Intractable Vasculitides of the Ministry of Health, Labor and Welfare of Japan, also demonstrated the current status of the clinical features and immunosuppressive treatment for ANCA-associated vasculitis in Japan. Rituximab treatment for ANCA-associated vasculitis has been covered by the national insurance scheme since 2013. Rituximab is a chimeric monoclonal antibody targeted against the pan-B-cell marker CD20. It was reported that rituximab was effective for MPA. There were no significant differences found between rituximab treatment and cyclophosphamide treatment groups with respect to the efficacy and adverse events of treatment for ANCA-associated vasculitis. In some cases, rituximab has been associated with serious side effects, such as breathing difficulty, heart problems, or severe infection. For these reasons, the use of rituximab is closely monitored. We will provide an update on the diagnosis and treatment of MPA.

S18-5

Clinical manifestations of granulomatosis with polyangiitis (GPA) in the upper respiratory tracts

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Conflict of interest: None

Most majority of initial symptoms and/or signs of ANCA-associated vasculitis, especially granulomatosis with polyangiitis (GPA), occurs in upper respiratory tracts (URT). However, 70% and 50% GPA patients in URT are not positive findings of histology and serum PR3-ANCA, respectively. The patients are often positive for MPO-ANCA. Otitis media is frequently seen in such patients, which is characterized by development into facial nerve palsy and hypertrophic poly meningitis, and then such disease is recently called otitis media with ANCA-associated vasculitis (OMAAV). Therefore, ANCA-associated vasculitis in URT (GPA and OMAAV) is difficult to diagnose. In this symposium, we will discuss about clinical manifestation of GPA in URT and OMAAV, together with audience.

S18-6

Diagnosis and Treatment of Eosinophilic Granulomatosis with Polyangitis: Update

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Conflict of interest: Yes

【Pathogenesis and Clinical manifestations】Basic organ involvement in EGPA is preceded by severe eosinophilic airway inflammation, including nasal polyposis, adult-onset asthma, and eosinophilic bronchitis and pneumonia. Furthermore, EGPA consists of two types of systemic organ insufficiency, namely, severe eosinophilic inflammation and ischemia due to small vessel vasculitis. Allergen immunotherapy, vaccination, and leukotriene modifier were speculated to cause EGPA; however, there was insufficient evidence. Recently, the percentage of female and/or older patients with EGPA has increased. Almost all EGPA patients show a history of asthma/nasal polyposis, and 90% of these patients show peripheral neuropathy. Two-thirds of EGPA patients show mild to severe cardiac, pulmonary, GI, and skin involvement. Moreover, atopic status and typical allergic rhinitis are not common.【ANCA significance】Only one-third of EGPA patients show ANCA positivity. The ANCA-positive EGPA patients frequently show renal involvement such as MPA patients; on the other hand, ANCA-negative EGPA patients frequently show cardiac insufficiency.【Prognosis】The fulminant type is detected in 2% of all EGPA patients, and their prognosis is very poor. Symptomatic cardiac insufficiency is a significant poor prognostic factor. Almost all peripheral neuropathies are long –lasting and resistant to conventional therapy.【Treatment】Both corticosteroids and immunosuppressive agents are essential for treating moderate to severe EGPA patients. IVIG therapy is a potential candidate for second-line treatment of EGPA patients, particularly those with neuropathy and/or cardiomyopathy, which are resistant to conventional therapy. Recent reports have claimed that the medication with anti-IL5 and anti-igE antibodies and rituximab are effective for steroid-resistant EGPA patients. In the near-future, these biologics may improve the prognosis of EGPA patients.

International Symposium

IS1-1

Recent trends in orthopedic surgery aiming to improve quality of life for those with rheumatoid arthritis in Japan

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Conflict of interest: None

Objective. To describe current trends in the numbers of rheumatoid arthritis-related surgeries performed in a large observational cohort of Japanese outpatients between 2001 and 2012. ***Patients and methods.*** Approximately 5,000–6,000 patients (equivalent to about 1% of all Japanese patients with RA) were involved in each phase of the Institute of Rheumatology, Rheumatoid Arthritis (IORRA) cohort study conducted from 2001 to 2012. The number of operations, including total joint arthroplasties (TJAs), was determined for these RA patients. ***Results.*** The total number of operations peaked in 2002 (n=283), gradually decreased thereafter, but began to increase again in 2008 (n=163). Similarly, the number of TJAs were found to decrease gradually since 2003 (n=142) but began to increase in 2008 (n=78), and the number of total knee arthroplasties (TKAs) were found to decrease gradually since 2003, while the number of total elbow arthroplasties, total ankle arthroplasties, and artificial finger prosthesis surgeries were found to increase gradually. Arthroplasties also gradually increased, but arthroscopic surgeries and synovectomies gradually decreased over the entire period. ***Conclusion.*** The combination of medical treatment and surgical intervention is thought to improve outcomes in patients with long-standing RA and high risk for developing joint destruction. Our results suggest that orthopaedic surgeries may change in response to changes in the drug therapy for RA.

IS1-2

Improvement of surgical treatment for lower extremities and changes of patients' background rheumatoid arthritis

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Conflict of interest: None

Recent treatment of rheumatoid arthritis (RA) was dramatically improved after introducing methotrexate (MTX) and biologics. In this paper, recent changes of orthopaedic surgery for lower extremities will be discussed. Based on our department's surgical registry, the number of hip surgery is showing down tone, knee surgery is maintaining, and toe surgery is on the continuous increase. **Hip** (total hip arthroplasty) Pelvic side: We have performed non-cement impaction auto bone graft method using the resected femoral head for protrusion of acetabulum. Femoral side: We have been using non-broaching impaction technique for stems. In this technique, a series of trial stems was used with the impaction technique for femoral canal without sacrificing cancellous bone. The mid-term results of these cases were very good without any revision case. **Knee** Typical recent changes of RA knee are reduced number of cases of cortical bone narrowing, decreasing of bone density at medullary canal, severe varus/valgus deformity with bone defects, and formation of huge geodes. We did not find any changes in Larsen grades, mean femoro-tibial angle, and laboratory data in cases of TKA. On the other hand, we found obvious increase of the cases with bony spur. From 2000 to 2012, the dosage of MTX has been increased and steroid use was decreased. The OA changes of RA knee thought to be reflected the changes of use of MTX and steroid. **Forefoot** We use Swanson type implant from 2004 for greater toe. In our early series, we found high incidence of recurrence of hallux valgus deformity. Then we increased amount of osteotomy of the hallux to equivalent to lessor toes. With this new surgical technique, we have no case of recurrence of hallux valgus. Additionally, we recently perform partial resection of metatarsal bone for lessor toes. Our short-term results showed that there are fewer cases with recurrence of hallux valgus in partial resection group than in resection arthroplasty group.

IS1-3

Current status of upper extremity surgery for rheumatoid arthritis in Japan

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Conflict of interest: Yes

The treatment strategy for rheumatoid arthritis (RA) has dramatically changed over the past decade with clinical introduction of biologic agents. The modern concept of comprehensive disease control (CDC) for RA includes clinical remission or low disease activity, no radiographic progression, and normal function. CDC should be the treatment target not only for patients with early disease, but for patients with long-standing disease who missed the "window of opportunity". In this line, surgical treatment still holds an important place for non-responders to non-biologic and biologic DMRADs, as a local treatment especially for partial responders, or for patients who cannot use optimal medication due to complications or economic problems. On the other hand, there is still little information about the patients' background including disease activity who required surgical intervention, and the effect of the surgery on disease activity or functional improvement has not been fully demonstrated. We retrospectively investigated a total of 1286 elective orthopaedic procedures for RA performed between January 2003 and December 2013. 226 procedures for 470 joints have been done in patients using biologic agents. The yearly number of surgery for patients under control with biologic agents increased, the number of total joint arthropasty decreased whereas wrist and finger joint surgery and forefoot surgery increased. We reviewed the total 105 of upper extremity procedures among RA patients with or without treatment by biologic agents, to evaluate the effects of orthopaedic surgery for disease control (DAS28) and functional outcome measured (DASH or Hand20). The verification for the change in surgery in these 10 years is needed, and surgeons should aim better surgical outcome and functional improvement for patients with good disease control by biologic DMARDs.

IS1-4

Surgery & Rheumatoid Arthritis in Europe: A decline in number but increase in complexity?

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Conflict of interest: None

The therapeutic management of rheumatoid arthritis (RA) has changed considerably in the last three decades. The introduction of combination therapies boosted remission of disease and have impact on outcome, like disease activity, functional disability, need for joint replacement surgery. The change in the management has been shown by several authors and is mainly related to the introduction of MTX but also in the different attitude of health professionals since the late '90s, on the importance of exercise therapy in these rheumatoid arthritis patients. Although MTX is considered very safe, for the use of Biologicals, increased infection rates (up to 2.4 times higher risk in a Japanese population with anti-TNF-alpha) and malignancies have been reported. Nevertheless, the incidence of destruction of large joint has greatly declined, mainly since the use of MTX for over 25 years. Although these total joint prostheses in rheumatoid arthritis patients are very successful, postponing surgery is always a better option since nor prosthesis will last for ever. The effect of the use of DMARDS and the changes in disease activity, function, joint damage and incidence of orthopaedic surgery over a period of 20 years (1989–2009) for patients with RA has been analysed by several authors. In a recent study in the Netherlands (Kievit et al), almost 800 patients were followed since 1989, the proportion of patients using MTX in-

creased from 5% to 62%, and the use of biologic response modifiers increased in that period from 0% to 22%. There was a significant trend towards lower incidence rates of orthopaedic intervention in the period 2006–2008 (0.02-0.03%) than in 1991-2005, about 0.06%). In summary, treatment strategy changed both with respect to medication (MTX and biologicals) as well as with respect to intensive exercise training changed the last three decades in RA patients.

IS1-5

Surgery for RA patients : Current status and trends for the future

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Conflict of interest: None

There is a significant decrease of handsurgical procedures in most first world countries in the world. This can be attributed primarily to the innovations in medical treatment. However there is a trend for recurrence under the biologicals after 4 to 5 years of treatment. In addition there is a significant number of patients without complete remission and residual medical problems. But more patients are seen with either a minor but residual inflammatory problem, often around the wrist, or severe courses of the disease with destruction in different parts of the hand. This changed the frequency and the type of intervention over the last years. Since the inflammation process is well controlled by the medication and destruction might go on, the x-ray findings resemble more to patients with a degenerative osteoarthritis than those of classic rheumatoid pattern. This offers a different spectrum of interventions including more arthroplasty procedures and the trend to partial fusion. Parallel to this evolution, patients evaluation are done in a more thoroughly way with specific outcome instruments. However with the RA patients suffering often from a multi-joint disease suitable instruments to measure the outcome correctly are difficult to design. Thus most often three different sets of outcome measurement must be used in order to evaluate the results of interventions: a general health questionnaire, a generic questionnaire and a joint specific measurement. But not only the patients perspective is important but also the referring doctor needs to be ask about his expectations concerning surgical treatment of his patients. Often a disagreement between the perception of a treatment result between patients, rheumatologist and hand-surgeons exist and needs to be sorted out in order to enhance the indication quality. The art of RA surgery in the hand remains the combination of determine the patients needs and expectations, the surgical possibilities and the technical skills.

IS1-6

Surgical techniques in rheumatoid foot

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Conflict of interest: None

The foot is the second common place, behind the hand, in manifestation of rheumatoid arthritis in the human body. The forefoot is affected more often than the hindfoot. Up to 72% of women and 58% of men suffering from RA display changes and degenerations in the hindfoot and ankle, whereas 91.3% of women and 84.9% of men have affected forefeet. These complaints, concerning the foot in RA, are the most frequent reasons to seek out a medical specialist. The pathological mechanism in rheumatoid foot is always a combination of statical, degenerative and inflammatory changes. The pathophysiology of the rheumatoid hindfoot is not separable from the forefoot. The talo-navicular joint ist he most affected joint, whereas the degenerated ankle ist the greatest risk for patient's immobility. The Hallux valgus complex, hammer toes and dislocated metatars-phalengeal joints are the earliest manifestations in rheumatoid forefoot and are the first painful areas. A multidisciplinary approach including rheumatologists, orthotists and orthopaedic surgeons is mandatory for a successful therapeutical outcome. Due to the high effectiveness of modern DMARD's, the number of surgical interventions decreased significantly. But still there are more or less fulminant cases with severe rheumatological destructions in several joints, requiring surgical procedures. Several surgical techniques have been developed and implants have been improved, to optimize function, durability and pain-relief in patients with RA. This talk is about the most common rheumatological disease pattern in back- and forefoot and its most frequent orthopaedic treatment procedures.

IS2-1

'ASIA' - Autoimmune (Auto-inflammatory) Syndromes Induced by Adjuvants

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Conflict of interest: None

Four enigmatic medical conditions were described recently, all characterized by hyperactive immune response and similar clinical and laboratory manifestations. These conditions (siliconosis, Gulf War Syndrome, macrophagic myofasciitis syndrome and post-vaccination phenomena) imply that environmental factors may play a role in inducing or aggravating autoimmunity and auto-inflammation. In rare occasions vaccines may induce autoimmune or auto-inflammatory conditions both in animals and in humans. These conditions - defined diseases (Gullian-Barre syndrome) or enigmatic ones - have been reported following vaccines and vaccination protocols. The susceptibility factors and the temporal association between vaccines and these immune mediated reactions remain to be defined; however, the similarities between vaccines and infections and the addition of adjuvants to almost every vaccine are considered major contributors to such adverse events. In MMF a cause was clearly delineated. MMF is a rare condition caused by deposition of alum, an adjuvant in different vaccines, which cause an immune mediated muscles disease. In genetically prone patients, alum may induce this syndrome. Another similar phenomenon is exposure to silicones. In a study, a group of patients with silicone breast implants had a statistically significant increase in 16 of 28 investigated symptoms consistent with fibromyalgia and chronic fatigue syndrome criteria, compared to a group of women who underwent reduction mammoplasties, congruent with the FDA's establishment of a link between fibromyalgia and ruptured silicone implants. A common denominator to these syndromes is the trigger entailing adjuvant activity. We suggest including these four conditions in one syndrome, the "Autoimmune Syndrome Induced by adjuvants" (ASIA).

IS2-2

CREM alpha controles cytokine expression and T cell subset distribution in SLE

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Conflict of interest: None

T lymphocytes from patients with systemic lupus erythematosus (SLE) display a complex array of cellular, molecular, and signaling anomalies, many of which have been attributed to increased expression of the transcriptional regulator cAMP responsive element modulator a (CREMa). Recent evidence indicates that CREMa, in addition to its regulatory functions on gene promoters in T lymphocytes, alters the epigenetic conformation of cytokine genes by interacting with enzymes that control histone methylation and acetylation as well as cytosinephosphate-guanosine (CpG) DNA methylation. I will summarize the most recent findings on CREM protein expression in various cell types, in particular its effects on T lymphocyte biology in the context of both health and SLE. I will emphasize CREMa as a key molecule that drives autoimmunity.

IS2-3

New concepts in neuropsychiatric lupus

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Conflict of interest: None

Approximately 80% of lupus patients exhibit some manifestation of neuropsychiatric lupus (NPSLE). It is now clear that brain-reactive antibodies contribute to disease pathogenesis in these syndromes. Most importantly, it is possible to model brain disease in lupus, using both human and mouse antibodies and a variety of histologic, electrophysiologic, cognitive, behavioral and imaging assessments to understand neuronal function in lupus in vivo. Our studies suggest that anti-DNA antibodies that cross-react with the NMDA receptor can cause both cognitive and behavioral manifestations of NPSLE and that the neuronal damage evolves over an extended window of time. Moreover, our studies suggest that decoy antigen may be a useful therapeutic modality o consider in SLE, as an alternative to current highly immunosuppressive therapies.

IS2-4

Can Clinical Care Catch up With Current Technology?

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Conflict of interest: Yes

Interpretation of clinical trials in SLE is hampered by the heterogeneity of the disease. This is further complicated by the aggressive background treatments used in trials leading to high placebo responses. Also some immune suppressants may interfere with the mechanism of a study treatment, others may be redundant or synergistic. How can treatment selection and dosing be optimized when the immunologic impact of combined agents remains so confusing? Exploratory analyses of trials has found that treatments perform better in the more severe patients, suggesting that high disease states may be less confounded by combination treatments. Does this mean that moderately active patients will be denied biologics because their trial results are more confusing? It is known that these patients have poor quality of life, progressive organ damage and early mortality on current therapies. The BOLD study (Biomarkers of Lupus Disease) was designed to test the feasibility and safety of a trial design for moderate patients with simplified immune suppressants. 41 patients entered with active, non-organ threatening disease, given brief steroid rescue until improvement, and background immune suppressants were withdrawn. The enduring response rate of this “placebo-like” group at 6 months was only 2.4% but as each patient flared (defining non-response) they were immediately treated and all improved again. Adverse events were comparable to traditional clinical trials. Cross sectional data from a total of 103 patients and longitudinal data from only the prospective cohort of 41 BOLD patients suggest that type 1 interferon gene signature differentiates signaling activity in distinct patient groups as well as the impact of different immune suppressants on multiple pathways. This may help define pharmacodynamic markers suitable for improved treatment selection and dosing, and lead to more strategic choices when certain biologics are being combined with background medications.

IS2-5

CD4+CD25-LAG3+ regulatory T cells and systemic autoimmunity

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Conflict of interest: Yes

It is not clear what kind of regulatory immune cell population controls systemic autoimmune diseases including systemic lupus erythematosus (SLE). Although CD4+CD25+Foxp3+ regulatory T cells may be associated with the suppression of systemic autoimmunity, the disease phenotype of Foxp3-mutated IPEX patients is quite different from that of SLE. Previously, we identified a CD4+CD25-Foxp3- regulatory T cells (Treg) population that expresses both lymphocyte activation gene-3 (LAG3) and early growth response gene-2 (Egr2). Interestingly, T cell-specific Egr2-deficient mice have been reported to develop a lupus-like autoimmune disease, and Egr2 is a genetic risk factor for SLE in a case-control association study. Here, we examined whether CD4+CD25-LAG3+ Treg play a role in the regulation of antibody production and systemic autoimmunity. In T cell specific Egr2-deficient mice, adoptive transfer of WT CD4+CD25-LAG3+ Treg reversed excessive development of follicular helper T cells (TFH) and germinal center B cells (GCB) in the spleen. In in vitro, CD4+CD25-LAG3+ Treg more efficiently induced B cell apoptosis and suppressed antibody production than CD4+CD25+ Treg. In lupus-prone MRL/lpr mice, adoptive transfer of CD4+CD25-LAG3+ Treg from MRL/+ mice significantly suppressed progression of nephritis and anti-dsDNA antibody production. Analysis of gene-targeted mice revealed that Fas, and Egr2 were required for CD4+CD25-LAG3+ Treg-mediated B cell suppression. In human peripheral blood and tonsil, we have also identified CD4+CD25-LAG3+ T cells that express IL-10, Egr2, and PD-L1. Human CD4+CD25-LAG3+ T cells suppressed antibody production in vitro and GVHD response in vivo. These results collectively indicated that CD4+CD25-LAG3+ Treg have the capacity to control humoral immunity and systemic autoimmune disease. Elucidation of the function of CD4+CD25-LAG3+ Treg may contribute to the understanding of systemic autoimmunity.

IS3-1

Improving outcomes in scleroderma

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Conflict of interest: None

Systemic sclerosis (scleroderma) remains a major clinical challenge despite recent advances in understanding of the disease biology and also better and more effective treatments for individual compilations of the disease. Currently patients re classified according to the extent of skin disease into diffuse or limited cases although long term outcome deepens more upon the presence of internal organ complications that can occur in either subset. Outcomes have improved over the past three decades with improved survival although still more than half of cases of systemic sclerosis die from their disease. Lung fibrosis and pulmonary hypertension are the main causes of death. There are now established therapies for most aspects of systemic sclerosis and emerging support for use of immunosuppression and targeted therapies for pulmonary hypertension and for other complications including digital vasculopathy and gastrointestinal tract disease. Outcomes are improving, in part due to better and more systematic follow up of cases with regular screening for major manifestations so that treatment is started as soon as necessary. However the burden of scleroderma remains high and needs to be tackled broadly without just focusing on life-threatening aspects of this challenging multifaceted disease. This presentation will review current approaches to management of systemic sclerosis and the impact that they are having by improving disease outcome. Lung fibrosis, pulmonary hypertension, gastrointestinal tract disease and scleroderma renal crisis will be discussed and current best practice management of these specific aspects of the disease together with more general strategies for assessment, screening and risk stratification of SSc will be discussed.

IS3-2

What at the possibilities for stratified medicine in the treatment of patients with rheumatic disorders

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Arthritis Research, UK

Conflict of interest: None

Treatment response varies in patients with the rheumatic diseases. This variation in response is exemplified by the results from the use of biologic agents in attempting to reverse the disease process in inflammatory joint disease: with some patients doing well and others having only minor benefits. It is also increasingly likely that there will be few ‘block buster’ drugs emerging from either industry or academic development. The challenge therefore is to identify which patients will respond to which drugs and adjust treatment schedules accordingly. Such identification leads to a stratification where groups of patients follow different treatment paths The benefits from such an approach can only be realised if there is a cost saving, or a reduction in risk of exposure to severe hazards, or that there is a reduction in delay in patients being directed to-

wards the path most suitable for them. In considering how to group patients into groups to make informed treatment decisions, there is an increasing option using biomarkers, which might be genetic, epigenetic, proteomic, into groups that have a predictable drug response based on the nature of the pathology and or the metabolism of the drug concerned. The value of this approach depends on the performance characteristics of the biomarkers. There are other patient-specific factors such as age, gender, aspect of disease severity or other issues such as psychological status that will affect treatment response. These factors may be called 'a personalised approach' and would influence treatment response in those whose disease and ability to handle drugs, for example as having a similar biomarker profile, was otherwise identical. Advances in the filed come from the development of new biomarkers for existing drugs, the development of new drugs using existing biomarkers, and increasingly (especially in oncology) the co-development of biomarker and drug to attack a single disease subset.

IS3-3

Guidelines for the management of gout

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Conflict of interest: Yes

Gout is a syndrome including acute arthritis, tophi, renal impairment and urinary stones caused by urate deposition with persistent hyperuricemia. Gout has long history from ancient ages, and has been an important disease in the rheumatology. Recently, the management of gout has been increasingly important because of the growing incidence in all countries, and the development of new drugs for hyperuricemia. In addition, I would like to emphasize that the importance of the management of gout had been unreasonably neglected in the rheumatology field by the underestimation of the pathological significance of hyperuricemia. As the result, many gout patients in Eastern countries developed gouty tophi and are refractory to the standard treatment for gout. On the other hand, management of hyperuricemia as well as gout has been well recognized in Japan, and controlling the serum urate of patients with marked hyperuricemia has been the standard management in daily practice. As the results, most gout patients in Japan are easily treated and very few patients developed gouty tophi. Since the pathogenesis of gout has been well understood, and treatment strategy of gout has been well established, guideline-driven standardization of the daily practice should be quite effective. Japanese Society of Gout and Nucleic Acid Metabolism published guideline for the management of hyperuricemia and gout in 2002 and updated in 2010 and 2012. This Japanese guideline includes the treatment strategy for the asymptomatic hyperuricemia. On the other hand, the recommendation for the management of gout from EULAR (2006) and the guideline for the management of gout by ACR (2012) include the therapeutic strategy only for the patients who has developed gouty arthritis. In this lecture, current views on the management of gout and hyperuricemia by the comparison of these management guidelines for gout will be discussed.

IS3-4

Growing evidence from cohort studies of rheumatoid arthritis in Japan

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Conflict of interest: Yes

During the last decade, seven biological disease-modifying antirheumatic drugs (biologicals) have been approved for the treatment of rheumatoid arthritis (RA) in Japan. The clinical trials of these biologicals provided ample evidence of their efficacy and safety in patients with RA. To garner evidence in clinical setting where a wide variety of patients use biologicals, prospective cohort studies were launched in various countries. In Japan, post-marketing surveillance programs for five biologicals were implemented by pharmaceutical companies as per approval condition. Numbers of enrolled RA patients were 5000 for infliximab, 13894 for etanercept, 7780 for adalimumab, 7901 for tocilizumab, and 3985 for abatacept. The results from these studies revealed incidence, characteristics, and risk factors of adverse drug reactions (ADRs) in the patients with RA who used the biologicals, and some of the reported ADRs were appeared to be unique to Japanese patients. In parallel with these industry-initiated cohort studies, several large-scale and investigator-initiated cohort studies have been established, such as IORRA, NinJa, and REAL. IORRA (the Institute of Rheumatology, Rheumatoid Arthritis) is a single-center, prospective cohort and enrolls virtually all RA patients who are seen in the Institute of Rheumatology, Tokyo Women's Medical University. NinJa (National Database of Rheumatic Diseases by iR-net in Japan) is a multi-center, prospective cohort administered by Sagamihara National Hospital. REAL (Registry of Japanese Rheumatoid Arthritis Patients for Long-term Safety) is a multi-center, prospective cohort of patients with RA administered by Tokyo Medical and Dental University and mainly focuses on safety of biologicals. Databases of these cohort studies have become a powerful research tool for clinical epidemiology and pharmacoepidemiology in Japan. In this symposium, I will review recent advances reported from these cohort studies and discuss future perspectives.

IS3-5

Clinical studies conducted by ultrasound imaging in RA

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Conflict of interest: None

Rheumatoid arthritis (RA) is a chronic, systemic, autoimmune disease characterised by joint inflammation, cartilage and bone destruction, as well as progressing loss of function. The disease involves both large and small joints, and is usually symmetric. The American College of Rheumatology (ACR) classification criteria of 1987 for RA underline the symmetric, polyarthritic character of the disease and the features are repeated, in a modified form, in the new European League of Rheumatism/ACR classification criteria for RA of 2010, where for the first time ultrasound (US) is named as helpful at establishing the diagnosis of RA. With US the assessment of joints can be performed in several regions at one session. It may easily be repeated without any limitations. Soft tissues, cartilage and bone can be assessed. The method's many advantages as easy accessibility for examination, accuracy, dynamic evaluation of joints make the technique a modern method supplying the clinical examination and conventional radiography with new and important findings. US has in the recent years become a useful rheumatological tool of assessment of patients with suspected, early and established RA. Based on the new classification criteria of RA, the clinical studies on detection and follow-up of US signs of inflammation and destruction are presented. Moreover, studies of predictive value of US for development of chronic arthritis and radiographic progression are reviewed. The data support the thesis that the diagnosis of RA can now be established with the help of US, as the cited studies suggest. Furtehrmore, US can monitor RA inflammatory and destructive changes. US assessment shows that patients in clinical remission are not necessarily in imaging remission. Presence of intra-articular power Doppler signal, as well as high grades of synovial thickening, can predict structural progression in RA patients.

Special Lecture

SL

Autoantibodies in rheumatic autoimmunity and in cancer - Two paradigms contributing to elucidation of autoimmune responses

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Conflict of interest: None

Different rheumatic autoimmune disorders have different profiles of autoantibodies and this characteristic feature has been important in the differential diagnosis of systemic lupus erythematosus, scleroderma, Sjogren's syndrome and other illnesses (1). Another feature is the occurrence of multiple autoantibodies in every autoimmune disorder. Mechanisms leading to these characteristics of distinct profiles and multiple autoantibodies have been a big enigma in rheumatic autoimmunity. Our studies on autoantibodies to tumor-associated antigens (TAA) in cancer have provided some insights (2). The occurrence of profiles of autoantibodies to TAAs in cancer is not uncommon, as is the presence of multiple autoantibodies. The targeted TAAs are either oncogene or tumor –suppressor gene products which are altered or mutated and are components of tumorigenesis pathways. These mutated gene products which have either gain or loss of function are the 'drivers' of the autoantibody response. Most cancer cells have more than five or six such 'driver' mutations before malignant transformation occurs, a phenomenon well documented in breast and colon cancer (3) and these gene mutations stimulate immune system responses to the abnormal gene products. The requirement for several gene mutations has been related to a process called 'synthetic lethality', in which mutation in one gene alone is not lethal, but simultaneous mutations in two or more genes produces sickness or lethality (4). These observations beg the question whether there might be similar mechanisms in rheumatic autoimmune disorders like lupus and raise the possibility that there could be 'autoimmunity pathways' which await discovery and elucidation of some basic mechanisms of rheumatic autoimmunity. Targeting molecules which are synthetic lethal is in the forefront of research in anti-cancer therapy and this approach could also be an objective in the future treatment of autoimmune rheumatic disorders. References 1. Tan E.M. Antinuclear antibodies: diagnostic markers for autoimmune diseases and probes for cell biology. Adv Immunol 44: 93-151, 1989. 2. Tan E.M., Zhang, J. Autoantibodies to Tumor-Associated Antigens. Reporters from the immune system. Immunol Rev 222: 328-340, 2008. 3. Vogelstein B., Papadopoulos N., Velculescu V.E., Zhou S., Diaz L.A.Jr., Kinzler K.W. Cancer Genome Landscapes. Science 339: 1546-1558, 2013. 4. Kaelin W.G.Jr. The concept of synthetic lethality in the context of anticancer therapy. Nat Rev Cancer 5: 689-98, 2005.

Educational Lecture

EL1

How to use DMARDs

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Conflict of interest: Yes

Disease modifying anti-rheumatic drugs (DMARDs) are strongly suggested to be used in the major recent guidelines and/or recommendations for management of patients with rheumatoid arthritis (RA). Twenty DMARDs have been approved by the regulatory office in Japan, that is, from injectable gold to biological agents and a new targeted synthetic DMARD. It is now very difficult, even for a rheumatologist, to decide how to use these DMARDs for individual RA patient. Among these DMARDs, methotrexate (MTX) is still an anchor drug for the treatment of RA patients. We measured MTX concentration in the red blood cells as a surrogate marker of the intracellular MTX in patients with RA who received MTX. Genetic polymorphisms of some molecules related to the intracellular metabolism of MTX were also determined. Using these data, we are now trying to make a personalized medicine for MTX treatment in RA patients. MTX is used as a monotherapy as well as combination therapies with other DMARDs. In this seminar, the efficacy of these therapeutic strategies in RA patients will be also summarized.

EL2

Autoinflammatory syndrome

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Conflict of interest: None

Autoinflammatory syndrome is characterized by 1) the episodes of seemingly unprovoked inflammations, 2) the absence of high titer of autoantibody or auto-reactive T cell, and 3) the inborn error of innate immunity. Main adult autoinflammatory syndromes are Familial Mediterranean fever (FMF) and TNF receptor associated periodic syndrome (TRAPS) in Japan. In this meeting, I focus the six adult autoinflammatory syndromes, such as FMF, TRAPS, Nakajo-Nishimura syndrome, PAPA syndrome, and primary hypertrophic osteoarthropathy, and I discuss with the mechanisms of inflammation about these syndromes.

EL3

Radiographic evaluation and scoring of joint destruction in rheumatoid arthritis

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Conflict of interest: None

The treatment of rheumatoid arthritis (RA) has remarkably advanced along with biologic agents targeting cytokines such as TNF or IL6. The current primary targets of the treatment of RA are clinical remission, radiological remission and functional remission. Moreover, keeping remission without any drugs has been tried in some studies. The joint destruction in RA proceeds rapidly in two years from the diagnosis resulting in irreversible functional disorder, however, appropriate treatment strategy has proved to be able to prevent the exaggeration of functional disorder. In those settings, the standardized method evaluating X-ray findings in RA is important in conducting clinical studies with high quality as well as in daily clinical practice. There have been proposed several methods how to evaluate radiological change in X-rays in patients with RA, such as Steinbrocker stage, Sharp method, Larsen method, and so on. Among those, van der Heijde modified Sharp score is now most widely used in the world to detect changes in joint damage and to evaluate the efficacy of drugs. In this method, 17 areas should be read for erosions (ERO) and 18 areas for joints space narrowing (JSN) in each hand including wrists with the maximum score per single joint for ERO of 5 and for JSN of 4.

Six areas should be read for both ERO and JSN in each foot with the maximum score per single joint for ERO of 10 and for JSN of 4. In total van der Heijde modified total Sharp score (mTSS) is at a range of 0-441. The radiological remission at the moment is defined as ΔmTSS/year ≤ 0.5. When scoring X-rays of patients with RA, what is most important is to detect changes during the time course comparing a couple of X-rays. In this lecture, I will talk about standardized procedures and pitfalls of scoring van der Heijde mTSS and data handling.

EL4

Ocular disorders associated with collagen diseases from the viewpoint of ophthalmologists

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Conflict of interest: Yes

The main ocular manifestations of collagen diseases are dye eye, scleritis, and uveitis. This presentation will review the criteria and current trends in the treatment of dry eye in collagen diseases in Japan with emphasis on Sjögren's syndrome (SS). Dry eye as defined by the Japanese dry eye society is a multifactorial disease of the tear and ocular surface, resulting in discomfort, visual disturbance and tear film instability with potential damage to the ocular surface. Dry eye can be categorized into aqueous-deficient and evaporative dry eye. SS is an autoimmune disease that affects exocrine glands, including the lacrimal gland. Lacrimal gland damage in SS leads typically to aqueous deficient dry eye In the revised Japanese Ministry of Health criteria for the diagnosis of SS (1999), dry eye diagnosis is made by the positivity to at least A) or B) A) Schirmer's test ≦ 5mm/5min and rose bengal test ≧ 3 according to the van Bijsterveld score B) Schirmer's test ≦5mm/5min and positive fluorescein staining test Sodium hyaluronate eye drops have been widely used in the treatment of dry eye due to its favourable effect on corneal epithelialization in addition to aqueous supplementation. Recently 2 novel mucin secretagogues, diquafosol and rebamipide have become available in the treatment of dry eye. Topical instillation of diquafosol improves tear film stability, by promoting mucin and water secretion from conjunctival tissue and rebamipide, a mucosal-protective agent originally used in the treatment of gastritis and gastric ulcer, promotes mucin secretion and maintenance of ocular surface mucosa as an ophthalmic suspension. In severe dry eye associated with SS, concomitant use of these eye drops and punctual plugs that block the lacrimal drainage system and retains tears at the ocular surface, are effective.

EL5

Current treatment of polymyositis and dermatomyositis

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Conflict of interest: Yes

Treatment of polymyositis (PM) and dermatomyositis (DM) is based on glucocorticoids and immunosupressants. The issues are 1) Determination of prognosis 2) Disease activity assessment 3) Treatment goals 4) Drug choice 5) Treatment of complications Prognosis can be predicted to some extent by profiles of the myositis-specific autoantibodies. Disease activities can be assessed by serum levels of CK, aldolase and myoglobins and by muscle strength. Since either will not be complete, composite measurement will be used in the future. Patients only with skin manifestations should be treated topically. If patients accompany acutely progressive interstitial pneumonitis (APIP) or have risk factors to develop APIP, they should be treated high-dose glucocorticoids together with immunosupressants such as cyclophosphamide and tacrolimus. The risk factors are being hypomyopathic, positive anti-MDA5 antibody, positive, anti-aminoacyl tRNA synthase antibody negative, and high serum ferritin. Without APIP, the patients should be treated with high dose glucocorticoids or intermediate dose of glucocorticoids together with immunosuppressants, including methotrexate, tacrolimus, cyclosporine A and azathioprine. Intravenous immunoglobulin can be used effectively before the therapeutic effects of immunosuppressants take place. Cardiac myopathy and dysphagia are serious complications that require intensive treatments. Malignancy should be diagnosed and treated first since elimination of malignancy itself can ameliorate myositis.

EL6

Drug treatments for osteoarthritis

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Conflict of interest: None

Osteoarthritis (OA) is the most common disease causing physical disability in Japan. Tissue involved in the process of OA are cartilage, synovium and subchondral bone. Most of drugs approved for indication of treating OA are used to reduce symptoms including pain, and there is none presently approved for slowing the structural progression of OA. **【Symptom modifying drug】** NSAIDs are most frequently used drugs, however the effect size of NSAIDs reported in meta-analysis is not so large as expected. Intraarticular injection therapy of hyaluronan is not estimated highly in the guideline for OA in Europe and USA. Several studies failed to show efficacy of anticytokine therapies including IL-1 and TNF-α. Tanezumab, a monoclonal antibody to NGF, demonstrated in hip and knee OA, however a serious adverse event of rapidly destruction of joint. **【DMOAD】** Large clinical study of bisphosphonate for knee OA (KOSTAR study) could not show significant effects against both clinical symptom and structural progression. Strontium ranelate is approved for the treatment of postmenopausal osteoporosis. Randomized placebo controlled study showed women received this drug had less progression of OA.

EL7

Pulmonary manifestations in collagen vascular diseases

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Conflict of interest: None

The collagen vascular diseases (CVD) that most commonly involve the lung are rheumatoid arthritis (RA), polymyositis and dermatomyositis (PM/DM), systemic sclerosis (SSc), Sjogren`s syndrome (SjS), systemic lupus erythematosus (SLE), ANCA-associated vasculitis, and lung-dominant connective tissue disease. The pulmonary manifestations are classified into two categories which consisted of primary lung lesions caused by CVD itself such as interstitial pneumonia (IP), alveolar hemorrhage, pleuritis, bronchiolitis, pulmonary hypertension, and secondly associated lung lesions such as drug-induced pneumonitis or opportunistic infection. Among these lung lesions, IP is a frequent pulmonary manifestation of CVD. HRCT scanning is generally sufficient to confirm the diagnosis of IP, although in a minority of cases, surgical lung biopsy may be required. The radiographic and histopathologic appearance of CVD-IP is heterogeneous and primarily mimics the patterns seen in the idiopathic interstitial pneumonias such as nonspecific interstitial pneumonia (NSIP), usual interstitial pneumonia (UIP), organizing pneumonia (OP), and diffuse alveolar damage (DAD). While the NSIP pattern predominates in most forms of CVD-IP, UIP pattern appears to predict worse survival in CVD-IP patients. The clinical presentation, the prognosis and response to therapy with corticosteroids and /or immunosuppressants vary depending on the radiological and/or hisotological pattern of IP, as well as on the underlying CVD. Moreover, preexisting IP is a well-known risk factor for drug-induced IP. It is important to distinguish drug-induced pneumonitis or opportunistic infection from primary CVD-IP lesions. We should make a treatment for CVD patients according to the cause of each lung lesions.

EL8

Glucocorticoid-induced osteoporosis

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Conflict of interest: Yes

Oral glucocorticoids are prescribed for a wide variety of medical disorders. Reduced bone formation is the key process in glucocorticoid-induced osteoporosis. The risk of vertebral fractures increases more than hip fractures, substantially in oral glucocorticoid users. In a General Practice Research Database study, the daily glucocorticoid dosage correlated with the fracture risk. There was no threshold daily dose for the occurrence of vertebral fractures. The data from two randomized controlled trials of risedronate were used to identify factors predicting vertebral fractures within 1 year in the control patients, who received oral glucocorticoid therapy. Baseline lumbar-spine BMD was among the predictive factors, with each 1 SD decrease in the T score having a relative risk for vertebral fractures of 1.85 (95% confidence interval: 1.06-3.21). However, comparatively to the non-glucocorticoid-treated women, the glucocorticoid-treated women were higher risk for fractures despite a lower mean age and higher baseline BMD values. Thus, glucocorticoid-induced osteoporosis is characterized by relative dissociation between the BMD values and the fracture risk, which is higher than expected based on the BMD values. Current Japanese guidelines indicated that the treatment objectives are patients that are using or planning to use oral glucocorticoids for 3 months or longer with a fragility fracture, with less than 80% BMD of young adult mean, and with 5mg predonisolone equivalent or higher doses per day. We are now working on the revision of Japanese guidelines. Assessment of fracture probability in glucocorticoid treated patients using FRAX or similar algorithms may underestimate risk, and the role of primary prevention of glucocorticoid-induced osteoporosis is often insufficiently emphasized in current guidelines. Oral bisphosphonates provide the front-line treatment option in the majority of patients with glucocorticoid-induced osteoporosis.

EL9

MRI of rheumatic disorders

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Conflict of interest: None

MRI offers advantages over conventional radiographs for evaluating structural damage to joints in rheumatic disorders. Visualization of bone, synovium, articular cartilage, ligaments and tendons allows the joints to be examined as a whole organ. **1) Synovitis** Thickened synovium due to synovitis shows low signal on T1WI, intermediate-high signal on T2WI and enhances on contrast enhanced (CE) images. The signal intensity patterns on T2WI are associated with the degree of fibrosis. **2) Tenosynovitis, bursitis** Tenosynovitis and bursitis are demonstrated as fluid collection with synovial thickening. Baker cysts often rupture into the calf, mimicking thrombophrebitis. MRI is useful in demonstrating the cystic change in the popliteal fossa with communication to the calf. **3) Bone erosion, bone marrow edema** Bone changes can appear as erosion and/or bone marrow edema. Erosion on MRI is defined as a well-circumscribed area of abnormal signal with focal loss of cortical bone. Bone marrow edema appears as a region of bone change without clear margins that shows high signal on STIR. Both lesions show contrast enhancement and represent bone marrow inflammation associated with osteoclast activation. **4) Inflammation at attachement of tendon, ligament or joint capsule (enthesitis)** Enthesitis is often seen in seronegative spondyloarthropathy. MRI (STIR or fat-saturated T2WI) shows high signal intensity with positive enhancement effect at the enthesis as well as adjacent soft tissue and bone marrow. **5) Joint cartilage** MRI can directly visualize the articular cartilage. However, it is difficult to evaluate cartilage lesions especially in small joints such as hands. **5) Soft tissue** Soft tissue inflammation, edema or abscess associated with arthritis can identified with great detail on MRI. Rheumatoid nodules associated with RA can show various signal intensity patterns depending on the degree of fibrosis and cystic components.

EL10

The management of immunosuppressants for the therapy of connective tissue diseases

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Conflict of interest: Yes

Connective tissue diseases are chronic systemic inflammatory disorders that affect multiple organ functions. However, over the past fifty years, survival in connective tissue diseases has improved dramatically. The reasons for this improvement in survival have included earlier diagnosis by progresses of diagnostic techniques and many advances in pharmaceutical agents such as immunosuppressant. Immnunosuppressants used in the treatment for connective tissue diseases are as follows; cyclophosphamide, azathioprine, cyclosporin, tacrolimus, methotrexate, mizoribine, mycophenolate mofetil and biologics (TNF blocking therapy, anti-B cell monoclonal antibody (Rituximab) and so on). These drugs are used as agents for remission induction or maintenance. Recently, in Japan, expanding indication of conventional immunosuppressants, such as cyclophosphamide and azathioprine for refractory rheumatoid diseases (SLE, systemic vasculitis and so on) (2010) and Rituximab for granulomatosis with polyangiitis (Wegener's granulomatosis) and microscopic polyangiitis (2013), progressed. However, because the pathology of connective tissue diseases is various, immnunosuppressants should be used properly depending on the pathology of each diseases and the condition of each patients, with our understanding of mechanisms of action, efficacy and toxicity of these drugs. This lecture will review the use of immunosuppressantsas mentioned above and combination therapy with national and international treatment guidelines, research reports and our cases. In addition, I will mention the prevention of immunosuppressive therapy-induced reactivation of hepatitis B virus infection and *de novo* hepatitis B.

EL11

Recent advances in pediatric rheumatology: diagnosis, genetics, pathophysiology, treatment and care management

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Conflict of interest: Yes

The incidences of juvenile idiopathic arthritis (JIA), systemic lupus erythematosus, and juvenile dermatomyositis (JDM) are 15-20, 8-10, and 3-5 per 100,000 children, respectively, in Japan. Vasculitis syndrome, mixed connective tissue disease, Sjogren syndrome, and anti-phospholipid antibody syndrome are following next. Chronic inflammation is located in the center of the pathophysiology of these rheumatic diseases on the basis of dysregulation of inflammatory and immune systems. The findings of gene mutation of the proteins responsible for inflammatory response system such as periodic fever syndrome contributed establishment of the concept, inflammation rather than immunity. Recently, pediatric rheumatology further involved juvenile fibromyalgia and complex regional pain syndrome. In the near future, psychogenic stimuli or stresses as inducing factors of these disorders will be revealed to be a stimulant of neuroinflammation. Serological approaches of rheumatic diseases revealed new markers for diagnosis and disease activity, and FDG-PET is proved to be a useful tool to diagnose patients with fever of unknown origin, especially patients with systemic-JIA. Inflammation has been proved to be due to inflammatory cytokines including IL-1β, IL-6, IFNγ, and TNFα, and excessive production of these cytokines called as 'cytokine storm' is closely related to the progression of the disease to macrophage activation syndrome. The pathogenic role of 'cytokine storm' is expressed in 2 ways; apoptosis of cells, and endothelial cell activation and coagulation/fibrinolytic abnormalities. Now, patients with such potentially fatal diseases can be saved their lives by monitoring markers of apoptosis (AST/LDH), coagulation/fibrinolysis (FDP/D-dimer), and cytokine-induced proteins (ferritin: TNFα, β2-microglobulin: IFNγ). According to the progress of the concept, 'inflammation', several new biologics have been developed, and successfully applied to patients with rheumatic diseases.

EL12

Report from the Japan College of Rheumatology Committee for the Standardization of Musculoskeletal Ultrasonography (JCR-CoSMUS)

Takao Koike

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Conflict of interest: Yes

Musculoskeletal ultrasonography allows detailed evaluation of arthritis by using two modes in real time: Grey Scale Ultrasonography (GS-US) and Power Doppler Ultrasonography (PD-US). Particularly PD-US, a method to evaluate abnormal blood flow within the inflammatory synovial tissue, is cost effective and noninvasive, and therefore popularized as an RA examination in clinics mainly in Europe. In recent years, the importance of RA treatments from the early phase has been pointed out, and accurate and objective diagnostic methods are desired to be established and popularized. Although evaluations by imaging, such as MRI and musculoskeletal ultrasonography, need to be standardized to accomplish this goal, there is no global consensus for a diagnostic and prognostic evaluation particularly for musculoskeletal ultrasonography. To overcome these situations, the Committee for the Standardization of Musculoskeletal Ultrasonography was established by the Japan College of Rheumatology in January 2010 (Chairman: Takao Koike; members: 15 representatives from the fields of internal medicine, orthopedics, radiology, and laboratory examinations). Discussions by the Committee defined three missions: (1) attempting to standardize ultrasonographic imaging in a diagnosis/activity evaluation of RA and an evaluation method for imaging results, (2) constructing new evidence for articular ultrasonography in medical practice for rheumatology through multicenter studies using standardized articular ultrasonography, and (3) attempting the popularization and technical improvement of articular ultrasonography in medical practice for rheumatology to improve the quality of medical practice in Japan. The present educational lecture reports the results accomplished by the Committee for Standardization until now and the mode of standardization in muskuloskeletal ultrasonography and related problems.

EL13

Total Knee Arthroplasty for Rheumatic Diseases

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Conflict of interest: Yes

Total knee arthroplasty is one of the established orthopaedic procedures for advanced knee osteoarthritis, rheumatoid arthritis, etc. Pain relief and longevity of the implant has been improved by progress of surgical technique, biomaterial, and design of the implant. Many studies, however, have reported that patient satisfaction after total knee arthroplasty is lower than total hip arthroplasty. Many factors are related to patient satisfaction after total knee arthroplasty. Increasing range of motion and achieving near-normal knee kinematics would possibly improve patient satisfaction. Unicompartmental knee arthroplasty is also indicated for medial or lateral compartmental knee osteoarthritis or osteonecrosis, but not for rheumatoid arthritis. Unicompartmental knee arthroplasty can preserve all the knee ligaments to maintain knee stability, which are related to higher patient satisfaction than total knee arthroplasty.

EL14

Rehabilitation for the patients with rheumatoid arthritis

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Conflict of interest: Yes

The treatment of rheumatoid arthritis proceeded recently. We could suppress inflammation and bone destruction using biological DMARDs, and could recover joint damages depending on the situation. The goal of the treatment should progress from clinical remission to improvement of QOL of RA patients resulting from achievement of structural remission and functional remission. For the achievement of remission, we have to treat RA strongly and rapidly, however, we could not provide such treatment for all patients. We could not treat the joint damage and contracture in the patients with RA using medication. Therefore, the medical-staff have to select the order-made treatment from physical therapy, occupational therapy, physiotherapy, orthosis and surgery for those patients. However, the evidences of rehabilitation for RA treatment have been few because of the difficulty in designing of research. In physical exercise in RA patients, there were some evidences of the combination of muscle exercise and aerobic exercise. The effect was also observed in the exercise of twice a week. Occupational therapy should be provided by the comprehensive program including patients' education, splint, self-help tools and functional exercise of upper extremity, and the evidences exist to all items. The evidence exist to orthosis and splint in neck collar, wrist orthosis, finger splints for swan neck and boutonniere deformity, custom made insoles and shoes. However, because of their difficulties of casting and adaptation for complicated deformities in fingers and feet of RA patients, we should cooperate among doctors, occupational therapist and prosthetist tightly, and we should correspond closely to the patient's needs and complaints. Rehabilitation for the patients with RA is effective to obtain a functional improvement in patients with RA which do not compensate the medication, and it is important treatment to improve QOL in the patients with RA which is the final goal of our treatment.

EL15

Modern managements of cervical spine disorders in patients with RA

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Conflict of interest: None

Although biological drugs may decrease progression of cervical disorders in patients with RA, real efficacy has not been established. With a progression of high-technology including computer-navigation and intraoperative CT, recent advances in surgical techniques are remarkable. However, as challenging surgery increases, new problems including neuro-vascular injuries by screw placements and adjacent diseases have become new problems.

EL16

Neuropsychiatric symptoms in patients with rheumatic diseases: A review of the current practices to establish a management strategy for rheumatologists

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Conflict of interest: None

Neuropsychiatric (NP) symptoms are common in patients with rheumatic diseases, particularly systemic lupus erythematosus (SLE). NPSLE is associated with poor prognosis, extensive cumulative organ damage, and low quality of life. Therefore, rheumatologists consider adequate management of NP symptoms important for patient outcome. Typically, the psychiatric differential diagnosis of medically ill patients includes syndromic and etiologic components. Regardless of the etiology, psychiatric manifestations are classified into 4 major syndromes: cognitive, including delirium and dementia; psychotic; mood; and anxiety. These categories were adopted by the American College of Rheumatology in 1999 to define NPSLE cases. The choice of psychotropic drug for symptomatic treatments is based on this syndromic diagnosis. The second step, the etiologic differential diagnosis, is often very difficult in SLE patients for the following reasons: (1) it is difficult to distinguish NPSLE from psychiatric disorders due to other etiology, such as corticosteroid-induced psychiatric disorders, solely on the basis of symptoms; (2) no disease-specific diagnostic markers or gold standard for NPSLE has been established; and (3) NPSLE may occur independently of the systemic activity of SLE. Therefore, the first step of the etiologic diagnostic work-up should involve excluding non-SLE-related conditions. The correct diagnosis is derived from careful analysis of the clinical, laboratory, and imaging data on a case-by-case basis. However, patients with rheumatic diseases often develop stress-related psychological distress that manifests as depression or anxiety and requires stress management or supportive psychotherapy. This lecture reviews the status of the diagnosis and management of NP symptoms in patients with rheumatic diseases, which will be useful for rheumatologists to establish a management strategy for NPSLE. The beneficial collaborative partnership with psychiatrists is also discussed.

EL17

Immunology Up Date

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Conflict of interest: None

Recent advance in the treatment of rheumatic diseases encourages clinicians to be familiar with immunlogy. In this lecutre, I'll briefly overview on recent findings in immunology including helper T cell subsets and innate immunity.

EL18

Cytokines and signal transduction

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Conflict of interest: None

Rheumatoid arthritis (RA) is an autoimmune disease characterized by the activation of autoreactive T cells followed by antoantigen production by B cells, polysynovitis and bone destruction. Th17 cells play an important role by producing IL-17 and inducing RANKL. Progress in understanding the RA pathogenesis has promoted the development of new therapeutic strategies including CTLA4-Ig and antibodies against CD20, IL-17, IL-23 and RANKL as well as anti-TNF and IL-6 therapies. Bone is a part of the skeletal system which supports the body and enables the locomotion, while the immune system protects the host from the pathogens. The bone and the immune system thus have totally different functions. However, the bone marrow harbors the immune cells including hematoipoietic stem cells and B cells, and it is often observed that the bone homeostasis is influenced by the activated immune responses. Therefore, osteoimmunology, the research on the interactions and shared molecules of the bone and immune systems, has attracted much attention. In particular, the studies on RA have been the driving force for the field of osteoimmunology. Here I will summarize the cytokines and their signal transduction that play crucial roles in RA pathogenesis in the context of osteoimmunology and discuss the recent development of new therapies for RA.

EL19

Adverse effects of synthetic disease modifying anti-rheumatic drugs (DMARDs) and their preventive measures in the treatment of rheumatoid arthritis

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Conflict of interest: Yes

Disease modifying anti-rheumatic drugs (DMARDs) have a central position in RA treatment. These drugs have capacity to improve or reduce signs and symptoms, disabilities, impairment of QOL, and progression of joint destruction. However, safety issues related to DMARDs therapy exist, and adverse effects are sometimes one of the major reasons for discontinuation of DMARDs. Adverse effects include myelosuppression, interstitial lung diseases, infections, serious skin reactions, liver dysfunction, proteinuria, and malignancy. DMARDs can be classified into two types on the basis of mechanism and action, immunosuppressive or immunomodulating profiles. The former includes MTX, leflunomide (LEF), and tacrolimus (TAC), and the latter includes salazosulfapyridine (SASP), bucillamine (BUC), D-penicillamine (DPC), iguratimod (IGU) and gold sodium thiomalate (GST). Myelosuppression occur sometimes during treatment with MTX and LEF. Cytopenia is also associated with SASP or DPC rarely. Drug-associated interstitial lung diseases (ILD) are reported in association with MTX, LEF, BUC, and GST. MTX-LPD is acute onset but is response to steroid. LEF-ILD occurs in patients with underlying lung diseases and sometimes becomes fatal. Recently, acute and chronic opportunistic infections increase in patients treated with immunosuppressive drugs. Serious skin reactions such as Stevens-Johnson syndrome and drug hypersensitivity syndrome might be associated with the treatment of LEF and SASP. We also have to be apprehensive for reactivation of HBV and lymphoproliferative disorders in patients under immunosuppression In this lecture, I discuss adverse effects of synthetic DMARDs and their preventive measures.

EL20

Diagnosis and treatment of Behçet's disease

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Conflict of interest: Yes

Behçet's disease (BD) is a multifactorial disease, major symptoms of which are recurrent aphthous stomatitis, skin lesions, uveitis and genital ulcers. Arthritis, epididymitis and neurological, vasculitis, intestinal involvements are also seen as accessory symptoms. The pathogenesis of BD is unknown so far, but environmental factors such as *Streptococcus Sanguinis* infection, and HLA associate genes such as HLA-B51, HLA-A26 are reported. There is not a specific symptom in BD and it's very rare that each symptom occurs at the same time. Instead, only one symptom occurs frequently. Therefore, there are many cases which are difficult to diagnose until having all the classic symptoms of BD occur. According to the analysis of our 412 cases, the number of major symptoms at the onset is only 1 symptom (70% is oral ulcer) in most cases. Only 20% of cases are seen with two symptoms. In specific types of BD, it takes a long time until the occurrence of specific symptom after the onset of first symptom in most specific type of BD. Therefore, practice guidelines (statement) of specific types of BD (neuro, intestinal, vasclo) mainly by members of the BD group of the Japanese ministry of Health, Labor and Welfare was introduced. Also, a practice guideline in uveitis was also reviewed by BD group ophthalmologists. Moreover, since there are two diagnosis criteria (International and Japanese), it will be addressed as a problem area. One of the reasons that practice guidelines of specific types of BD have been rarely proposed so far, is due to the paucity of information from only a few case reports. Case reports of specific types of BD will be talked in this presentation. As to treatment, Infliximab for intractable uveitis, and Adalimumab for intestinal BD have been approved by the government recently. The results of these clinical trials and questionnaires for affiliations of whole of country including clinical problems on those will be discussed.

EL21

Management of rheumatoid arthritis by biologics - how to select from 7 kinds of biologics available in Japan -

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Conflict of interest: Yes

Rheumatoid arthritis (RA) is a chronic progressive inflammatory disease mainly affecting the synovial membrane of joints and is characterized by lymphocyte activation, synovial proliferation, and bone/cartilage destruction. In 2010, ACR/EULAR proposed rheumatoid arthritis classification criteria to classify patients with progressive arthritis and introduce methotrexate-based therapy in early stage disease. It also issued a new definition of RA remission, leading to higher remission rates, a treatment goal. With early therapeutic intervention using biologics, RA treatment with clinical, structural, and functional remission has become a reality. So far now, three different kinds of mode of action of biologics are available in Japan. Thus we can choose one among five TNF inhibitors including infliximab, etanercept, adalimumab, golimumab, certolizumab pegol and anti-IL6 receptor antibody; tocilizumab and abatacept; an inhibitor of T-cell activation. In terms of efficacy of these agents to biologics naïve RA patients, it has been shown there is no difference among 7 biologics in the recent report. However, the evidence is based on the clinical trials and it is a very important issue how to select biologics in daily clinical practice. The factors should be considered regarding choice of biologics are mode of action, pharmaceutical properties such as structure, half life time, immunogenicity etc., tolerance to MTX, safety, methods of administration, the possibility of treatment holiday after achieving clini-

cal remission, medical economics and so on. In the lecture, I will report the clinical results of seven biologics in Japanese PMS data together with the latest overseas findings and discuss where each biologics fits into RA treatment based on its pharmaceutical proper.

EL22

The ideal way of team medical care and medical cooperation in RA practice

Akira Murasawa
Niigata Rheumatic Center

Conflict of interest: None

With the progress of drug therapy in rheumatoid arthritis (RA), a paradigm shift has occurred in the treatment of RA. However, it was hard to deal with this situation in the medical field under the traditional medical system. As biologics has been used as the treatment, it has been seen more medical care disparities among facilities and regions. We had therefore launched into efforts by medical cooperation to be able to use safely and equality in all patients anywhere. Medical cooperation of RA practice begins with the team medical care in the hospital, and then develops into the regional medical cooperation by linking RA specialist and RA primary care doctors, and then is being spread to the medical network of the county unit. Team medical care in the hospital includes multidisciplinary of each specialty to share the patient`s information. As patients and their families are at the center of this system, it has been thought that the nurse who takes more time to contact and talk with the patient is qualified as the coordinator of conjoined with each job. The smallest unit of RA medical cooperation in the area is to perform a circular -shaped medical facilities in which RA specialist and RA primary care doctors share the role of each other. This system is in cooperation with general hospitals and family doctors of other department such as dermatology and ophthalmology. It is also required a collaboration with the emergency center in the event of an emergency. The fact of medical cooperation in RA practice is composed of regional collaboration and biological products. The number of the patients in biological treatment increased rapidly from 2007 to 2008, and hospital treatment of intravenous formulation had therefore reached the limit in our RA center. We had launched a regional collaboration team in hospital and medical cooperation with local medical institutions since July 2008.

EL23

Aesthetics of the defense

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Conflict of interest: None

Patient safety and risk management are widely acknowledged concepts at medical institutions. By contrast, the public is increasingly placing strenuous demands on hospitals and physicians such that death resulting from professional negligence has become the status quo to a level that is unheard of in other countries. In order for the hospitals to thrive in the current medical environment, the upkeep of day-to-day tasks is critical, hence the need to reevaluate those activities; in particular, the relationship between medical practitioners and patients and the collaboration between health care providers require careful reconsideration. The number of malpractice lawsuits by speciality has revealed that those involving pediatricians are much fewer relative to other specialists. This is thought to stem from the strong trust that develops between physicians and parents -- parents who regard the physician of their child as an exalted figure. In sharp contrast, malpractice lawsuits against emergency physicians are high. This phenomenon is a reflection of the difficulty in developing a relationship based on trust in an emergency setting where the encounter between the physician and patient is necessarily brief. It is said that the impulse underpinning malpractice lawsuits is the level of patient care, and therefore, improving the relationship between the physician and patient has become imperative. The most important act on the part of a health care provider is to handle the information provided by the patient with sincerity and humility, the essence of which is somewhat captured in the axiom “information revealed is handled with care”. If we foster a relationship wherein the patients “become better simply by being seen” or “being in the presence” of their health care provider, malpractice lawsuits and medical corruption may gradually become a thing of the past.

EL24

Autoantibodies in systemic autoimmune diseases - their association with clinical significance, pathogenic involvement and proposed mechanism of production -

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Conflict of interest: Yes

In systemic autoimmune diseases, determination of autoantibodies (auto Abs) is critical for diagnosis, estimation of patients’ prognosis, and evaluation of disease activity. Anti-dsDNA and Sm Abs for systemic lupus erythematosus (SLE), anti-topoisomerase I Abs for systemic sclerosis, or anti-Jo-1 Abs for polymyositis is well known to be disease-specific marker Abs. Also, anti-ribosomal P and anti- MDA5 Abs are specific to neuropychiatric SLE (NPSLE) and acute interstitial pneumonia in clinically amyopathic dermatomyositis, respectively. These Ab detections can help a treatment decision making. Anti-dsDNA and antineutrophil cytoplasmic Ab titers correlate with disease activity, so their sequential determination is useful to evaluate patient’s response for treatment. Thus, auto Ab detection has several clinical significances in the management of systemic autoimmune diseases. Pathogenic roles of the majority of auto Abs in systemic autoimmune diseases, however, remain undetermined. We have shown that the presence of anti-U1RNP Ab in CSF appears to be associated with high levels of CSF-IFN-α and MCP-1, which are supposed to be neurotoxic inflammatory mediators in NPSLE. CSF-anti-U1RNP Abs (or anti-U1RNP immune complex) may be involved in brain injury mediated by inflammatory mediators. Mechanisms of auto Ab production are still unknown. Breaking tolerance for autoantigens may occur probably because of cryptic epitope development, antigen modification by external factors, and activation of innate immunity in addition to genetic factors. Also, autoreactive T cell activation and abnormal expression of costimulatory molecules, which are essential for cognate interaction of T and B cells, will be involved. Clinical features in systemic autoimmune diseases are various and totally different among individuals. For optimization for immunosuppressive treatment, it may be helpful to determine the association between disease-specific auto Abs and pathogenic inflammatory mediators.

EL25

Our approach to regenerative medicine for osteoarthritis of the knee

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Conflict of interest: None

Mesenchymal stem cells (MSCs) are attractive cell source for cartilage and meniscus regeneration. Our *in vitro* and *in vivo* chondrogenic assay demonstrated that synovial and bone marrow MSCs had a higher chondrogenic ability than adipose and muscle MSCs (Arthritis Rheum 2005, Cell Tissue Res 2008). Human synovial MSCs expanded more in human serum than bone marrow MSCs (Arthritis Rheum 2008). In rat, rabbit, and pig studies, transplantation of synovial MSCs promoted cartilage and meniscus regeneration (Stem Cells 2007, Stem Cells 2009, Cytotherapy 2012, Osteoarthritis Cartilage 2012, J Bone Joint Surg Am 2012, Biochem Biophys Res Commun 2013). Current cell therapy for cartilage and meniscus regeneration requires invasive procedures. We have developed a novel implantation procedure with synovial MSCs. Cartilage or meniscus defect is filled with synovial MSC suspension for 10 minutes. According to our *in vitro* and *in vivo* studies, more than 60% cells adhered to the defect, and promoted cartilage and meniscus regeneration (Arthritis Res Ther 2008, J Orthop Res 2013). We are currently doing clinical trial for cartilage regeneration. All patients have their cartilage defects filled with synovial MSCs arthroscopically. Favorable results are obtained by MRI imaging in many cases, by second look arthroscopies, and by biopsies. Our method has such advantages that no periosteal

coverage or scaffold were required and that transplantation is possible arthroscopically. We are going to another clinical trial for meniscus treatment with synovial MSCs. Also, we are trying to regenerate osteoarthritis of the knee with HTO or meniscus centralization by using synovial MSCs.

EL26

Recent progress of pathophysiology and treatment of pulmonary hypertension in patients with connective tissue diseases-----including data from MCTD Research Committee of MHLW-----

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Conflict of interest: Yes

Pulmonary hypertension (PH) is defined as a state of mean pulmonary artery pressure equal or more than 25 mmHg. The prevalence of idiopathic pulmonary arterial hypertension (IPAH) in the general population is 1-5 per million but PH is much more frequently associated with connective tissue diseases (CTD) and affects the prognosis of CTD. 1. Prevalence Doppler echo cardiography is generally used for diagnosis of PH in CTD patients, which has been sometimes criticized for its inaccuracy. Recently the prevalence of PH in SSc patients was finally confirmed by right heart catheterization as high as 5-6% in Europe. But we should keep in mind that the structure of CTD in CTD-PH is different between Europe and Asia. These differences may be important for evaluating the response of treatment. 2. Diagnosis Revised ACR/EULAR classification criteria for SSc in 2013 include PH as one criterion item. In Japan, the MHLW's MCTD Research Committee set revised 2011 diagnostic criteria for PH. In that, actual cut off values for estimated pulmonary artery systolic pressure have been established. The revised criteria emphasize that right heart catheterization is not mandatory for PH diagnosis, but is strongly recommended. Exercise echo cardiography may be useful for decreasing false negative PH case in echo cardiography at rest. 3. Pathophysiology CTD-PH is mainly occurred by pulmonary artery involvement, but also by pulmonary involvement, left heart diseases, and thromboembolism. However not a few CTD-PAH patients have been found pulmonary venous involvement, which might partially explained the poor prognosis of CTD-PH (NCVC, Ogo Dr). 4. Treatment Recently several reports including retrospective and prospective study about the usefulness of the immunosuppressants for treating PH have been published. There seem several efficacious cases in SLE and some of MCTD, but not SSc. These results may indicate the difference of the pathophysiology of PH between SLE and SSc.

Meet the Expert

MTE1

Pathophysiology and Treatment of Osteoarthritis: Up-to-date

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Conflict of interest: None

The molecular backgrounds underlying the osteoarthritis (OA) development are not fully clarified. Using mouse experimental OA models by producing instability in the knee joints surgically, type X collagen (COL10A1) that is characteristic of hypertrophic differentiation of chondrocytes was strongly expressed prior to cartilage degradation. Chondrocyte hypertrophy is known to initiate the endochondral ossification process which is not seen in the joint cartilage under physiological conditions, but is an essential step for skeletal growth. To identify signals to induce endochondral ossification and OA development, we performed a screening of transcription factors using a promoter assay of *COL10A1* gene, and identified hypoxia-inducible factor 2α (HIF2A) as the most potent transactivator, which may represent a therapeutic target for OA in mice and humans. Recent mouse genetic approaches also found that endochondral ossification signals like Runx2, C/EBPβ, carminerin, hedgehog, etc. are involved in the OA development. We have recently found that the RBPjκ-dependent Notch signaling in chondrocytes controls cartilage degradation during OA development, and intra-articular injection of a small compound Notch inhibitor to the mouse knee joints under OA induction prevented cartilage degradation, representing a extracellular and molecular therapeutic target. The endochondral ossification process is likely to cause cartilage degradation at the center of the joint and osteophyte formation at the periphery. At the periphery, vascularity is accessible from the synovium or tendon, which completes endochondral ossification and forms osteophytes, just as it does during skeletal growth. However, in the center, the vascularity is not accessible from the edge, so that it may end up with cartilage degradation without being replaced by bone. Molecules related to the endochondral ossification signals might become therapeutic targets altering the course of this disabling disease.

MTE2

How to Determine Rheumatoid Arthritis Findings

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Conflict of interest: Yes

Rheumatoid arthritis (RA) is evaluated by the presence of pressure pain and swelling. In the ACR core data set, 68 joints and 66 joints for swelling. In the simplified DAS evaluation, pressure pain and swelling are evaluated in 28 joints. **Basics of Joint Findings** Degree of pain varies depending on whether it is spontaneous or exercise pain. Hence, pressure pain is used as an objective assessment method. Basically, the position in each joint and location of the pressure point are arranged, and pressure is applied such that the nail bed of the examinee turns white. Swelling is a more objective evaluation. Joint swelling is initially determined by visual observation, and comparing right and left joints. However, in cases of swelling on both sides, conclusive determination requires manipulation. **Determining findings of individual joints** Upper limb joints are examined with the patient sitting upright. For the mandibular joint, RA can be confirmed by limited mouth opening. Pressure pain of the shoulder joint is difficult to evaluate, so exercise pain such as passive abduction and addiction is used. The elbow joint is examined in a slightly flexed position (approx. 80°). Wrist joint is examined in both hands. MP joints of the fingers are examined in a bent position by pinching with the thumb and index finger, and PIP joints are examined in the extended position. Joints of the lower limbs are examined with the patient in the supine position. For hip joints, swelling findings cannot be obtained, and pressure pain is judged by rotational exercise pain. Pressure pain in knee joints is examined in a lightly flexed position, and swelling is examined in the extended position. For ankle joints, including the subtalar joints, both swelling and pressure pain should be examined. Toe MTP joints are examined from the dorsum and sole of the foot by pinching with both hands or the thumb and index finger. By daily practice, one can become familiar with this method and carry it out quickly.

MTE3

MR Imaging of Rheumatic Diseases

Tamotsu Kamishima
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Conflict of interest: None

MR imaging (MRI) allows assessment of all the structures involved in rheumatoid arthritis (RA). MRI bone marrow edema appears to represent the link between joint inflammation and bone destruction. A recent study demonstrated that high MRI synovitis score predicts radiographic progression in patients in clinical remission/low disease activity. In this session, the practical way of RA image interpretation will be provided according to RAMRIS for RA activity and damage. MR findings of RA involving other synovial spaces such as large joints and bursae will also be covered, because MR images of such anatomical structures may be obtained if there is a specific clinical indication. In addition, MR images of complication of RA (secondary osteoarthritis, tendon rupture, and septic arthritis) and differential diagnosis of RA (ankylosing spondylitis, psoriatic arthritis, SAPHO syndrome, RS3PE syndrome, and spondyloarthropathy) will be demonstrated in this session.

MTE4

Biologics and orthopedic surgery aiming to improve quality of life for those with rheumatoid arthritis

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Conflict of interest: Yes

Rheumatoid arthritis (RA) is an immune-mediated process involving the joints, and is associated with marked functional disability. In recent years, disease-modifying anti-rheumatic drugs (DMARDs) have been used to inhibit or halt the underlying immune process and prevent long-term damage. Moreover, biological DMARDs have increased the number of treatment options. However, sustained RA remission is really uncommon in daily clinical practice. Despite the availability of such aggressive therapies, ongoing progressive destruction of joints occurs in a subgroup of RA patients, who eventually require joint surgery. Therefore, orthopedic procedures, including joint replacement surgeries, are still needed to improve the overall function and quality of life of these patients with RA. We previously investigated whether or not the number of orthopaedic operations, including total joints arthroplasties, had decreased among Japanese outpatients in a single institute-based large observational cohort (IORRA). And, arthroscopic surgeries and synovectomies gradually decreased over the entire period, but arthroplasties gradually increased. The combination of medical treatment and surgical intervention is thought to improve outcomes in patients with long-standing RA and high risk for developing joint destruction. At present there are seven biological DMARDs, and new non-biological DMARDs such as tacrolimus, iguratimod, and tofacitinib can be prescribed in Japan at the present time. Therefore, we are thinking that orthopaedic surgeries should change in response to changes in the drug therapy for RA.

MTE5

Management of liver injuries in rheumatic diseases

Toshihide Mimura
Saitama Medical University

Conflict of interest: Yes

There are several major pathogenic mechanisms causing liver damages experienced in the clinical settings of the rheumatic diseases. Drug-induced liver damage is the most common among them. Methotrexate causes elevation of hepatic transaminase occasionally, which may be recovered by administration of folic acid or its discontinuation. Liver damage is seen in some rheumatic conditions, including systemic lupus erythematosus and adult Still's disease. Liver damage may also be seen in the systemic viral infections, e.g. cytomegalovirus and Epstein-Barr virus. Recently reactivation of hepatitis virus in immunosuppressed patients has received much attention. Reactivation of hepatitis B virus (HBV) in the HBs Ag-negative patients with HBs Ab-positive and/or HBc Ab-positive may occur after treatment of immunosuppression, including rituximab + glucocorticoid, MTX or cyclophosphamide. Covalently closed circular DNA of HBV stays long in hepatic cells without its detection in serum. However, once immunosuppression occurs, the balance between viral proliferation and immunological regulation attenuates and HBV proliferates (HBV reactivation). After finishing the immunosuppression, immunological competency attacks infected liver cells causing hepatitis (de novo HBV hepatitis). Because this type of hepatitis may cause fatal fulminant hepatitis, it is the most important to screen the potentially risky patients before immunosuppression. Prophylactic administration of a nucleotides analogue may be necessary for the patients who show HBs Ab- and/or HBc Ab-positive and HBV DNA quantitatively positive. In this session, the management of liver damages in rheumatic diseases will be discussed with the audience.

MTE6

The evaluation of synovitis with musculoskeletal ultrasound

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Conflict of interest: Yes

Musculoskeletal ultrasound (MSUS) is a sensitive method for the detection of both early inflammatory soft tissue lesions (eg, synovitis, tenosynovitis, and bursitis) and early bone lesions (eg, erosions) in arthritic joint diseases. Accurate assessment of disease activity and joint damage is important for monitoring treatment efficiency and for prediction of the outcome of the disease. On the other hand, it is widely known that MSUS is highly operator dependent. In clinical practice, semiquantitative four-grade system is frequently used, but with lack of definition of each grade among various joint lesions, there are intra- and inter-observer variabilities in the grading of synovitis. It is reported that with the use of an ultrasonographic atlas as reference, these variabilities can improve. In this lecture, I would present images of various degree of synovitis to the audience and try to grade them. I would also like to introduce the pitfalls of the interpretation of MSUS images. It is important to understand the merits and demerits of MSUS and to use MSUS as a complementary tool in clinical practice and research.

MTE7

Treatment for refractory systemic lupus erythematosus (SLE)

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Conflict of interest: None

Most recent studies have reported 5-year survival rates of 90% or more, which would seem to suggest a good prognosis of SLE. However, some Western studies have shown 20-year survival rates of around only 70%. Considering that SLE usually develops in people in their 20s to 40s, these reported survival rates are unsatisfactory. About one-third of the deaths in patients with SLE are attributable to difficult control of SLE itself, while other causes of death include infections, vascular diseases, and malignancies. Treatment with glucocorticoids (GC) is strongly associated with the development of infections and vascular disorders. We therefore consider the following principles as being important for successful treatment to improve the prognosis of SLE: 1) prompt control for acute, fatal pathophysiologic conditions and 2) appropriate dose control for GC therapy. Fatal conditions in patients with refractory SLE include severe lupus nephritis, CNS manifestations, pulmonary alveolar hemorrhage, and pulmonary hypertension. There is, however, a lack of adequate evidence for appropriate treatment of these conditions. In this situation, the essential principles of treatment are 1) Precise understanding of the present illness: Clinicians should try and obtain as much useful information about the patient as possible before starting treatment 2) Selection and use of proper assessment methods: Clinicians should determine appropriate methods to estimate the treatment effects before starting therapy. 3) Selection of the most effective treatment method: Clinicians can provide treatment based on the standard treatment protocol for lupus ne-

phritis, since the protocol is supported by the highest level of evidence. 4) Proper execution of the treatment plan: It is important to optimize treatment by predicting the patient's response to therapy. This strategy would help clinicians individualize the treatment plan, especially for the case of patients who do not respond to standard therapy.

MTE8

Rehabilitation for rheumatoid arthritis (Focus on short-term rehab & education at our hospital)

Masahiko Yasuda[1,2]
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Conflict of interest: None

Biologics have greatly advanced treatment for RA, preventing bone destruction and deformities by controlling synovial inflammation early on. However, even biologics are ineffective in about 30% of cases, making rehabilitation indispensible as an aid to functional remission. Since 1987, our hospital has used early rehab & education to conserve ADL function, prevent joint deformities, and deepen patients' understanding. We explain the content of the program and examine when to start rehab in order to achieve functional remission, based on actual cases. In the previous report, patients with no change in medication showed improvement in ADL/QOL indices of FS (face scale), VAS, and mHAQ after rehab & education. This time, we investigated in more detail with a larger number of cases. We found that about 8% of patients were using biologics when admitted, and this group already had functional remission but showed further improvement with short-term rehab & education. Unlike the remission + low disease activity group, the group with moderate to high activity (DAS28CRP) failed to achieve functional remission although tending to improve. In terms of mHAQ, the group with disease duration < 10 years achieved functional remission, but the group with duration ≥ 10 years did not, although tending to improve. The results suggest that early RA rehab while disease activity is in clinical remission or kept low with medication is an important tool that can lead to the kind of functional remission that is hard to achieve with pharmacotherapy alone. Apart from rehab, we have also admitted many patients whose disease has progressed to the drug-resistant stage or who cannot benefit from biologics because of complications. Comparing cases where rehab precedes induction of biologics with those where it follows, we explain the importance of rehabilitation as a pillar of total management care.

MTE9

Refractory RA patients

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Conflict of interest: Yes

Refractory and challenging patients with rheumatoid arthritis (RA) are divided into the following 2 categories: refractory RA to available therapies, and RA patients with severe comorbidities and/or those with advanced RA. Therefore, we need to make the best use of available agents, and at the same time, to explore new therapeutic targets. The first step for the optimal use of available drugs should be the acknowledgement of the limitation of methotrexate (MTX), an anchor disease-modifying antirheumatic drug (DMARD) in RA treatment. Then, we should consider the choice of agents to be added to MTX in patients showing an inadequate response to MTX, based on the understanding of the significance of combined use of MTX and anti-tumor necrosis factor (TNF) biological agents. High plasma TNF level may be a poor prognostic factor, suggesting an inadequate response to MTX. Thus, neutralization of TNF by biological agents improves the potency of MTX. The dosage of biological agents should be determined by the amount of molecule to be targeted. The reasons for refractoriness include the limitation in the dosing regimens approved by regulatory authorities. On the other hand, pulmonary diseases, chronic kidney diseases and malignancies are among important comorbidities, having an impact on the treatment decision. Therefore, we need to discuss possible therapeutic options for those patients, referring to domestic and international recommendations and guidelines for the management of RA.

MTE10

How to treat with glucocorticoids

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Conflict of interest: None

Glucocorticoids have been used as one of a crucial agent for treatment of rheumatic diseases for more than two decades. Although it is well known that glucocorticoids should be used carefully because of a large number of serious adverse effects, an empirical use of glucocorticoids may be sometimes seen. In this section, scientific and evidence-based treatment with glucocorticoids will be clarified through discussion with attendances. Specifically, 1) variety of glucocorticoids and their characteristics, 2) routes of administration, 3) prevention and treatment of adverse effects, 4) interaction with other agents, 5) pregnancy and lactation, 6) limit of glucocorticoid treatments will be discussed.

MTE11

Nuts and bolts of imaging of chest diseases in patients with RA

Takashi Hajiro
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Conflict of interest: None

Patients with RA are frequently complicated with a wide variety of chest diseases, such as pulmonary infection (e.g. bacteria, tuberculosis, non-tuberculous mycobacterium, Pneumocystis), interstitial lung diseases, bronchiectasis, and drug-induced lung diseases. Accurate diagnosis and proper management for those complications are challenging for not only rheumatologists but also pulmonologists. Respiratory symptoms are non-specific with regard to diagnosis, therefore importance of chest imaging, particularly chest X-ray films, should be emphasized. It is recommended that rheumatologists have basic knowledge of analyzing chest imaging (chest X-ray films and CT scans). In this program, I would like to share nuts and bolts of imaging of chest diseases interactively and present actual chest X-ray films and CT scans commonly seen in patients with RA. Specifically, the audience will be able to learn about comparisons between chest images and anatomical structures, common nomenclature of description (e.g. airbronchogram, silhouette sign, ground glass opacity), systematic view of chest X-ray films and the right time to consult a pulmonologist. I am looking forward to having this interactive program with you.

MTE12

Biological agents and its effects for recent changes of orthopaedic surgery in rheumatoid arthritis

Yuichi Mochida[1], Katsushi Ishii[1], Yuji Yamada[1], Naoto Mitsugi[1], Tomoyuki Saito[2]
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Conflict of interest: Yes

The orthopaedic surgeries for rheumatoid arthritis (RA) are performed for pain relief, restoration of joint destruction, functional recovery, and improvement of quality of life MTX and other DMARDs come to be used widely for RA in Japan for approximately 15 years, additionally, the uses of the biologics are on the increase. As benefits of these changes of medication, the case which indicates the thinning of cortex bone, decreased bone mineral density at medullary bone, significant abnormality of joint alignment, and the giant geode or bone defect are remarkably decreasing. With the recent changes of joint destruction, there are many reports for the change of the number of the surgery of RA. We also realize increased cases of relatively low inflammatory joints with spur formation. On the other hand, the cases of severe destruction with high levels of inflammation are decreasing. This change may lead to differences of surgical technique between hospitals that may influence the

postoperative results and complication rates. Whereas most of patients for RA surgery still have multiple organ complications with relatively long-term duration of disease. These cases are usually inhibited their immune system by updated medical treatment. It is very important to confirm the condition of each patient and we notice small abnormality and prevent complications. In this session, the reported change of the number of the surgery for RA and the recent changes of various joints will be discussed. Then the expected changes of surgical procedure, preoperative preparations, and the actual methods of prevention of perioperative complication in "the biologics era" will be debated.

MTE13

Early diagnosis and treatment of systemic sclerosis

Hironobu Ihn
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Conflict of interest: None

Systemic sclerosis (SSc), the focus of this lecture, is a generalized connective tissue disease that involves sclerotic changes in the skin and sometimes various other organ systems. Clinical outcomes have improved probably due to better management of the complications, but SSc is still considered to be incurable and diffuse cutaneous SSc carries high risk of fatality. In this lecture, I would like to talk about early diagnosis, clinical aspects, and treatment of this disease. I would also like to review recent clinical and basic topics of SSc.

MTE14

Clinical aspects of inflammatory myopathy

Hitoshi Kohsaka
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Conflict of interest: Yes

If the case is typical, diagnosis and treatment of dermatomyositis and polymyositis is not very tough. Therapeutic approach is simply administration of high-dose glucocorticoids. However, rheumatologists, dermatologists and neurologists still do not agree in detailed aspects of the diseases. Globally accepted criteria was set more than 30 years ago. Tanimoto's criteria used for diagnosis for medical expense support by Japanese government is nor widely utilized even in Japan. Open muscle biopsy offers a gold standard for muscle pathologists, but is not performed in many cases. Although administration of high dose glucocorticoids is conventional treatment, its continuation for a month induces steroid myopathy, and following muscle weakness. Exercise seems to be the only method to prevent the steroid myopathy, but sometimes induce re-elevation of muscle enzymes. Immunosuppressants are often used in the cases resistant or dependent on steroids. However, approved in Japan are azathioprine and cyclophosphamide while cyclophosphamide is not used in other countries. The other approved medication is intravenous injection of immunoglobulins, which costs high and exerts temporal effect. No one is certain about the best indicator of the muscle inflammation. Where should we go in this chaotic world? Through active discussion, we aim to clarify 1. How we make correct diagnosis 2. What we should choose for initial treatment 3. How we monitor the disease activity 4. What we should choose after the failure of the first treatment.

MTE15

Management of glucocorticoid-induced osteoporosis

Satoshi Soen
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Conflict of interest: Yes

A participant becomes available for the following issues by participating in this program. 1. You understand epidemiology of glucocorticoid-induced osteoporosis 2. You understand mechanisms of glucocorticoid action 3. You understand effects of glucocorticoids on bone and fracture risk 4. You understand general measures for glucocorticoid-induced osteoporosis 5. You understand assessments of fracture risk in glucocorticoid-induced osteoporosis 6. You understand medication for glucocorticoid-induced osteoporosis

MTE16

Hand deformity and its surgical reconstruction

Hajime Ishikawa
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Conflict of interest: None

In the era of biological therapy, disease activity of RA is controlled well. However, even if it achieves at remission or low disease activity, functional disorder remains in some joints and the patient hopes to get a higher level of ADL and QOL. Manifestation of the disease in the hand has changed in this new era. It is uncommon to see a remarkable synovial proliferation with severe pain, but, in some of the patients, joint deterioration progresses to typical deformity, contracture and/or instability in the hand. Due to uneasiness such as "Even if the appearance of the hand improves after the operation, it becomes hard to use.", "Mobility is lost.", "Deformity might recur." surgical treatment of the rheumatoid hand has been often hesitated. But now, we don't have to worry about them, if the reconstructive surgery was performed under the appropriate indication in a good timing, and if a postoperative hand therapy is performed well. Relief of pain is usually provided by surgical procedures. Many procedures used to be carried out for pain relief, but recently they are carried out for the purpose of correction of deformity and restoration of hand function. Forearm rotation improves after surgery at the distal radioulnar joint. Range of finger motion is increased by flexor tenosynovectomy and tendon reconstruction for its rupture. When arthrodesis is indicated, the patient wears a static splint to perform a simulation before the operation, and tries whether the patient can use a hand well. Grip or pinch power increases after arthrodesis at the thumb IP/MP joints, the finger PIP joints and the wrist joint. Prehension pattern improves after arthroplasty for severe deformity, despite significant increase in hand power is not expected. While recurrence of deformity rarely occurs after the operation due to suppressed local inflammation, secondary arthrosis and tendon rupture due to over use of the hand are felt uneasy.

MTE17

How to use MTX

Naoto Tamura
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Conflict of interest: None

Methotrexate (MTX) has been used for cancer therapy since the 1970s, and low dose intermittent medication of MTX allowed utilizing it for treatment of rheumatoid arthritis (RA) since the latter half of 1970s. In Japan, MTX was approved up to 16 mg /week as a first-line DMARD in Feb 2011, and then, making the best use of MTX has been becoming more and more important. Because the intracellular uptake of MTX is so rapid that it is no use measuring the blood concentration. After the intracellular uptake, MTX is ploylglutaminated (MTX-PGs) at the site of original glutamine, and it is thought that the MTX-PGs are effective to indicate the medicinal action for RA. It takes several weeks from commencement of MTX to achieve the steady concentration of MTX-PGs, suggesting that the dose of MTX must be escalated quickly to obtain the appropriate effect. MTX is contraindicated in women and also in men planning pregnancy, and pregnancy should be avoided at least for 3 months after cessation of MTX. The side effects of MTX is more frequent in patients with renal dysfunction, so that MTX is contraindicated in patients with GFR < 30 ml/min. It is important to give patients previous information that MTX should be skipped in case of having high fever or acute gastroenteritis that possibly induces dehydration. The blood cell counts, liver function and renal function should be monitored. In patients having poor prognostic factors, MTX is stared with 8 mg/week and increased every 2-4 weeks up to 16 mg if it is tolerable. Stomatitis, digestive symptoms, elevation of liver enzymes, and cytopenia may be observed. Vaccination is required to prevent influenza and pneumococcus

infection, and prevention of pneumocystis pneumonia is necessary in the high risk patients. Daily education is important to find such infections earlier. In this seminar, I would like to show the recent evideces of MTX and discuss the case presentations with the participants to deepen the comprehension of MTX treatment.

MTE18

The management of NSAIDs-induced gastrointestinal lesions

Hajime Sano
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Conflict of interest: None

NSAIDs are widely used for the therapy of rheumatic diseases. The action of NSAIDs is exerted by suppresion of COX activity. COX-1 produces PGs for protection of living body, and COX-2 produces PGs for inflammation and carcinogenesis. NSAIDs have a lot of side effects such as gastrointestinal disorders. Almost 60% of RA patients taking NSAIDs for 3 months had gastrointestinal disorders in several studies. The causes of gastric ulcer are mainly *Helocobacter Pylori* and NSAIDs. Recently, *H. Pylori* can be removed by antibiotics. The increase of NSAIDsinduced ulcer as well as a low dose aspirin-induced ulcer become a important problem to overcome. The feature of NSAIDs ulcer is painless, multiple, and an occurrence of pyloric region. NSAIDs ulcer is easy to bleed. The mortality of gastrointestinal bleeding is as same as the number of death by HIV in USA. The risk factors of NSAIDs ulcer are an aged person, past histry of gastric ulcer, steroid, 2-3 kinds of NSAIDs users, anticoagulant, users and combined serious generalized diseases. NSAIDs induce a secretion of gastric acid in stomach. Therapy of NSAIDs ulcer is discontinue of taking NSAIDs. If patients with ulcer can not discontinue NSAIDs, therapy of NSAIDs ulcer by PPI or PG drug are recommended in guidleine for peptic ulcer. The prevention of NSAIDs ulcer by PPI or PG drug is also reported on the clinical trial. There are very few in the rate of ulcer in COX-2 inhibitors. NSAIDs-induced lower intestinnal disorders are paid most attention to now. In thia lecture, I would like to introduce recent evidence of NSAIDs-induced gastrointestinal disorders and the manegement of NSAIDs for the therapy of rheumatic diseases.

MTE19

Orthopaedic surgery for rheumatoid arthritis in the biologic era

Keiichiro Nishida
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Conflict of interest: Yes

The natural course of joint destruction in RA has dramatically changed over the past decade with new treatment strategies and introduction of biologic DMARDs. However, biologic DMARDs are not always effective in all the patients, cannot be applied for patients with complications, side effects or their risk factors. Economic matter is also a big problem for their use. Among patients under control by biologic agents, some patients show continuous inflammation of a specific joint, or other patients might already have joint destructions with irreversible functional impairments. Treatment strategy should include medication, surgery, and rehabilitation in all RA patients in a custom made fashion, and its practice and accumulation of the evidences of outcome would be required. The aims of the surgery are: pain relief and reduce of joint swelling, prevention of further joint destruction, and reconstruction of joint deformity and function. The surgery for RA includes open or arthroscopic synovectomy, joint arthroplasty, arthrodesis, joint replacement and tendon reconstruction. Surgery should be considered when patient had cervical disorder with neurological deficiency, shoulder and elbow surgery in patients with bilateral involvement, hip and knee lesion with walking disability, tendon rupture and entrapment neuropathy. The most appropriate surgical procedure should be selected which could improve the joint function which disturbing the ADL, or cosmetic problem. It is also important to evaluate the medical disease control, complications of other organs, and patient's motivation before and after the surgery.

MTE20

Management of renal disease induced by rheumatic disease

Yoshihiro Arimura
Nephrology and Rheumatology, First department of Internal Medicine, Kyorin University School of Medicine

Conflict of interest: None

Several rheumatic diseases complicate renal disease. These include ANCA-associated vasculitis (AAV), systemic erythematosus (SLE), systemic sclerosis (SSC), mixed connective disease (MCTD), IgA vasculitis (Henoch-Schonlein purpura), Sjogren syndrome (SjS), rheumatoid arthritis (RA) and gout. Of these rheumatic diseases, the most commonly occurring with renal involvement are AAV and SLE. In this meeting, we will discuss the management of AAV with renal involvement (ANCA-associated glomerulonephritis) and lupus nephritis through the presentation of an intractable case. ANCA-associated glomerulonephritis is a rapidly progressive glomerulonephritis (RPGN). Renal histopathology in patients with RPGN reveals necrotizing crescentic glomerulonephritis. Lupus nephritis exhibits several clinical syndromes, such as nephrotic syndrome, chronic glomerulonephritis, acute nephritis and rapidly progressive glomerulonephritis. Renal histopathology in patients with lupus nephritis is classified into six levels ranging from minimal to sclerotic glomerular disease. The renal biopsy findings must be interpreted by the referring rheumatologist in the context of the patient's entire clinical presentation, including the serologic findings. There are several problems in the diagnosis and treatment of these two diseases. Methods of early diagnosis, histological assessment, remission induction therapy, and predictive markers for relapse in these two diseases will be discussed. This meeting will assist rheumatologists to improve their understanding and management of renal disease induced by rheumatic disease, especially ANCA-associated glomerulonephritis and lupus nephritis.

MTE21

Respiratory infectious diseases under immunosuppressive treatments

Naoki Hasegawa
Center for Infectious Diseases and Infection Control, Keio University School of Medicine, Tokyo, Japan

Conflict of interest: Yes

Immunosuppressive treatments, central therapeutic strategies against rheumatoid diseases, is associated with the increased risk of complication of infectious events, while it is not proved that rheumatoid diseases themselves would be directly related to development of infection. Although duration and intensity of each immunosuppressive treatment has related to the possibility of interference with cytokine function, inhibition of the second signal required for T-cell activation, leading to cellular rather than humoral immunity, while combination of them in most cases. In these situations typical clinical symptoms including fever and radiological findings are not necessarily observed, often associated with acute onset and rapid worsening, and delayed resolution of lesions. In this session respiratory infectious diseases complicated in the course of immunosuppressive treatment against collagen vascular diseases will be presented, reviewing causative pathogens in connection with clinical features, mode of development including new infection or reactivation of latent infection, pattern of radiological findings mainly on chest CT images, and diagnostic measures, and treatment. In addition it is increasingly important to manage them from the scope of infection control and prevention, for example in the sight of primary and secondary prophylaxis. Through case presentations we will discuss how to detect and manage pulmonary infectious diseases during immunosuppressive treatment. Although there is no clear monitoring ways regarding in vitro immune functions correlated with development of infection and therapeutic effectiveness. The keys are proper assessment of clinical status of each case, timely radiological evaluation comparing past films, and every efforts to reach microbiological diagnosis with appropriate sampling of respiratory specimens as well as lung tissue, if necessary, using invasive procedures such as bronchoscopy, CT-guided biopsy and open lung biopsy.

MTE22

Rheumatic diseases of the elderly

Koichi Amano
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Conflict of interest: Yes

Rheumatologists may more frequently encounter elderly patients with rheumatic diseases due to longer life expectancy than before. Although vasculitides such as giant cell arteritis and microscopic polyangiitis are very important diseases to be properly diagnosed, I will have a brief talk about 3 main rheumatic diseases in the elderly; osteoarthritis (OA) (especially erosive osteoarthritis = EOA), polymyalgia rheumatic (PMR) and pseudogout. Hand OA/EOA must be the most challenging disease for physician rheumatologists. And it'll be more complicated when RA will develop in the same patient with OA/EOA. I will show some patients with OA complicated with RA and would like to discuss how to understand the diagnosis of such patients. PMR may be the most important rheumatic disease in the elderly. In 1979 the diagnostic criteria for PMR was proposed by Bird et al. (ARD 1979; 38: 434) and has been used for a long time until new criteria by EULAR and ACR was developed in 2012 (Arthritis Rheum 2012; 64: 943). However, differential diagnosis between seronegative RA and PMR is not easy and is still challenging for many rheumatologists (ARD 1991; 50: 619). Recently PET-CT can clarify the pathological lesions of PMR such as ischial tuberosities, greater trochanters and spinous processes. PET-CT could be one of the promising diagnostic tools for PMR (Joint Bone Spine 2013; 171). I'd like to talk about RS3PE in the view of differential diagnosis of RA and /or PMR. Pseudogout is a acute mono-arthritis (mostly affecting knee joint) in the elderly. Among 7 clinical types, acute pseudogouty attack is typical. Sometimes there is a very unusual case with pseudogout such as crowned dens syndrome (Rheumatology 2004; 43:1508).

Workshop

W1-1

Serum cytokine measurement study in patients with rheumatoid arthritis for evaluation of effective treatment by ant-rheumatic agents (SWEET cohort study)

Koji Takasugi[1], Masamitsu Natsumeda[1], Misuzu Yamashita[1], Kayo Ezawa[1], Kazuhiko Ezawa[1], Yoshihisa Nasu[2], Keiichiro Nishida[4], Wataru Yamamoto[3]
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Conflict of interest: None

【Aim of the study】The serum concentration Infliximab (IFX) and anti-infliximab antibody (AIA) have been reported to influence the effectiveness of IFX. We aimed to determine the other background factors that predict the efficacy of IFX dose escalation in patients with rheumatoid arthritis (RA) who showed inadequate response to low-dose IFX.【Methods】Various background factors of RA patients who required IFX dose escalation were included into the independent variable, and univariate and multivariate analysis (logistic regression) were conducted for IFX discontinuation one year after IFX dose escalation.【Results】Presence of AIA before IFX dose escalation did not affected the IFX continuation. Serum level of IL-6 before IFX dose escalation affected the IFX continuation rate one year after IFX dose escalation. ROC analysis revealed that serum concentration of IL-6 over 5.16 pg/ml predicted the IFX discontinuation one year after dose escalation (sensitivity 0.923, specificity 0.625). The one-year continuation rate of the patients with serum concentration of IL-6 over 5.16pg/ml, and below 5.16pg/ml before IFX dose escalation was 90.9%, and 33.3%, respectively.【Conclusion】IL-6 can be a promising predictive factor of the validity and continuity of IFX after IFX dose escalation.

W1-2

Prospective study on the efficacy of etanercept therapy in RA patients with moderate disease activity – ENCOURAGE Study: Results of Period-II (Comparison of the efficacy between etarnercept continuation and discontinuation groups in the 2nd year of treatment) –

Hisashi Yamanaka[1], Shohei Nagaoka[2], Tsuyoshi Kasama[3], Hitomi Haraoka[4], Yuichi Nishioka[5], Yukitaka Ueki[6], Yohei Seto[1], Makoto Nishinarita[7], Naoto Tamura[8], Noriko Kimura[9], Kazuyoshi Saito[10], Tetsuya Tomita[11], Yasushi Nawata[12], Sadahiro Suzuki[13], Yoshiaki Ishigatsubo[14], Yasuhiko Munakata[15], Yuichi Makino[16], Yoshiya Tanaka[10], Tsutomu Takeuchi[9]
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Conflict of interest: Yes

[Objectives] An interim analysis of the Period 2 of the prospective clinical study, ENCOURAGE for early RA patients. [Methods] An inter-

national, multi-center study in 30 institutes (Japan; 28, Korea; 2) to investigate the therapeutic strategy for MTX- resistant RA (n=225) with moderate disease activity and disease duration ≦5 years. A total 99 patients who maintained clinical remissions for ≧6 months with etanercept (ETN) plus MTX were randomly allocated to either ETN continuation (C) or discontinuation (D) arm. The primary endpoint is the remission rate, and analysis was conducted by LOCF. [Results] An interim analysis with 66 patients (C: 35, D: 31, mean age 56.1 years) were conducted. There was no significant difference in baseline disease duration (1.6, D: 2.2Y), DAS28 (1.6, 1.9) and HAQ (0.1, 0.1). The clinical remission rates at both 6/12 months (C: 95.7/82.6%; D: 60.0/50.0%). and functional remission from baseline at 6/12 months (C: 39.1/39.1%; D: 40.0/35.0%) was higher in C than D. % patients who completed the protocol for one year was C; 91.3% and D; 56.5%. [Conclusion] In early RA patients who achieved sustained remission by ETN plus MTX maintained remission by the continuation of ETN and MTX, however, a half of patients who discontinued ETN also maintained clinical remission.

W1-3

Solid cancer risks in patients with rheumatoid arthritis treated with bilogics

Toshikazu Kamada[1], Hiroshi Nakamura[2], Kenji Takahashi[2], Masahito Koiwa[3], Hiroshi Kaneko[4], Kenji Takenouchi[2], Akiko Sato[5], Hidemi Kawaji[5], Shinro Takai[5]
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Conflict of interest: None

[Objective] To determine the risk and characteristics of solid cancer in RA patients receiving biologics. [Method] From our medical records, cancer occurrence and characteristics of tumor were analyzed in 451 cases receiving biologics (infliximab 161, etanercept 157, adalimumab 37, tocilizumab 53, abatacept 38 and golimumab 5) and randomly selected 457 RA patients who were naïve to biologics. [Result] Solid cancers occurred in 11 cases (2.4%) receiving biologics. All of the cases were treated with TNF inhibitors. On the other hand, cancers occurred in 18 biologics naïve patients (3.9%). Frequency, type of cancers, extension did not differ between both groups. [Conclusion] As far as we examined, no carcinogenic risk was found in biologics treatment.

W1-4

Biological agent-associated peripheral neuropathy (BAPN)

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Conflict of interest: Yes

[Objectives] Biological agent-associated peripheral neuropathy (BAPN) is relatively rare, but one of the important drug-related adverse effects. We previously experienced 2 cases with BAPN (infliximab-induced peroneal motor neuropathy and CIDP observed during anti-TNF therapy). In this study we extensively examined the BAPN cases previously reported in the literature during the treatment of RA, psoriasis, and ankylosing spondylitis. **[Results]** In the oversea literature 60 cases with BAPN were found. Among them, demyelinating neuropathies were found in 47 cases, and axonopathies were 8 cases. All reported cases were associated with anti-TNF therapy. Although a good prognosis after cessation of biological agents was reported, around three-quarters of cases with BAPN required immunosuppressive therapies in our survey. The responses to immunosuppressive therapy were variable, and complete remission was around 30%. In our country 9 BAPN cases including our 2 cases were reported, and immunosuppressive therapies were performed in most cases. **[Conclusion]** It is necessary to establish a solid database, such as prospective post-marketing studies, to understand the real risk of BAPN in our country. Also, we should make the guideline for the management of BAPN to improve its outcome.

W1-5

Inhibitory factor for radiographic progression of cervical lesions in patients with rheumatoid arthritis receiving infliximab treatment from Japanese TBCR; Three years of follow-up

Yasuhide Kanayama[1], Toshihisa Kojima[2], Yuji Hirano[3], Yuichiro Yabe[4], Nobunori Takahashi[2], Koji Funahashi[2], Yukiyoshi Oishi[3], Naoki Ishiguro[2]
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Conflict of interest: None

[Objectives] Treatment with Biolosics agents are more clinically effective than the DMARDs that were in use previously, in particular, with their efficacy in suppressing joint destruction having been emphasized. However, most clinical studies on the efficacy of biological agents in suppressing joint destruction in the hands and feet. Therefore we investigated the efficacy and inhibitory factor of IFX for inhibiting the radiographic progression of RA cervical lesions at this time. [Methods] We used IFX treating Japanese patients with active RA. The final study cohort of each 60 patients received continuous IFX treatment for at least 3 year. For evaluation of cervical lesions, ADI, SAC and Ranawat value were measured by plain lateral radiographs in the flexion position, at initiation, 1, 2, and 3year. [Results] In 32 cases that suppress progression of cervical lesions in all three parameters, SAC at initiation was higher level and disease duration at initiation, TSS at initiation, DAS28 at 3 year, average DAS for 3 years and ΔTSS/y wear lower levels (p=0.001, 0.012, 0.041, 0.007, 0.006, <0.001). [Conclusion] IFX treatment can be used to suppress the progression of RA cervical lesions, as well as hand and foot joints lesions.

W1-6

The 3 years results between methotrexate (MTX) monotherapy and adalimumab (ADA) therapy, with particular reference to comprehensive disease remission (CDR) and comprehensive disease control (CDC)

Kazuko Shiozawa[1], Yasushi Tanaka[1], Ryosuke Yoshihara[1], Miki Murata[1], Takashi Yamane[1], Chihiro Tanaka[1], Noriaki Yo[1], Shigeaki Imura[1], Natsuko Nakagawa[1], Kozo Kohyama[1], Yasuhiro Terashima[1], Hironobu Yokoyama[1], Koji Tateishi[1], Shunichi Shiozawa[2]
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Conflict of interest: None

[Objectives] CDR and CDC rates after 3 years treatment with MTX (n=161) or ADA (n=96) were compared. [Methods] RA patients with MTX inadequate response (MTX-IR) initiated ADA and compared with RA patients who started MTX. [Results] DAS28-CRP and mHAQ in the baseline were similar in both groups but grip strength was significantly higher in MTX group than ADA group. Although the baseline values of TSS and yearly progression rates (ΔTSS) were significantly higher in ADA group than those of MTX group (58.6 vs 18.6 and 9.5 vs 7.9, respectively), the significance of ΔTSS were disappeared after one year treatment. Two years later, the structural remission rates (65.1%) in ADA group was much higher than that (41.4 %) of MTX group, as well as after 3 years (73.2% vs 50.4%, p<0.005). Grip strength in ADA group was improved every year, but gradually decreased in MTX group after 1 year. CDR rates at 3 year were much higher in ADA group (43.2%) than MTX group (18.3%) as well as those of CDC (45.9% vs 24.0%, respectively). [Conclusion] It was demonstrated that even in the patients who were managed RA disease for 3 years with MTX alone, grip strength gradually decreased and ΔTSS was more progressed than ADA group and ADA treatment to MTX-IR could achieve higher CDC and CDR rates over 3 years.

W2-1

Optimal rheumatoid arthritis patient selection for biological DMARDs treatment from pharmacoeconomic perspectives based on the Institute of Rheumatology, Rheumatoid Arthritis (IORRA) cohort

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Conflict of interest: Yes

[Objectives] To determine the optimal timing of biologics administration to RA patients. [Methods] A state-transition model-based probabilistic simulation was conducted. RA patients who had been started on either one of four biologics (adalimumab, etanercept, infliximab, or tocilizumab [TCZ]) [Biologics group] or MTX [MTX group] between 2008 and 2011 were extracted from the IORRA (n=421). In the Biologics group, sequences with and without TCZ were also considered. The incremental cost-effective ratios (ICERs) of the Biologics groups against the MTX group were estimated. Scenario sensitivity analyses were done for different backgrounds of the initial population classified by age, disability levels and disease duration. [Results] The ICERs in the Biologics group with or without TCZ were JPY3817971 and JPY4885450, respectively, which were below an assumed threshold in Japan. Scenario sensitivity analyses showed that the most influential factors on the ICER were age and J-HAQ scores. ICER was always lower in biologics sequence with TCZ regardless of patient background. [Conclusion] From pharmacoeconomic perspectives, biologics are cost-effective for RA patients in Japan, and the best population for biologics use is younger RA patients with moderate J-HAQ baseline scores and using TCZ.

W2-2

Investigation of Serological Factors and Disease Activity on Clinical Response by Adalimumab

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Conflict of interest: None

【Objectives】Although it was reported elsewhere that auto-antibodies such as RF and anti-CCP may predict treatment efficacy of anti-TNF biologics, no consensus has been accepted yet. Here, we investigated association of baseline serological markers and disease activity with treatment response by Adalimumab (ADA).【Method】67 patients who started ADA treatment between Sep 2008 and July 2010 were divided in groups by means of RF, anti-CCP, ANA, γ-globulin, MMP-3, and disease activity. Following evaluations were performed: ADA retention, DAS response, DAS remission, and factors predicting ADA treatment efficacy.【Result】Patients with high anti-CCP showed good treatment efficacy and DAS response was significant at 24w. Patients with low RF and anti-CCP found less ΔTSS progression. Patients with low MMP-3 and LDA showed higher DAS remission rate until 52w but DAS response at 104 w was significantly higher in patients with high disease activity. Significant DAS remission rate and good response at 104 w were found in patients with concomitant MTX use as well.【Discussion】Analysis on anti-CCP revealed dissociation between clinical response and structural progression and it is important for patients with high anti-CCP to facilitate "tight control" and concomitant use of MTX.

W2-3

Clinical efficacy of adalimumab treatment on rheumatoid arthritis depends on the dose of methotrexate

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Conflict of interest: Yes

[Objectives] To analyze the efficacy of adalimumab (ADA) in the presence/absence of methotrexate (MTX) and its dose from the extended observation through 48 weeks. [Methods] Enrolled were 55 patients who started ADA from Jul 2008 to Sep 2013, followed for 48 weeks. Pearson's product-moment correlation coefficient was used to assess the correlations between improvement in DAS28-ESR and MTX dose. [Results] Mean durations of illness were 10.5±9.6 years in 47 patients with MTX (mean dose 9.1±2.4 mg/week) and 16.7±14.5 years in 8 patients without MTX. Mean DAS28-ESR at baseline and week 48 were, 4.7±1.2 and 2.9±1.4 in patients with MTX, 4.5±1.0 and 4.3±1.6 in patients without MTX respectively, and 49% and 25% of them achieved clinical remission. In patients receiving MTX at ≧8 mg/week, DAS28-ESR decreased from 4.6±1.2 at baseline to 3.5±1.2, 2.9±1.2, and 2.8±1.4 at week 4, 12, and 48, respectively. Clinical remission was achieved in 53%, and 36% of those receiving MTX at ≧8 mg/week (36 patients) and <8 mg/week (11 patients), respectively. A significant correlation was noted between the improvement in DAS28-ESR and MTX dose. Achievement of low disease activity showed MTX dosage dependency. [Conclusion] Combination with a sufficient dose of MTX enhances the clinical efficacy of ADA.

W2-4

Comprehensive Disease Remission achieved by treatment with Certolizumab Pegol, and factors associated with Certolizumab Pegol Comprehensive Disease Remission, in Rheumatoid Arthritis patients with predominantly High Disease Activity

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Conflict of interest: None

Objective: To evaluate comprehensive disease remission (CDR: DAS28 (ESR)<2.6; HAQ-DI≤0.5; and yearly ΔmTSS≤0.5) rates of certolizumab pegol (CZP) in RA patients (pts) with high disease activity, and to investigate associated factors. Methods: CDR of CZP 200mg and placebo (PBO) groups were evaluated at Wk24 of the two double-blind (DB) trials with and without MTX. CDR for DB CZP 200 mg were evaluated at open label extension (OLE) entry and at OLE Wk52. Factors associated with CDR at OLE Wk52 were analyzed for all DB CZP pts, using several Wk12 clinical response measures. Results: CZP treatment resulted in higher CDR than PBO at Wk24 (with MTX: 13.4% and 0.0%; without MTX: 15.5% and 0.0%). CDR with CZP were comparable between monotherapy and with non-MTX DMARDs (16.7% vs. 14.5%). The CDR rates with CZP increased up to OLE Wk52. The likelihood of CDR at OLE Wk52 could be predicted based on good clinical response at Wk12 (DAS remission or HAQ remission) which could be regarded as the associated factors. Also, the failure of clinical response at Wk12 (HDA or HAQ≥1.0) was predictive of a low probability of achieving CDR at OLE Wk52. Conclusion: Continuous CZP provides long-term CDR either as monotherapy or in combination with DMARDs including MTX, and increases the likelihood of CDR.

W2-5

The economic costs of biologics (BIO) in rheumatoid arthritis (RA) versus improvement in the clinical disease activity index (CDAI)

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Conflict of interest: None

(Purpose) Based on many reports, the effects of all BIO can be considered to be nearly equal. However, the real cost of improvement is unclear. It is economically advantageous that BIO induces low disease activity quickly and controls the disease as BIO are expensive. The cost for treatment with BIO for each patient based on clinical disease activity index (CDAI) was calculated. (Methods) The real cost of BIO for each or 414 patients for six months and one year was calculated -infliximab (IFX), etanercept (ETN), adalimumab (ADA), tocilizumab (TCZ), abatacept (ABT), golimumab (GOL). CDAI was also analyzed and cost calculated of improvement per CDAI level. (Results) The CDAI range at the start of BIO treatment was 32~18. ETN showed the most improvement. The least expensive BIO were ABT for six months, ADA for a year. We analyzed those data to compare the moderate disease activity and high disease activity groups as determined by CDAI. In the MDA, the least expensive BIO is TCZ for six months and ETN for one year, in the HDA group it was TCZ at both six months and one year. (Conclusion) Cost of treatment with BIO is affected by frequency, quantity, body weight and cost of BIO, but it is important to calculate the true cost BIO treatment by improvement of RA disease activity.

W2-6

Stratified analysis of the treatment effect of golimumab based on disease activity at baseline

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Conflict of interest: None

[Objectives] Golimumab (GLM)-treated patients in our hospital were stratified into a high disease activity group (H group) and a moderate to low disease activity group (M-L group), and the treatment effect was analyzed. [Methods] DAS28-CRP scores were analyzed over time after the treatment with GLM for 12 months in 25 patients in the H group (DAS28-CRP>4.1) and 22 in the M-L group (DAS28-CRP≤4.1). The changes over time in DAS28 of the H group were also analyzed with respect to use and non-use of concomitant MTX. [Results] The mean ages of the patients in the H and the M-L groups were 68.7 and 56.4, respectively. The mean disease durations of the H was 23.3 years, in the M-L groups 14.6 years. The mean DAS28-CRP scores of the H and the M-L groups were improved from 5.50 to 3.55 and from 3.38 to 2.61, respectively. The mean DAS28-CRP scores of the concomitant MTX and the GLM-alone subgroups in the H group were improved from 5.05 to 4.20 and from 5.91 to 3.22, respectively. The mean dose of concomitant MTX was 7.69 mg/week. [Conclusion] The DAS28 scores were improved in both the H and M-L groups. The magnitude of improvement was especially large in the H group regardless of the use of MTX.

W3-1

Tocilizumab induced acquired Factor XIII deficiency in patients with rheumatoid arthritis

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Conflict of interest: None

[Objectives] Factor XIII is one of the twelve coagulation factors and also known as a fibrin-stabilizing factor. In 2012, we encountered a male RA patient with hemorrhagic factor XIII deficiency who had been treated with tocilizumab for two years. There are few reports regarding the relationship between tocilizumab and factor XIII. [Methods] We measured the factor XIII levels in the plasma of 41 RA patients (10 patients treated without biologics, 31 patients treated with biologics (15 patients treated with TNF inhibitors, and 16 patients treated with tocilizumab)) and 19 healthy controls. [Results] The tocilizumab group exhibited lower levels than the other three groups according to the Steel-Dwass test ($P<0.01$). Furthermore, the plasma factor XIII concentrations in RA patients with tocilizumab were lower than in the healthy controls ($P=0.049$). According to the multiple regression analysis, the treatment with tocilizumab is an independent risk factor for plasma factor XIII reduction in RA patients ($P<0.001$). [Conclusion] The mechanisms underlying the reduced factor XIII activity observed in RA patients treated with tocilizumab may result from the quantitative reduction in the plasma. These data imply that IL-6 plays an important role in maintaining the factor XIII activity level.

W3-2

Effectiveness of tocilizumab (TCZ) as the first biologics (Bio) -comparison by the induction periods-

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Conflict of interest: Yes

[Objectives] To examine the clinical effect of TCZ as the first Bio. [Methods] The subjects were 36 cases who received TCZ as the first Bio and were observed for 24 weeks. They were divided into 2 groups ((group 1: introduced from May, 2008 to March, 2010) and (group 2: from Apr, 2010 to Dec, 2012)). DAS28-ESR, Boolean remission, TJC, SJC, ptVAS, ESR, CRP, RF, MMP-3, survival rate and characteristic of dropout patients were evaluated. [Results] Group 1 consisted of 25 and group 2 consisted of 11 cases. The average duration of RA in group 1 was significantly longer (18.5±12.0 vs 8.4±8.6 years). The average dose of methotrexate was significantly higher in group 2 (2.2±3.2 vs 5.5±4.8 mg/W). The Stage was significantly higher in group 1. The DAS28-ESR was significantly higher in group 2 (4.71±1.19 vs 5.66±0.68). Group 1 had more complications. Boolean remission rates of group 1 and 2 were 20 and 30%, respectively. Each parameter was comparable at 24 weeks although group 2 had high disease activity (HDA) at the introduction of TCZ. The survival rates of group 1 and 2 were 75.0 and 87.5%, respectively. There were many dropout patients with amyloidosis in group 1. [Conclusion] TCZ should be used for patients who have HDA, short duration of disease and few complications as a first Bio.

W3-3

Study for tapering methotrexate (MTX) first for rheumatoid arthritis (RA) patients suffering in good control treated with tocilizumab (TCZ) and MTX

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Conflict of interest: None

[Objectives] Study for tapering MTX for RA patientstreated with

TCZ and MTX. [Methods] 135cases treated with TCZ and MTX, and enrolled. 6months' administration, we divided into 4groups, Quit MTX, Reduce MTX, Maintain MTX, and Increase MTX. We evaluated disease activity by DAS28ESR, before introduction, 6 months after, and 12 months after. [Results] 120 cases were cleared annual MTX administration. For 23cases, Group Quit, at first, average MTX dose was 6.4mg/week. For 31cases, Group Reduce, average MTX dose was 8.6mg at first, and 5.8mg at 6 months. For 59cases, Group Maintain, average MTX dose was 7.8mg/week. For 7cases, Group Increase, average MTX dose was 6.3mg at first, and 8.6mg at 6 months. Average DAS28ESR of Group Quit was 4.9 at first, 2.8 at 6 months after, 2.6 at 12months after. Average DAS28ESR of Group Reduce was 5.1 at first, 2.7 at 6 months after, 2.6 at 12months after. DAS28ESR of Group Maintain was 5.9 at first, 2.9 at 6 months after, 2.7 at 12months after. Average DAS28ESR of Group Increase was 6.0 at first, 2.7 at 6 months after, 2.8 at 12months after. [Conclusion] We can say, RA treated with MTX and TCZ well, can reduce MTX first and also quit MTX first, and can control the activity of RA patients with TCZ and MTX reduction.

W3-4

Interleukin-6 blockade reduces circulating N-terminal pro-brain natriuretic peptide levels in patients with active rheumatoid arthritis

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Conflict of interest: None

[Objectives] Individuals with rheumatoid arthritis (RA) have a 1.5–2.0 fold higher risk of developing congestive heart failure than the general population. Small increases in NT-proBNP level are predictive of left ventricular dysfunction. Data on the effects of IL6 blocking agents on NT-proBNP levels in active RA patients (pts) are limited, but may be informative. [Methods] Sixty consecutive RA pts (mean age, 57 ± 10 years) with active disease without a clinical diagnosis of cardiovascular disease were enrolled. The RA pts received anti-IL6 antagonist tocilizumab (TCZ) once a month after 24 wk. NT-proBNP levels were measured at baseline and at 24 wk. We examined the association of NT-proBNP with RA disease activity and severity of outcomes. [Results] NT-proBNP levels decreased significantly after 24 wk of TCZ treatment (median NT-proBNP level, 142.0 pg/mL vs. 97.5 pg/mL, $p = 0.004$). Changes in NT-proBNP levels were associated with changes in the DAS28 ($r = 0.27$, $p = 0.03$). On multivariable analysis, changes in DAS28 were independently associated with changes in NT-proBNP levels. [Conclusion] These results show that TCZ decreases NT-proBNP levels by approximately 32% in patients with RA without cardiac symptoms. This suggests no treatment-induced deterioration in cardiac function.

W3-5

Tocilizumab significantly reduces serum oxidative stress compared with other biologic agents

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Conflict of interest: Yes

[Objectives] Recent studies have pointed out relationship between rheumatoid arthritis (RA) and oxidative stress. We also showed that serum reactive oxygen metabolities (ROM) were associated with CRP in patients with RA. It was shown that tocilizumab (TCZ) dramatically reduced serum ROM revels, but no reports have shown comparison between TCZ and other biologics on serum ROM levels. [Methods] Twenty-seven biologics-naïve patients were included in this study. Patients were divided into two groups; tocilizumab-group (Group T: 12 cases, mean age: 64.9 y) and other biologics-group (Group O: 15 cases, mean age: 54.2 y). Serum ROM, CRP, MMP3 levels, DAS28-ESR, CDAI, and HAQ-DI were investigated at the initiation of biologics, 12 and 24 weeks. [Results] There are no significant factors between groups at the baseline. At 12 weeks, the median ROM level was 263 U.Carr in group T and 359 U.Carr in group O, with a significant difference ($P<0.05$). CRP was significantly low in group T ($P<0.01$). At 24 weeks, the median ROM level was 282 U.Carr in group T and 342 U.Carr in group O ($P = 0.078$). CRP was significantly low in group T ($P = 0.01$). [Conclusion] TCZ significantly reduces serum oxidative stress compared with other biologics, which may lead to improvement of vital prognosis for RA patients.

W3-6

ADAMTS5 is a biomarker for the efficacy prediction of tocilizumab in rheumatoid arthritis

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Conflict of interest: Yes

[Objectives] In this study, we investigated whether the efficacy of tocilizumab (TCZ) can be predicted by the baseline blood a disintegrin and metalloproteinase with thrombospondin motifs 5 (ADAMTS5) mRNA level because recently IL-6 has been reported to suppress ADAMTS5 expression. [Methods] Sixty randomly selected active RA patients were treated with TCZ. Peripheral blood samples were collected at baseline and ADAMTS5 and IL-6 mRNA was quantified using real-time PCR (BiologicMate®). [Results] Baseline ADAMTS5 mRNA levels in the responder (2.87 ± 2.35 Index) was significantly ($p<0.05$) higher than that in the non-responder (1.53 ± 0.77 Index) at 12 wks' treatment with TCZ. DAS28 at 12 wks was significantly ($p<0.05$) lower in the High-ADAMTS5 (≥1.70 Index) group than in the Low-ADAMTS5 group. The accuracy, sensitivity, specificity, PPV, and NPV of the baseline High-ADAMTS5 (≥1.7 Index) for predicting the clinical remission at 12 wks with TCZ was 76.0%, 95.3%, 49.2%, 45.9%, and 94.9%, respectively. Interestingly, we observed negative correlation between baseline IL-6 and ADAMTS5 mRNA expression. [Conclusion] The baseline ADAMTS5 mRNA level, which might be related to baseline IL-6, is a candidate biomarker for prediction of the response to TCZ in RA patients.

W4-1

Predictive factors for remission in treatment with tocilizumab: results from observational cohort study using Tsurumai Biologics Communication Registry (TBCR)

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Conflict of interest: Yes

[Objectives] To explore predictive factors for remission in treatment with tocilizumab using Tsurumai Biologics Communication Registry (TBCR). [Methods] A total of 240 RA patients who received TCZ were selected from TBCR, in which 2316 cases were registered up to 2012. Predictive baseline factors for DAS28-ESR remission at 52 weeks were determined by multivariable analysis. [Results] In patients with high disease activity (HDA; DAS28-ESR>5.1), remission rate was 31 %. Concomitant MTX therapy and DAS28 (/-1 point) significantly impacted achievement of remission [OR 2.63 (1.16-6.29), 2.64 (95% CI: 1.53-4.86), respectively] while previous biologics use was not, for remission. In patients with moderate/low disease activity (M/L DA), remission rate was 58%. There was no significant predictive factor. The patients with M/L DA who did not achieved remission had no significant improving of swollen, and tender joints counts, and patients general assessment. [Conclusion] MTX could have important role on control of high disease activity during tocilizumab treatment. In patients with M/L DA, treatment to local joint factors might be considered as well as systemic therapy.

W4-2

Maintenance of Radiographic Remission in Rheumatoid Arthritis Following 3 years Treatment with tocilizumab (TCZ)

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Conflict of interest: None

Objective: RA patients treated for more than three years with TCZ were examined to assess the duration of maintenance and of radiographic remission by ultrasound (US) method. Method: Sixty-five patients with RA on TCZ were studied. Imaging of synovitis were semi-quantitatively evaluated by a 4-Grade scale based on the EULAR criteria ultrasound (Grade 0: radiographic remission). Until disappearance of synovitis US evaluation was performed every visit of TCZ treatment, after that evaluation was performed every 6 month. Results: Disease activity after 3 years treatment was significantly lowered in each scores used, viz. DAS28 (ESR) 5.23→2.38, CDAI 25.8→7.4, mHAQ 0.88→0.56 (P<0.05). Treatment continuation rate in 3 years was 80%. The US assessment at baseline and after 3 years for the 284 joints showed as follows: Grade 0: 26%→76%, Grade I: 36%→19%, Grade II: 20%→8%, with complete disappearance of Grade III joints (P<0.05). One hundred ninety-nine joints were achieved remission, of which 86 joints (43.2%) were maintained remission for more than 24 weeks. Conclusion: In long term treatment of RA with TCZ, maintenance of radiographic remission by US assessment were possible in spite of US grading difference at the initiation and also possible to keep for long term period.

W4-3

Long-term data on 225 cases on tocilizumab in 6 associated hospitals of Juntendo University School of Medicine

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Conflict of interest: None

[Purpose] Five years have elapsed since tocilizumab was approved in Japan. However, there is little report on the long term results. We have examined its efficacy and safety in actual clinical practices. [Method] We have used TCZ with 225 rheumatoid arthritis (RA) patients. Background of the patients, adverse events, efficacy, continuation ratio have been evaluated retrospectively. As an assessment of activity, DAS28-ESR (4), CDAI, and mHAQ have been evaluated every six months. [Result] For the background of the patients, 60% has a history of use of biological product, an average DAS28-ESR (4) was 5.2. Remission ratio of DAS28-ESR (4) after one year of administration showed 57.2%. Even that of after four years of administration has been maintained at a high level of 50.0%. Continuation ratio at the time of 4th year was as high as 75.3%. There were many cases observed where reduction of MTX / PSL has been discontinued after starting use of TCZ. There are 11 cases of active discontinuations. The 10 patients who achieved DAS remission have maintained the state even 6 months later. Side effects on the entire patients in this study was 21%. [Conclusion] Our study findings suggest that TCZ is a safety agent with high remission and continuation ratio, regardless of diverse patient background.

W4-4

Correlation between efficacy of tocilizumab and levels of oxidative stress markers in patients with rheumatoid arthritis: an interim analysis

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Conflict of interest: None

[Objectives] Enhanced risk of atherosclerotic cardiovascular (CV) disease is a key feature of rheumatoid arthritis (RA). Oxidative stress is deeply associated with atherosclerosis. In this study we have studied the correlation between efficacy of tocilizumab (TCZ) and levels of oxidative stress markers in RA patients. [Methods] EPatients treated with TCZ were prospectively studied with informed consent. Efficacy of TCZ and levels of 8-OHdG and 8-iso-PGF2a in urine were evaluated at baseline, 6 and 12-months. [Results] ITwelve out of 30 patients with RA (mean age 63.1 years; mean disease duration 8.2 years; first biologic 83%; concomitant MTX 58%) were studied at 6 months as an interim analysis. Levels of 8-OHdG and 8-iso-PGF2a in urine were decreased (at baseline, 14.6 ng/mg Cr and 363.3 pg/mg Cr; at 6 months, 11.0 ng/mg Cr and 343.1 pg/mg Cr). DAS28 (ESR) was decreased from 5.54 to 2.38. The rate of DAS28 (ESR) and Boolean remission was 67% and 33%, respectively. [Conclusion] There was a trend that efficacy of TCZ correlated with reduced levels of oxidative stress markers in RA patients. This trend was noted in patients treated with TCZ as the first biologic drug. Whether these findings are associated with the rate of future CV events remains to be established.

W4-5

The efficacy and safety of tocilizumab in rheumatoid arthritis with interstitial lung disease

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Conflict of interest: None

[Objectives] To evaluate the efficacy and safety of tocilizumab in rheumatoid arthritis with interstitial lung disease. [Methods] We analyzed the patients with rheumatoid arthritis and interstitial lung disease who was administered tocilizumab in our hospital from November 2008 to July 2013. [Results] The mean age, disease duration of RA and DAS28-CRP was 67 years, 7.86 years and 4.56. 4 patients had previously been diagnosed with interstitial lung disease and another 18 was found to have lung abnormalities like interstitial pneumonia in chest CT. After 6 months, 11 patients achieved DAS28CRP remission (< 2.3). 2 patients discontinued tocilizumab in 6 months without efficacy, and 3 with adverse events, which were not associated with lung disease. Among 18 patients who continued tocilizumab over 6 months, one patient ceased with adverse event until November 2013. During the mean observation period of 21 months, 2 patients required hospitalization for infection and continued tocilizumab after improvement. No acute exacerbation of interstitial lung disease occurred in the duration. [Conclusion] Tocilizumab was effective and well tolerated in patients with rheumatoid arthritis and interstitial lung disease.

W4-6

Evaluation of the remission-keeping factors after withdrawal of tocilizumab in RA patients

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Conflict of interest: None

[Objectives] We discontinued tocilizumab (TCZ) for the rheumatoid arthritis (RA) patients who had clinical remission by TCZ. Furthermore, we performed a subsequent evaluation and examined the factor which had an influence on the withdrawal maintenance. [Methods] We conducted a retrospective study in RA which discontinued TCZ. Patients with DAS28-ESR >3.2 twice consecutively who resumed TCZ were considered to have relapsed. [Results] The case that withdrawal was able to maintain was 27/42 case (64.3%), 10/18 case (55.6%) at 24, 52 weeks, respectively. As a result of univariate analysis, a withdrawal maintenance percentage was significantly high as the factor which had an influence on the withdrawal maintenance in stage I+II group, the tacrolimus combination group. We showed the tendency that a withdrawal maintenance rate was high in the MTX non-combination group. [Conclusion] We could maintain remission in case of stage I+II even if we discontinued TCZ. Further examination about combination DMARDs was necessary.

W5-1

Characteristics of antiphospholipid-associated nephropathy in patients with lupus nephritis

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Conflict of interest: None

[Objective] To clarify the characteristics of antiphospholipid-associated nephropathy (APLN) in patients with lupus nephritis (LN). [Methods] Patients with LN proven by renal biopsy from January, 2000 to July, 2013 were included. APLN was diagnosed when both antiphospholipid antibodies (aPL) and at least one of the pathological features were present: thrombotic microangiopathy, fibrous intimal hyperplasia, fibrocellular arterial occlusion, focal cortical atrophy or tubular thyroidization (J Thromb Haemost 2006). Patients with antiphospholipid syndrome were excluded. Clinical features of APLN patients were retrospectively analyzed. [Results] 57 patients were recruited in this study. The median age and mean disease duration was 33 years old and 5.1 years, respectively. Eleven patients (19.3%) were diagnosed as APLN and 6 as APLN-like disease defined as presence of pathological findings without aPL. Patients with APLN had higher frequency of hypertension ($p<0.001$) and developing thrombosis ($p=0.024$) during follow-up period than patients without APLN. In aPL positive patients, the prevalence of hypertension and thrombosis was higher in patients with APLN than patients without. [Conclusion] APLN is found in one-fifth of patients with LN and associated with hypertension and development of thrombosis.

W5-2

Thrombocytopenia in primary antiphospholipid syndrome is related to thrombotic risk

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Conflict of interest: None

[Objectives] To clarify the association between thrombocytopenia and thrombosis in primary antiphospholipid syndrome (PAPS). [Methods] This study comprised of 60 consecutive PAPS patients who visited the Rheumatology clinic at Hokkaido University Hospital from January 2001 to November 2013. 70 patients with autoimmune diseases other than systemic lupus erythematosus (SLE) and APS were included as a control group. The occurrence of thrombosis and laboratory manifestations were retrospectively analyzed. [Results] PAPS patients had high frequency of thrombocytopenia compared with the control group (19/60 vs. 4/73, $p<0.001$). In the PAPS group, patients with thrombocytopenia (PAPS+Th) showed a high antiphospholipid antibody (aPL)-score which is a risk marker of thrombosis (39[29-43.5] vs. 20[4-36], $p=0.009$), and high frequency of arterial thrombosis (12/19 vs. 14/41, $p=0.021$) compared with patients without thrombocytopenia. Serum complement levels were lower in the PAPS+Th, but titers of anti-DNA antibody, anti-Sm antibody and rate of developing SLE during the observation period were similar between the two groups. [Conclusion] Patients with PAPS and thrombocytopenia had high frequency of arterial thrombosis and high aPL-Scores indicating the importance of anti-thrombotic therapies.

W5-3

Risk factors for mixed connective tissue disease (MCTD) and systemic lupus erythematosus (SLE)

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Conflict of interest: None

[Objectives] To evalutae risk factors for MCTD and SLE [Methods] Two case control studies were conducted to evaluate risk factors for MCTD and SLE. Cases were 48 MCTD female patients and 54 SLE female pateints. Controls were182 female patients who visited the clinics of gneral medicine. [Results] Former and current smokers (vs. never smokers, OR=2.20), and bread (once/day or more, OR=1.93) showed the increased age-adjusted risk for MCTD and green tea (7-9 cups/day or more, OR=0.26) tended to reduce the risk. On the other hand, fomer and current smokers (OR=2.13), drinking (1-3/week or more, OR=2.03), and walking (30 min/day or more, OR=2.15) increased the age-adjusted risk of SLE. Even after controlling age, smoking and drinking, bread increased the risk of MCTD and walking increased the risk of SLE [Conclusion] The present study suggests that smoking may increase the risk of both MCTD and SLE, and also suggests that traditional dietary habits (green tea) may dreduce the risk of MCTD while Westernized dietary habits (bread) may increase the risk. On the other hand, walking may increase the risk of SLE due to the exposure of sunlight. This work was partly suppported by a Grant-in-Aid for Scientific Research on Intractable Diseases from the Japanese Ministry of Health, Labour and Welfare.

W5-4

A case of microangiopathic antiphospholipid-associated syndrome, also classifiable as catastrophic antiphospholipid syndrome, presenting with heart failure without evidence of massive myocardial ischemia

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Conflict of interest: None

A 32-year-old woman with antiphospholipid syndrome was admitted to our hospital because of progressive dyspnea and disturbance of skilled movements of the limbs 18 days before admission. She had prior history of thrombotic microangiopathy in her fifth pregnancy. High-dose corticosteroids and intraveneous immunoglobulin and immunoadsorption resulted in poor improvement and fetal death. Emerging renal dysfunction,

marked hypertension (200/130 mmHg) with severe thrombocytopenia (28,000/μL), acute-stage multiple small cerebral infarctions, a platelet-rich microthrombus in the superficial dermis, undetectable haptoglobin, normal D-dimer and TAT led us to the diagnosis of microangiopathic antiphospholipid-associated syndrome (MAPS). Echocardiography showed severe diffuse hypokinesis but tests for cardiac enzymes had remained normal. Large vessel occlusion could not be confirmed. ^{123}I-BMIPP scintigraphy showed normal myocardial uptake of radioisotope. Plasma exchange (PE) produced clinical efficacy and additional 20 mg/day of prednisolone improved the disease and permitted her to be withdrawn from PE therapy. We think that heart failure in this patient occurred due to MAPS. As far as we know, this is the first case report of MAPS presenting with heart failure.

W5-5

Pathological analysis of the membranous nephropathy in 8 cases with anti-U1-RNP antibody

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Conflict of interest: None

[Objectives] To determine the specific clinical and pathological features of membranous nephropathy in patients with anti U1-RNP antibody. [Methods] We analyzed the pathological features (light microscopy, immunofluorescences, electron microscopy) in anti-U1-RNP antibody-positive 8 patients (female 6, male 2) of biopsy proven membranous nephropathy. Clinically, the patients indicated low titer of anti-dsDNA antibody, normal range of complements, and were negative for anti-Sm antibody. [Results] In light microscopy, all patients demonstrated bubbling appearance and spike formation in glomerular basement membrane (GBM) and 37 % of them showed mesangial proliferation. Immunofluorescence revealed granular IgG deposit along GBM (subclass G1 60%, G2 60%, G3 60%, G4 50 %). C1q was negative in 40 % of them. Electron microscopy indicated pure subepithelial dense deposits in 5/8 cases, and other cases showed mesangial + subepithelial deposits. [Conclusion] Our data suggest the existence of U1-RNP specifically related membranous nephropathy that differs from classical pathway related lupus nephritis

W5-6

Heart Rate Variability Analysis for Autonomic Nerve System Function in Patients with Mixed Connective Tissue Disease

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Conflict of interest: Yes

[Objectives] To evaluate cardio-pulmonary autonomic nerve system function in MCTD, SSC, and SLE patients who sometimes have Raynaud's phenomenon, we analyzed heart rate variability (HRV) using frequency domain analysis method. [Methods] Fifteen HRV data series were obtained from 9 MCTD, 3 SSC, 3 SLE patients by 24 hours Holter monitor. All patients have Raynaud's phenomenon. We excluded HRV data series form patients with heart disease and pulmonary hypertension. We analyzed two parameters, spectrum of high frequency (HF) representing parasympathetic nerve system (PSNsys) activity and ratio of power spectrum of low frequency and high frequency (LF/HF) representing sympathetic nerve system (SNsys) activity, using generalized liner mixed model. [Results] There was no significant difference of PSNsys activity in these connective tissue diseases (CTD). Meanwhile SNsys activity was significantly higher in patients with SSC, MCTD, and SLE in order. [Conclusion] We demonstrated that imbalance of autonomic nerve system activity was different in these CTD patients complicated with Raynaud's phenomenon.

W6-1

Influence of sleep apnea syndrome on sleep quality in RA

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Conflict of interest: None

【background】RA patients are easy to be complicated with sleep apnea syndrome (SAS). Little is known about the influence that SAS gives on sleep quality in RA patients.【object】To investigate relationship between SAS and sleep quality in RA.【method】We examined 42 RA patients (9 men and 33 women), 70.3 ± 8.9 years of age. SAS was assessed by portable SAS monitor. In 24 patients of them, objective sleep quality was assessed by single-channel EEG.【result】Apnea hypopnea index (AHI) levels were 12.3/h. Approximately 70% of them had a diagnosis of SAS (AHI≧5). By Spearman Rank correlation, AHI was correlated positively with age (p = 0.0021) but not BMI. By single-channel EEG, time in bed was 435 min, total sleep time was 267 min, sleep latency was 57 min, and wake time after onset was 106 min in 24 RA patients. AHI showed a correlative negative tendency with sleep latency (p=0.0683) and positive correlation with wake time after onset (p=0.0167).【conclusion】Almost of RA patients had already complicated with SAS, regardless of the degree of obesity. It was suggested that SAS might be intimately associated with decline of sleep quality in RA.

W6-2

Sleep in RA

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Conflict of interest: None

【background】RA patients are suffering from body pain and mental stress. Both of pain and stress could be the risk factors of sleep disorder.【object】To investigate sleeping situation in RA patients.【method】We examined 92 RA patients (20 men and 72 women), 67.6 ± 12.7 years of age. In all patients, Sleep-related QOL and Health-related QOL were assessed by Pittsburgh Sleep Quality Index (PSQI) and SF-36, respectively. In 24 patients of them, objective sleep quality was assessed by single-channel EEG.【result】PSQI levels were 8.6 ± 4.4. Approximately 76% of them had a diagnosis of sleep disorder (PSQI ≧5.5). By Spearman Rank correlation, PSQI was correlated negatively with body pain of subscale in SF-36 (p = 0.0043). But, PSQI was correlated negatively with mental components (p = 0.0275) but not with physical components (p =0.0605) in two summary scales of SF-36. Total sleep time was 267 min by single-channel EEG, though they answered in questionnaires of PSQI that total sleep time was 390 min in 24 RA patients.【conclusion】It was suggested that body pain and mental condition might be intimately associated with decline of sleep quality in questionnaires in RA. Furthermore, actual total sleep time assessed by EEG was extremely short more than RA patients considered.

W6-3

Characteristic of Deep Venous Thrombosis (DVT) in patients with autoimmune disorders

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Conflict of interest: None

[Objectives] We examined clinical features of patients with autoimmune disorders who developed deep venous thrombosis (DVT) after admission. [Methods] Twenty two hospitalized patients with autoimmune disorders diagnosed with DVT by ultrasonography in our division from April 2007 to July 2013 were assessed. [Results] Out of 22 DVT patients, 9 were male, 13 were female. The mean age was 74. The major underly-

ing autoimmune disorders were RA (10 patients) and microscopic polyangiitis (3 patients). Regarding risk factors of DVT previously reported in other diseases, BMI≧25 and immobilization (bed rest) were shown in 2 patients (9.1%), in 9 patients (22.7%), respectively, and 21 patients (95%) received glucocorticoids during their hospitalization. Prednisolone-equivalent cumulative dose from admission was 100mg or more in 15 patients (68%), and was less than 100mg in 7 patients (31.8%). Higher prevalence of acute infection (5 (71%) vs. 2 (13%), p=0.014) and higher CRP level (mean 9.36mg/dl vs. 1.82mg/dl, p<0.002) were observed in less glucocorticoids users as compared to more glucocorticoids users. [Conclusion] DVT occurred even in the patients with low cumulative glucocorticoids dose who had characteristics of comorbidity of acute infection or high level of CRP.

W6-4

The present situation of elderly patients with rheumatoid arthritis

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Conflict of interest: None

【Objectives】We investigated the present situation of the elderly patients with rheumatoid arthritis (RA).【Method】RA patients who are visiting a hospital for treatment in our department, 75 years or older. We investigated a contraction of a disease period, disease activity score (DAS-28 CRP), concurrent disease and cooperation with other medicine.【Results】RA patients 75 years or older were 17 men, 41 women, 58 people in total. The average age was 79.7 years old, and the most advanced age was 89 years old. Seven patients were administrated biologics, 42 patients were given conventional DMARDs. The administration of methotrexate were only 16 cases (27.6%), and prednisolone were 33 cases (56.9%). DAS-28 CRP of biologics cases was 2.24 whereas non biologics cases was 2.94. Most cases had other disease. 15 cases are given RA treatment in cooperation with a medical practitioner. Ten cases received medication from internal medicine, and the case that we evaluated joint symptom and X-ray, gave surgical treatment.【Conclusion】As for the elderly RA patients, a therapeutic medications are often limited for various reasons. It was suggested the possibility that moderate disease activity was persisted in non biologics cases in particular and troublesome in the super-aging society.

W6-5

A study of efficacy and safety of biological DMARDs in elderly RA patients

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Conflict of interest: None

[Objectives] We attempt to clarify the efficacy and safety of biological DMARDs in elderly rheumatoid arthritis (RA) patients. [Methods] The elderly RA patients were picked up from inpatient and outpatient database of our hospital from the duration of 2011 Jan to 2013 Aug. Elderly RA patients treated with biological DMARDs were compared from non-elderly RA patents in the present situation, a treatment regimen, complications, convalescence and examined an effect and safety of their treatment. [Results] Elderly RA cases were three-hundred and seven people, and 42 cases were treated with biological DMARDs. Disease activity evaluated with SDAI was sufficiently suppressed as well as non-elderly cases. There were some cases of infection such as pneumonia, but the number of complication was not significantly higher in case of elderly cases. Some medication bias by glucocorticoid and methotrxate was considered to affect the some influence on results. [Conclusion] Further study was needed to clarify the adequate use methods in elderly RA patients.

W6-6

Investigation on the treatment response of elderly-onset rheumatoid arthritis

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Conflict of interest: None

[Objectives] It has been reported that RA patients with onset at an age of 60 years old or older are increasing along with the development of an aging society. We investigated the characteristics of elderly-onset rheumatoid arthritis (EORA). [Methods] The subjects consisted of 24 cases (7 male cases, average age: 74.7 years old) of patients aged 60 years old or older who consulted our department within the two years and commenced treatment. An investigation was carried out regarding therapeutic drugs, disease activity, treatment response, and adverse events. [Results] A total of 69% cases were positive for anti-CCP antibodies, with an average DAS28 upon initial consultation of 4.53±1.33. The therapeutic drug used on commencing treatment was PSL and bucillamine in many cases, with MTX initiated for some cases with poor prognosis factors. Remission and low disease activities were observed in 70% of cases within 12 months and the DAS28 decreased to an average value of 2.47±1.02. There were no serious adverse events. [Conclusion] In our department, many cases of EORA showed a remission of disease activity by the treatment with a small amount of PSL and DMARDs other than MTX at the early stage of onset even when there were poor prognosis factors.

W7-1

Clinical significance of serum IL-16 in rheumatoid arthritis patients

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Conflict of interest: Yes

[Objective] High-throughput serum protein screening by nucleic acid aptamers identified IL-16 as an up-regulated cytokine, which positively correlated to serum MMP-3 in untreated rheumatoid arthritis (RA) patients. Although increase of RA synovial fluid and serum IL-16 concentration has been reported, clinical significance is still unclear. [Methods] Serum IL-16 concentrations in 44 untreated RA patients and 30 healthy controls (HC) were measured by ELISA and statistically analyzed with clinical parameters. [Results] Average IL-16 concentration of RA patients was 170.84 pg/ml, significantly (p=0.0049) higher than those of HC (141.8). Cut-off value was 155.7 (sensitivity 0.66, specificity 0.73). MTX treatment for 12 weeks significantly (p=0.0013) decreased IL-16 from 171.6 to 116.9 and IL-16 correlated with CRP (r=0.52), ESR (r=0.43), MMP-3 (r=0.43) and DAS28-CRP (r=0.39). Compared to two groups divided by cut-off value, DAS28-CRP at 12 weeks compared to baseline was significantly (p=0.0002) decreased only in IL-16 high group. [Conclusion] High serum IL-16 relates to good response with MTX treatment in untreated RA patients.

W7-2

Immunoregulatory Role of IL-35 in regulatory T Cells from Patients with Rheumatoid Arthritis

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Conflict of interest: None

[Objectives] Interleukin (IL)-35 is the newest member of the IL-12

family. It consists of Epstein-Barr virus-induced gene 3 (EBI3) and IL-12α chain p35. We investigated whether IL-35 enhances the in vitro immune suppressive function in peripheral blood from rheumatoid arthritis (RA) patients. [Methods] Peripheral blood from 17 active RA and 10 inactive RA patients were collected. IL-35 concentrations were quantified with an enzyme-linked immunosorbent assay (ELISA). IL-35 FLAG-tagged at the carboxyl-terminal was constructed by covalently linking EBI3 and IL-12α (p35). IL-35 function was evaluated by suppression assay with T cells isolated from human RA patients, employing CD2, CD3 and CD28 antibodies. [Results] Serum IL-35 levels and Treg cell numbers were significantly decreased in patients with active RA. There was a significant correlation between serum IL-35 and DAS28-ESR in patients with active RA. IL-35 treatment enhanced regulatory function, thereby suppressing inflammatoly cytokines such as IL-17 and IFN-γ, and the cellular growth of effector T cells stimulated by conjugation with CD2, CD3 and CD28. [Conclusion] Our study showed that IL-35 might participate in the suppressive regulation of T cell activation in peripheral immune responses of RA.

W7-4

A disintegrin and metalloprotease (ADAM)-10 is overexpressed in rheumatoid arthritis and mediates cell adhesion and proliferation

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Conflict of interest: None

【Background】We examined the expression of a disintegrin and metalloprotease (ADAM)-10 in rheumatoid arthritis (RA) and the role it plays inflammation.【Methods】ADAM-10 expression was determined in serum and synovial fluids from normal (NL) subjects, osteoarthritis (OA) patients and RA patients. To determine whether ADAM-10 was expressed by RA synovial fibroblasts, qPCR and immunofluorescence were performed. In order to confirm the role of ADAM-10 in RA synovial fibroblasts, ADAM-10 siRNA was transfected. Cell proliferation and THP-1 adhesion assays were performed.【Results】ADAM-10 in RA serum was significantly higher than NL serum. ADAM-10 in RA synovial fluids was also significantly higher than OA synovial fluids. The expression of ADAM-10 mRNA in RA synovial fibroblasts was induced by stimulation with TNF-α after 4 hours. After transfection with ADAM-10 siRNA in RA synovial fibroblasts, cell proliferation and THP-1 adhesion were decreased. Finally, number of migrated THP-1 towards ADAM-10 depleted RA synovial fluids were decreased compared with sham depleted RA synovial fluids.【Conclusions】These data show that ADAM-10 is overexpressed in RA, and this study suggests ADAM-10 may play a role in a RA inflammation

W7-5

The effects of etanercept on serum cytokine profile in patients with rheumatoid arthritis, in comparison with infliximab

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Conflict of interest: None

[Objectives] To investigate effects of etanercept on serum cytokine profile in patients with rheumatoid arthritis (RA), and to elucidate their associations with clinical responses in comparison with infliximab. [Methods] 24 and 46 RA patients, who received etanercept or infliximab, were included in the study. Serum levels of 11 inflammatory cytokines (IL-1β, IL-2, IL-6, IL-6R, IL-8, IL-10, IL-12, TNFα, TNFβ, IFNγ and GM-CSF) were measured at week 0, 22 and, 54. Associations between cytokine profile and clinical data were analyzed. [Results] As well as infliximab, etanercept had apparent effect to reduce serum IL-6 level, associated with treatment response. Infliximab treatment increased serum IFNγ and TNFβ, but etanercept didn't influence a value of IFNγ (TNFβ after starting etanercept couldn't measure properly). Although this difference might originate in the difference in an effect on TNFβ or membrane-type TNFα, there was no correlation between these cytokine levels and treatment response. To elucidate the clinical meaning, the further analysis including a rate of second failure, the profile of side effects, etc. is required. [Conclusion] IL-6 reduction is a common pathway to control RA activity by etanercept and infliximab. Two drugs have different effect on IFNγ and TNFβ.

W7-6

Allograft inflammatory factor-1 accelerates chemokines production from human peripheral blood mononuclear cells and induces chemotaxis

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Conflict of interest: None

[Objectives] Allograft inflammatory factor-1 (AIF-1) is about 17kDa polypeptide which was originally identified in chronic rejection of rat cardiac allografts. AIF-1 expresses on the cells such as macrophages, lymphocytes, fibroblasts, etc and accelerates inflammation. We stimulated human peripheral blood mononuclear cells (PBMCs) by administering AIF-1 and evaluated the production of chemokines and the effect of chemotaxis. [Methods] CD14+ mononuclear cells (CD14+ cells) were purified from PBMCs isolated from healthy volunteers using magnetic microbeads. We extracted total RNA from CD14+ cells stimulated by AIF-1 and searched the genes by using RNA Microarray. The chemokines corresponding to the expression genes were analyzed by ELISA. We demonstrated the chemotaxis of PBMCs using the chemokines by Cell Migration Assay. [Results] AIF-1 stimulation to CD14+ cells resulted in increase of RNA expression of CCL1, CCL2, CCL3, CCL7, CCL20, and IL-6. The production of CCL3 and IL-6 were significantly up-regulated. The chemokines produced after AIF-1 stimulation introduced PBMCs migration in the dose-dependent manner of AIF-1. [Conclusion] AIF-1 increases the expression of several chemokine genes and produced mainly CCL3 and IL-6 in PBMCs. These chemokines actually induced PBMCs migration.

W8-1

Comparison of the image of ultrasonography and synovium pathology of the joints in the patients with rheumatoid arthritis using biological agent

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Conflict of interest: None

Objectives: The objectives of this study were to investigate whether the image of ultrasonography (US) at the operated joint reflect synovium pathology or clinical indicators, and to compare the results in the patient using non-biological agent (NB) and biological agent (Bio). Materials and methods: Rheumatoid arthritis (RA) related orthopaedic surgery was performed at 301 joints including 5 shoulders, 43 knees, 36 elbows, 90 wrists, 75 fingers, 9 ankles and 43 toes. Preoperatively, US was performed and grade of Power Doppler (PD) signal was weighed. Rooney score of the synovium pathology, DAS28-ESR (4), MMP-3, CRP were investigated. Patients using Bio were IFX13, ETN22, TCZ18, ADA7, ABT1, GLM4, CZP3. Results: PDS, DAS28, MMP-3 and Rooney score in the patients using Bio were significantly lower than those in the patients using NB. Patients using ETN were higher than patients using IFX in MMP-3, and than patients using TCZ in DAS28. DAS28 and Rooney

fibrosis in patients using TCZ were significantly lower than those in patients using TNF. Conclusion: The activity of RA synovitis at operated site was suppressed in patients using Bio. There were some differences in clinical data, pathological score, PDS and DAS among Bio.

W8-2

Orthopaedic surgery of the RA upper extremity with biologic agents

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Conflict of interest: None

[Introduction] It has been reported that biologic agents inhibit the progression of the joint destruction in rheumatoid arthritis (RA). For this reason, these agents have been often used for the treatment of RA recently. The purpose of this study is to evaluate the effectiveness of orthopaedic surgery of the RA upper extremity with biologic agents. [Patients and methods] Two hundreds and twenty-nine surgeries of RA patients with biologic agents were performed (IFX: 49, ETN: 130, ADA: 25, TCZ: 19, ABT: 6). They underwent orthopaedic surgery from 2003 to 2012. The mean age at operation was 57 year-old. Eighty surgeries in upper limbs of RA patients with biologic agents were evaluated. Drugs for treatment, response to biologic agents for different operations respectively, complication were evaluated. [Results] At the time of follow-up, no deep infectious episode related to biologic agents were observed in patients who received orthopaedic surgery of the RA upper extremity. In spite of observed minor complication, the postoperative clinical courses of these patients were good, and the results of the surgeries were excellent. [Conclusion] Orthopaedic surgery of the RA upper extremity under biologic agents' therapy is thought to be safely performed and useful for RA patients.

W8-3

Effect of total elbowa arthroplasty on disease activity and HAQ in rheumatoid arthritis patients treated with biologics

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Conflict of interest: None

[Objectives] We examine the effect of TEA on post-operative disease activity, and the HAQ and MEPS in RA patients treated with biological products. [Methods] 18 joints of RA patients from 2006 to 2013. FINE Total elbow system was used for all cases. Disease activity was evaluated using DAS 28-ESR and CDAI. Dysfunction was evaluated using the HAQ and MEPS pre and post surgery. [Results] The condition improved; DAS 28-ESR went from 4.3 to 3.4 and DAS from 14.2 to 8.8. However, no significant difference was observed. The HAQ improved significantly, from 2.2 to 0.4. The HAQ showed improvement in lower extremity function as well as upper extremity function. MEPS improved significantly, from 50.6 to 96.3. [Conclusion] It was thought that due to preoperative low disease activity, there was no effect on the improvement of postoperative disease activity. Dysfunction improved significantly; in the HAQ, the function of lower limbs also improved. The RA patients might have been affected since elbow joints are weight bearing joints. After TEA, the disease activity was not affected; however, improvement in the HAQ was observed. In RA patients using biological products where bone destruction is in progress, medical treatment of upper limb surgery is useful in improving physical function.

W8-4

Risk factors for incidence of total joint replacement in patients with rheumatoid arthritis during treatment with Etanercept

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Conflict of interest: None

[Objectives] Total joint replacement (TJR) surgery in patients with rheumatoid arthritis (RA) is the essential marker of severe joint destruction. The aims of this study were to identify the risk factors that predict the need for TJR in RA patients treated with Etanercept (ETN). [Methods] A retrospective multicenter study was performed. Of 652 RA patients treated with ETN, 42 patients underwent 58 TJR (34 TKA, 19 THA, 3 TEA, 1 TAA and 1 TSA) during treatment with ETN. Risk factors for incidence of TJR were identified by Cox proportional hazards regression analysis. [Results] Patients were predominantly female (83.9%), and had a mean age of 59 years, disease duration of 10.9 years and DAS28-ESR of 5.4 at initiation of ETN. MTX was concomitantly used with 69.2% of the patients. Mean time between initiation of ETN and TJR was 1.5 years. Age [HR 1.075; 95% CI (1.024–1.129)] and no concomitant MTX use [HR 3.532; 95% CI (1.328–9.391)] were identified as the independent risk factors for incidence of TJR. [Conclusion] Combination therapy with ETN plus MTX was superior to ETN alone in reducing the incidence of TJR. Strict control of arthritis using ETN with concomitant MTX is important for preventing destruction of large joints as well as hand and foot joints.

W8-5

Perioperative complications with etanercept therapy in patients with rheumatoid arthritis

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Conflict of interest: None

[Objectives] To investigate the perioperative discontinuation of etanercept (ETN) in patients with rheumatoid arthritis (RA) relevant to the surgical site infection (SSI) and flare-up of the disease. [Methods] Between 2005 and 2013, 102 orthopaedic procedures were performed in RA patients who were treated with ETN. Clinical evaluations included the perioperative discontinuation period of ETN, pre- and post-operative CRP, complications and frequency of the flare-up. [Results] The mean pre- and post-operative discontinuation period of ETN were 9.9 days and 13.2 days, respectively. Serum CRP before withheld of ETN, preoperative, postoperative, and two weeks after surgery were 1.02 mg/dl, 1.02 mg/dl, 2.83 mg/dl, and 1.00 mg/dl, respectively. Four patients experienced the flare-up. There was no case with SSI. [Conclusion] The revised guidelines from the Japan College of Rheumatology in 2008 suggest that treatment with ETN should be withheld 2–4 weeks before major surgical procedures. However, because of the concern about the flare-up, the mean discontinuation periods of ETN before surgery have been becoming shorter in our institute. In the current study, the surgeries in RA patients were performed safety with few flare-up and no SSI with average 9.9 days of ETN discontinuation period.

W8-6

Investigation of postoperative deep infection cases in patients with rheumatoid arthritis using biologic DMARDs

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Conflict of interest: None

[Objectives] We investigated the postoperative deep infection cases in RA patients treated with biologic DMARDs in our institution. [Meth-

ods] Between January 2004 and October 2013, nine cases with the RA patients with RA suffering from deep infection after surgery. We have examined follow-up period, the sites of infection, surgical techniques, and species. We have researched whether they had achieved re-administration of the previous biologics. [Results] The mean follow-up period was 2.0 years. Infection sites (surgical procedures) are one hip (Bipolar Hemiarthroplasty), 4 knees (Total Knee Arthroplasty), 4 elbows (Total Elbow Arthroplasty), one hand (Metacarpophalangeal Joint Arthroplasty), one cervical spine (Magerl technique), one lumbar spine (Transforaminal Lumbar Interbody Fusion). As a result of investigating the infecting species, *MSSA* is four cases, *MRCNS, Pseudomonas aeruginosa, Listeria, Mycobacterium intracellulare,* and bacteria species unknown was one case each. Only two cases had re-administered the previous biologic DMARDs. [Conclusion] We should consider the need for careful observation of the patients with rheumatoid arthritis using biological DMARDs because they may be suffered more than one site deep infection after surgery.

W9-1

Contribution of *IRF2* polymorphisms to susceptibility to systemic lupus erythematosus

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Conflict of interest: None

[Objectives] Interferon regulatory factor 2 (IRF2) has roles in type I interferon responses and Th1 differentiation. Here we examined whether *IRF2* polymorphisms contribute to susceptibility to systemic lupus erythematosus (SLE). [Methods] 501 SLE and 551 healthy controls in a discovery set and 239 SLE and 200 healthy controls in a replication set were examined in an association study of *IRF2* SNPs. An effect of *IRF2* SNPs on transcriptional activity was analyzed using a reporter assay. [Results] Analysis of tag SNPs detected association of rs13146124 with SLE ($P=7.4X10^{-4}$, odds ratio [OR] 1.60). rs62339994 and rs66801661, which were in linkage disequilibrium with rs13146124, were also associated with SLE (rs62339994: $P=9.4X10^{-4}$, OR 1.59, rs66801661: $P=8.2X10^{-4}$, OR 1.75) and rs66801661A-rs62339994A haplotype was increased in SLE ($P=2.7X10^{-4}$). Meta-analysis of the discovery and replication sets showed the significant association of rs62339994 ($P_{combined}=4.0X10^{-4}$, $OR_{combined}$ 1.54) and rs66801661 ($P_{combined}=0.0011$, $OR_{combined}$ 1.59). A reporter assay demonstrated association of the SLE risk haplotype with higher transcriptional activity ($P=1.3X10^{-4}$). [Conclusion] *IRF2* SNPs with functional relevance were found to be associated with SLE in a Japanese population.

W9-2

Down-regulated expression of microRNAs *microRNA-155, 17, and 181b* together with increased expression of *IFN-a* and *AID* mRNA in in peripheral blood mononuclear cells from patients with systemic lupus erythematosus

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Conflict of interest: None

[Objectives] Recent studies for systemic lupus erythematosus (SLE) showed that microRNAs are involved in the pathogenesis of SLE. However, analyzed microRNAs are limited. [Methods] In this study, we performed quantitative real-time reverse transcription-polymerase chain reaction analyses of peripheral blood mononuclear cells (PBMCs) from 31 SLE patients and 31 healthy subjects to estimate *microRNA-155, 17, and 181b,* and *IFN-a* and *activation-induced cytidine deaminase (AID)* mRNA expression levels. [Results] Expression levels of *microRNA-155, 17, and 181b* in SLE patients were significantly lower than those in healthy controls. However, expression levels of *IFN-a* and *AID* mRNAs in SLE patients were significantly higher than those in healthy controls. Expression levels of *microRNA-155, 17, and 181b* correlated inversely with those of *IFN-a* and *AID* mRNA in SLE patients. [Conclusion] These results suggest that down-regulated expression of *microRNA-155, 17, and 181b* together with increased expression of *IFN-a* and *AID* mRNA in PBMCs also contribute to the pathogenesis of human lupus.

W9-3

Decreased expression of SF2 in T cells from patients with systemic lupus erythematosus

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Conflict of interest: None

[Backgrounds] Down-regulation of MAPK pathway has been recognized in T cells from SLE patients that results in hypo-methylation of DNA. We have reported defective RasGRP1 transcripts correlated with lower levels of RasGRP1 protein in lupus T cells. ASF/SF2 is a splicing protein that binds pre-mRNA to regulate the alternative splicing, for instance in CD3 zeta. [Objective] To clarify the relationship between aberrant splicing of RasGRP1 and ASF/SF2 expression in SLE T cells. [Methods] Forty-five SLE patients and eighteen healthy subjects were included in this study. Expression levels of ASF/SF2, RasGRP1 and DNMT1 transcripts were assessed by quantitative PCR. RNA electrophoretic mobility shift assays (EMSA) and immunoprecipitations (IP) were performed to confirm the direct binding of ASF/SF2 to RasGRP1 RNA. [Results] Expression levels of ASF/SF2 transcripts were significantly lower in SLE patients compared with healthy subjects (p=0.001), especially in active SLE. Expression levels of SF2/ASF correlated with those of normally spliced RasGRP1 and DNMT1 (r=0.517, p=0.023 [RasGRP1]; r=0.557, p=0.013 [DNMT1]). EMSA and IP studies suggested that ASF/SF2 binds directly to RasGRP1 RNA. [Conclusion] ASF/SF2 would be critical for normal splicing of RasGRP1, as in the case of CD3 zeta.

W9-4

The role of Egr2 and Egr3 for the regulation of autoimmune diseases

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Conflict of interest: Yes

[Objectives] Egr2 (early growth response gene-2) is one of the SLE susceptibility genes, belonging to the Egr family of zinc finger transcription factors. The Egr family includes Egr1, 2, 3 and 4 of which Egr2 and

Egr3 are NFAT1 target genes and involved in the regulation of T cell tolerance and anergy. Recently, it was reported that mice deficient for both Egr2 and Egr3 in B and T cells died prematurely and presented lethal and early-onset systemic autoimmunity. However, there are no reports about T cell specific Egr2- and Egr3- deficient mice and it remains unclear how Egr2 and Egr3 cooperate in T cells. [Methods] We constructed a mouse strain in which both Egr2 and Egr3 were deleted specifically in T cells (CD4-Egr2$^{-/-}$Egr3$^{-/-}$) using the Cre-loxP system. We measured serum dsDNA antibody titers and serum inflammatory cytokines and performed pathological analysis of the affected organs. [Results] CD4-Egr2$^{-/-}$Egr3$^{-/-}$ mice developed lupus-like syndrome, such as glomerulonephritis, from early age compared with CD4-Egr2$^{-/-}$ mice. [Conclusion] Egr2 and Egr3 play an important role in the pathogenesis of SLE, while complementing each other in T cells.

W9-5

The role of autoantigen TRIM21 in pathogenesis of systemic lupus erythematosus

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Conflict of interest: None

[Objectives] The increased expression of type I interferon (IFN)-inducible genes, called “IFN signature”, has been suggested to have important roles in pathogenesis of systemic lupus erythematosus (SLE). Here, we investigated the pathological role of TRIM21, an autoantigen also called Ro52 or SSA1, in SLE. [Methods] We collected peripheral blood mononuclear cells (PBMC) from 20 patients with SLE and 24 healthy controls (HC). The mRNA expression levels of TRIM21, type I IFN-inducible genes and type I IFNs were analyzed by quantitative RT-PCR. We also investigated the protein levels of TRIM21 and IRF family genes by Western blotting. [Results] The mRNA levels of TRIM21 and other type I IFN-inducible genes were higher in PBMC from patients with SLE as compared to HC. TRIM21 mRNA level correlated positively with other type I IFN-inducible genes. Although the mRNA levels of type I IFNs showed negative correlations with TRIM21 mRNA level in HC, these correlations were not observed in SLE. After treating with MG-132, the protein levels of IRFs were increased in PBMC from HC, but not in the PBMC from patients with SLE. [Conclusion] These results suggest that the malfunction of TRIM21 as an E3 ubiquitin ligase for IRF family may lead to the increased expression of type I IFNs in SLE.

W9-6

Antiribosomal P protein antibodies enhance the production of IL-8 in activating monocytes

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Conflict of interest: None

[Objectives] Autoantibodies to ribosomal P proteins (anti-P) are detected in 30-40% of patients with systemic lupus erythematosus (SLE). We have disclosed that anti-P react with activated human peripheral blood monocytes and enhance their production of several cytokines. It has been shown that serum IL-8 concentrations in SLE patients are rarely increased. On the other hand, our recent study demonstrated that anti-P enhance the IL-8 production of human peripheral blood mononuclear cells. The current study was undertaken to explore the effects of anti-P on the production of IL-8 in monocytes. [Methods] IgG anti-P were affinity-purified from sera of anti-P positive lupus patients. Highly purified peripheral blood monocytes were cultured for 2 days in a 24-well microtiter plate with or without N-acetylcystein (NAC) in the presence of anti-P or control IgG. The concentrations of IL-8 in the culture supernatants were measured using ELISA. [Results] Anti-P significantly enhanced the production of IL-8 in monocytes, compared with normal IgG. Of note, the up-regulation of IL-8 production by anti-P was abrogated by addition of NAC. [Conclusions] These results indicate that the activation of NF κB might be involved in the enhancement of IL-8 production in activating monocytes by anti-P.

W10-1

Role of granzyme B-producing B cells in patients with systemic lupus erythematosus

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Conflict of interest: None

[Objectives] B cells play a pathogenic or regulatory role in autoimmune diseases. A recent study showed that human B cells, unlike mouse B cells, can produce granzyme B (GzmB) upon stimulation. In this study we have determined the mechanism of GzmB production in B cells from normal subjects and SLE patients. [Methods] Expression of GzmB mRNA and protein was assessed using real-time quantitative PCR and intracellular staining. GzmB-producing B cells were co-cultured with activated T cells, and proliferation and survival of T cells were evaluated using flow cytometry. [Results] IL-21 was the potent inducer for GzmB production in normal B cells and it acted synergistically with BCR stimulation. Among B cell subsets, naïve B cells produced high levels of GzmB mainly via a STAT3-dependent pathway. GzmB-producing B cells partially suppressed T cell survival and proliferation. Notably, upon BCR/IL-21 stimulation, SLE B cells produced high levels of GzmB as compared with normal B cells. Pretreatment with type I IFN enhanced BCR/IL-21-induced GzmB production in B cells. [Conclusion] In the extracellular milieu of SLE, B cells could produce higher levels of GzmB. How GzmB-producing B cells contributed to the pathogenesis of this disease remains to be established.

W10-2

“Anti dsDNA-NcX ELISA” kit detects antibodies not only for ds-DNA but also ss-DNA and nucleosome

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Conflict of interest: None

[Objectives] “Anti dsDNA-NcX ELISA” kit (EURO IMMUNE) has been available for detecting anti-DNA antibody in Japan. However, antigen specificity of ELISA has not been fully evaluated, and clinical meanings of the antibodies detected with the ELISA remain to be elucidated. [Methods] Autoantibodies levels in the serum samples from 70 patients, were measured with “anti dsDNA-NcX ELISA”, conventional anti-ds DNA Ab ELISA, anti-ss DNA Ab ELISA and anti-nucleosome Ab ELISA. Correlations of titers of the same samples gained with each ELISA were analyzed and the relation between the titers and disease activity was examined. [Results] Moderate correlation between titers by “anti dsDNA-NcX ELISA” and those by conventional ds-DNA ELISA was found (r=0.54), although regression analysis revealed its coefficient of determination (R2) was low (0.27). Samples whose anti-ds-DNA level were less than detection level in conventional assay were positive in “anti dsDNA-NcX ELISA” assay in 56%. Titers with “anti dsDNA-NcX ELISA” had strong correlation to those of anti-ss-DNA Ab (r=0.83, R2 =0.54) and anti-nucleosome Ab (r=76, R2=0.50). [Conclusion] Anti dsDNA-NcX ELISA” kit detects antibodies not only for ds-DNA but also ss-DNA and nucleosome.

W10-3

Qualitative abnormality of B cells in SLE patients: subset classification by chemokine receptors and its pathological significance

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Conflict of interest: None

Objectives: SLE is characterized by an expanded population of peripheral memory B cells. However, little is known about the qualitative abnormality of B cells associated with pathogenesis of SLE. We experimented with the subset classification of B cells and investigated the pathological relevance of B cells. **Methods:** PBMCs obtained from subjects with 56 SLE, 31 RA and 8 healthy donors (HD) were analyzed. B cells and T cells were categorized by expression of chemokine receptors such as CXCR3, CXCR5 and CCR6. **Results:** 1) The proportion of effector memory (EM) B cells has significantly increased in SLE compared to HD and RA ($p<0.01$). 2) $CXCR5^{-}CXCR3^{+}$ EM B cells characteristically detected in SLE compare to HD and RA ($p<0.01$). 2) The proportion of activated Tfh/Th1 cells also increased in SLE, and this was positively correlated with those of $CXCR5^{-}CXCR3^{+}$ EM B cells ($p<0.05$). 4) The proportion of EM B cells and Tfh cells were not correlated with disease activity, but both was positively correlated with anti-Sm antibody ($p<0.05$). **Conclusion:** The results revealed that not only quantitative increase of memory B cells but also qualitative abnormality of EM B cells, which lose CXCR5 and express CXCR3, play important roles in autoantibody production through the interaction with Tfh cells.

W10-4

Induction mechanism of regulatory B cells in normal subjects and SLE patients

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Conflict of interest: None

[Objectives] B-cell depletion therapy highlights a role of B cells in the pathogenesis of systemic lupus erythematosus (SLE). Regulatory B cells (Bregs) exert regulatory functions via IL-10 production. In this study, we assessed suppressive function of Bregs, and investigated the induction mechanism of Bregs in normal subjects and SLE patients. [Methods] Gene expression in B cells was assessed using quantitative PCR. Bregs were co-cultured with T cells, and proliferation and IFNγ production of T cells were assessed. [Results] Bregs inhibited proliferation and IFNγ production of T cells in an IL-10-dependent manner. Intriguingly, CpG-induced IL-10 production was remarkably abrogated in B cell subsets of SLE patients. Accordingly, the regulatory function of Bregs towards T cells was significantly impaired in SLE patients. A previous report showed that levels of PRDM1 (Blimp1) expression are associated with induction of Bregs in mice, and we confirmed that the same is true for human Bregs. High levels of Blimp1, however, inhibited IL-10 production, suggesting a requirement of optimal levels of Blimp1 for Breg induction. [Conclusion] These findings provide a novel clue to manipulating the generation of Bregs for the treatment of autoimmune diseases such as SLE.

W10-5

Impaired balance of B cell - T cell - dendritic cell axis in the pathogenesis of systemic lupus erythematosus

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Conflict of interest: None

[Objectives] To investigate the interactive activation between B cells and surrounding immunocompetent cells including T cell and dendritic cell (DC) in the pathogenesis of systemic lupus erythematosus (SLE). **[Method]** Circulating B cell, T cell and DC subsets were defined by multicolor flow cytometry in the peripheral blood of 34 SLE patients. **[Results]** The number of effector B cells and plasmablast has increased, whereas IgM memory B cells decreased, in SLE compared to healthy donor (HD). Likewise, the proportion of effector memory T cells and effector T cells increased in SLE. The frequency of myeloid DCs decreased in SLE and that of plasmacytoid DCs was not different with HD. A new population of DCs that express neither CD11c nor CD123 has characteristically detected in SLE. The proportion of IgM memory B cells negatively correlated with the BILAG. The new DCs subset showed positive correlation with both the population of plasmablast and the serum level of IgG and anti-dsDNA antibody. **[Conclusion]** The effector subsets of B and T cells are increased in SLE patients with an active disease. The specific population of DCs which correlates with increased plasmablast and antibody production may contribute the pathogenesis of SLE in cooperation with B cell activation.

W10-6

CaMK4 promotes T_H17-driven autoimmunity though Akt/mTOR and CREM-α

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Conflict of interest: None

[Objectives] To determine the molecular mechanisms whereby calcium/calmodulin-dependent protein kinase IV (CaMK4) controls the generation of T_H17 cells. [Methods] The expression of CaMK4 was examined under T_H1, T_H2, T_H17 or T_{reg} conditions. We induced EAE in B6 mice or B6 *Camk4*$^{-/-}$ mice and evaluated the disease activity. MRL/*lpr* mice were treated with KN-93, an antagonist of CaMK4, and examined IL-17 producing T cells in *in vitro* and *in vivo*. Furthermore, we analyzed an epigenetic remodeling and signaling pathways related to CaMK4 induced T_H17 cells. To determine the relevance of our findings to human SLE, we analyzed the effect of CaMK4 inhibition on T_H17 cells function in T cells from patients. [Results] CaMK4 is solely expressed under T_H17 condition. EAE and MRL/*lpr* lupus-like disease are ameliorated by genetic or pharmacological inhibition of CaMK4 along with a decrease in the frequency of IL-17-producing T cells. The effects of CaMK4 on T_H17 cell generation are mediated through the mTOR pathway and CREM-α which controls the epigenetic remodeling of *Il17*. Importantly, silencing of CaMK4 in T cells from patients with SLE decreases the expression of IL-17A. [Conclusion] Our results suggest that CaMK4 inhibition may be a promising therapeutic agent for T_H17-driven autoimmune diseases.

W11-1

Gene expression in labial salivary glands between patients with IgG4-related disease and Sjögren's syndrome by DNAmicroarray

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Conflict of interest: None

[Objective] To compare gene expression in labial salivary glands (LSGs) of IgG4-related disease (IgG4-RD) with Sjögren's syndrome (SS)

patients. [Methods] Gene expression was analyzed by DNA microarray in LSG of IgG4-RD (n=5) and SS patients (n=5). 1) Differentially expressed genes (DEGs) were identified, and gene-annotation enrichment analysis of these DEGs was performed using Gene Ontology (GO) annotation. 2) Validation was performed by quantitative PCR using LSGs from patients with IgG4-RD (n=9), SS (n=10), and healthy controls (n=4). [Results] 1) Gene expression patterns in IgG4-RD and SS were quite different in hierarchical clustering. In IgG4-RD, 1351 up-regulated and 1431 down-regulated genes were identified as DEGs (false discovery rate<0.05). GO analysis indicated that the up-regulated set of DEGs in IgG4-RD encoded proteins that function in cell proliferation, extracellular matrix organization, and organ development. 2) qPCR validated significantly higher expression of lactotransferrin (LTF), EGF-containing fibulin-like extracellular matrix protein 1 (EFEMP1), and chemokine (C-C motif) ligand 18 (CCL18) in IgG4-RD than SS patients (P<0.05). [Conclusion] Results clearly showed that the gene expression pattern in LSGs of IgG4-RD patients is different from that of SS patients.

W11-2

Etiological clue of IgG4 related disease

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Conflict of interest: None

[Background] IgG4 related disease (IgG4-RD) has little evidence of mechanism. We focued on the histological features of IgG4-RD are IgG4 positive plasma cell expansion, formation of lymphoid follicules and fibrosis, then we examined the role of monocytes, macrophage and follicular dendritic cell in the tissue of IgG4-RD cases. [Methods] 5 tissues of IgG4-RD cases (2 of submandibular glands and each one of bile duct and pancreas, retroperitoneum and lymph node), 3 of reactive hyperplasia of a lymph node and 3 of multicentric Castleman disease were examined. Immunohistochemical staining for monocytes (CD14, CD16), macrophage (CD68), M2 macrophage (CD163), follicular dendritic cell (CD21), B-cell (CD20), and T-cell (CD3) was adopted, and each distribution were confirmed. [Result] In IgG4-RD tissue, CD14+ inflammatory monocytes as well as follicular dendritic cells were present in germinal center of the lymphoid follicule. CD163+ M2 macrophages were present around the lymphoid follicules like previous reports. [Conclusions] Inflammatory monocytes and follicular dendritic cells may play a role of formation of IgG4-RD, and further examination including cytokine and/or chemokine expression from these cells is necessary.

W11-3

The sensitivity and the specificity of IgG4 related dacryoadenitis / sialadenitis (so-called Miculicz's disease) and suspected cases of those, compared comprehensive diagnostic criteria for IgG4-related disease (IgG4-RD), 2011 with diagnostic criteria for IgG4-related Miculicz's disease, 2008, multicenter retrospective study

Takuji Nakamura[1], Yasufumi Masaki[1], Motohisa Yamamoto[2], Shoko Matsui[3], Takako Saeki[4], Tomoki Origuchi[5], Shintaro Hirata[6], Tomomi Sato[1], Haruka Iwao[1], Akio Nakajima[1], Hisanori Umehara[1]
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Conflict of interest: None

[Objectives] Some cases get a diagnosis of possible (or probable) IgG4-RD in comprehensive diagnostic criteria for IgG4-RD, 2011, but get a definite diagnosis of IgG4-related Miculicz's disease in diagnostic criteria for IgG4-related Miculicz's disease, 2008. We reconsider the significance of diagnostic criteria for IgG4-related Miculicz's disease. [Methods] Collaboration hospitals enter data (age, sex, clinical diagnosis, serum IgG, serum IgG4, IgG4+/IgG+ plasma cells on pathological tissue, IgG4+ plasma cells/HPF on pathological tissue, other histopathological features, serum IgE, hypocomplementemia, exclusive diagnosis, clinical course) in survey sheets and the bureau (Kanazawa Medical University) statistically analyze the survey sheets. [Results] Registered cases are 109.75 cases meet a criterion for comprehensive diagnostic criteria for IgG4-RD.60 cases meet a criterion for diagnostic criteria for IgG4-related Miculicz's disease and 1 case finally diagnose Castleman disease. The sensitivity of comprehensive diagnostic criteria for IgG4-RD to diagnostic criteria for IgG4-related Miculicz's disease is 98%, the specificity is 67%, the false-positive rate is 33%. [Conclusion] From these results, diagnostic criteria of IgG4-MD may be useful, but further analysis will be required.

W11-4

Clinical analysis of patients with IgG4-related disease complicated with perivascular lesions

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Conflict of interest: None

[Objective] To clarify the clinical features of IgG4-related disease (IgG4-RD) complicated with perivascular lesions (PLs). **[Methods]** We examined the clinical features such as 1) clinical background, 2) serum examinations, 3) location of PLs, 4) other organ involvements, 5) response to treatment in 7 patients with IgG4-RD who had PLs followed up at the University of Tsukuba Hospital from April 2010 to October 2013, retrospectively. **[Results]** 1) Six males and one female, and mean age was 64.8±6.8 yrs. 2) The serum IgG4 levels were higher than 135 mg/dl in all 7 patients (mean was 933±527 mg/dl). CRP levels were elevated in only 2 out of 7 patients (mean was 1.41±3.56 mg/dl). 3) PLs were located in thoracic aorta (n=2), pulmonary artery (n=1), coronary artery (n=1), abdominal aorta (n=6), celiac artery (n=1), SMA (n=1), renal artery (n=2), IMA (n=4) and iliac artery (n=3). 4) Other organ involvements were identified in 6 of 7 patients. 5) All 7 patients were treated with prednisolone (0.6 mg/kg/d), and PLs rapidly improved in all 7 patients as well as other organ involvements. **[Conclusion]** This study revealed that PLs in IgG4-RD had wide variety of distributions and elevation of CRP was mild or not detected. Corticosteroid was effective for PLs in IgG4-RD as well as other involvements.

W11-5

A retrospective study of 26 patients with IgG4 related-disease

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Conflict of interest: None

【Objective】To evaluate the clinical characteristics of IgG4 related-disease (RD).【Method】We retrospectively analyzed the clinical characteristics and the levels of serum IgG4 of 26 patients with IgG4-RD at October 2013 in Kobe University Hospital.【Results】We analyzed 14 definite, 1 probable, and 11 possible cases of IgG4-RD (21 males and 6 females). The organ involvements were submandibular gland (16 cases), retroperitoneal fibrosis, lymph nodes (13 each), lacrimal gland (9), submandibular gland (7), interstitial nephritis (6), lung, prostate (5 each), aorta, pancreatitis (4 each), skin (3), joint, bile duct, heart, pituitary, episcleritis, hypertrophic pachymeningitis (1 each). We treated 22 patients with predonisolone, and 7 patients relapsed. All the 7 patients who relapsed showed elevation of serum IgG4 prior to the clinical relapse. Six out of 16 patients with serum IgG4 levels over 405 mg/dl, and 1 out of 10 patients with its levels under 405 mg/dl relapsed. In addition, 2 out of 16 patients with 3 or more organ involvements, and 5 out of 10 patients with

2 or less organ involvements showed relapse.【Conclusion】The levels of IgG4 and the number of organ involvements were not correlated with the frequency of relapse. All patients who relapsed showed elevation of serum IgG4 prior to the clinical relapse.

W11-6

Multicenter prospective clinical study of steroid therapy for IgG4-RD

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Conflict of interest: None

[Objectives] To determine the universal consent of how to use glucocorticoid for IgG4-RD patients, we have planned and conducted multicenter prospective clinical trial for establishment of standard glucocorticoid therapy. [Methods] We enrolled definitive patients diagnosed according to IgG4-RD comprehensive diagnostic criteria. Glucocorticoid treatment was implemented using oral prednisolone at an initial dose of 0.6 mg/kg per day, with tapering by 10% every 2 weeks. We defined that the primary endpoint was response rate, and secondary endpoints were glucocorticoid maintenance dose, relapse rate and adverse events. [Results] Target number of enrollment cases was 57 per five years, and finally 61 cases have already been registered and thus enrollment had been finished. Treatment and follow-up period will be finished soon for later registered cases. From an interim analysis of 38 patients, CR rate was 63.2%, and response rate 88.9%. Main adverse effects are glucose intolerance in almost half cases, and various infection, dyslipidemia, hypertension, osteoporosis, psychosis, and so on. [Conclusion] We must establish treatment strategy for IgG4-RD in a step by step manner.

W12-1

Validation of the Diagnostic Criteria for IgG4-related Mikulicz's Disease (2008)

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Conflict of interest: None

[Objectives] The IgG4-related Mikulicz's disease (IgG4-MD) diagnostic criteria (MDDC) and the comprehensive diagnostic criteria (CDC) have been used for clinically diagnosing IgG4-MD. The only difference of criteria is histological parameters, so we analyzed their diagnostic reliability. [Methods] We analyzed the rate of positive histological examination using MDDC in 64 IgG4-MD cases diagnosed using CDC. Next, we calculated the rate of positive hematological and histological examinations using CDC in 85 IgG4-MD cases diagnosed using MDDC. Furthermore, we examined whether these 85 cases correspond to definite, probable, or possible diagnosis of CDC. [Results] The rate of positive histological examination using MDDC was 100% in cases with definite diagnosis obtained using CDC. In 85 cases diagnosed using MDDC, the rate of positive hematological and histological examinations was 98.8% and 97.0%, respectively. In addition, the number of cases with definite, probable, and possible diagnoses of CDC was 64, 1, and 20, respectively. [Conclusion] The results indicate that the both diagnostic criteria were in accordance with each other, if the histological analysis of lacrimal or submandibular glands was performed.

W12-2

Usefulness of FDG-PET Imaging in IgG4-related Disease

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Conflict of interest: None

(Objective) Elevated serum IgG4 level is one of the diagnostic criteria for IgG4-related disease (IgG4-RD) Malignancy or other diseases should be excluded using pathological examination to confirm IgG4-RD diagnosis. Previous reports suggested FDG-PET/CT is helpful to indicate biopsy site. In this study, we investigated usefulness of FDG-PET/CT in IgG4-RD. (Method) We studied patients suspected IgG4-RD in our facility between Dec. 2008 and Nov. 2013. We retrospectively studied the relation of serum IgG4 level, pattern of FDG uptake, maximum standardized uptake value (SUVmax), pathological findings and each clinical course. (Result) Biopsy were performed in 36 patients suspected IgG4-RD with examination of FDG-PET/CT. We could diagnose with IgG4-RD or other disease 27 patients. There were 9 cases difficulty to decide the biopsy site by examination except FDG-PET/CT. There was no correlation between serum IgG4 and SUVmax. And we report the association between accumulation of FDG and histopathological finding. (Conclusion) Pathological examination is important to differentiate IgG4-RD and other diseases. FDG-PET/CT would be useful to improve a diagnosis rate. It is desirable to diagnose IgG4-RD with FDG-PET/CT regularly.

W12-3

Clinical characteristics including the relationship between laboratory and imaging findings in Japanese patients with IgG4-related disease

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Conflict of interest: None

【Objective】To evaluate clinical characteristics of patients with IgG4-RD.【Methods】The clinical symptoms, laboratory, pathological and FDG-PET/CT findings of patients with IgG4-RD (n=14) were assessed. Several data of IgG4-RD with multiple organs' involvements (MOI) (n=7), IgG4-RD with limited organ's involvement (LOI) (n=7) and ANCA-associated vasculitis (AAV) (n=10) were comparatively examined.【Results】In IgG4-RD, FDG-PET/CT imaging revealed enlargement and increase of FDG accumulation of submandibular glands, lymph node, lung, spleen, kidney, periaorta and prostata. Interestingly, a part of these organs was asymptomatic. Follow-up FDG-PET/CT after steroid treatment showed a significant decrease in FDG accumulation in IgG4-RD lesions. Serum IgG4 level was 847±711 mg/dl. Four cases with hypocomplementemia and elevated immunocomplex of 14 IgG4-RD cases revealed renal involvements, and moreover, these 4 cases also had interstitial lung involvements. Notably, ChE and T-cho levels in IgG4-RD cases with MOI significantly decreased than in IgG4-RD with LOI and AAV ($p<0.05$).【Conclusion】FDG-PET/CT imaging and measuring serum ChE and T-cho levels might help us not only to evaluate widespread lesions and monitor disease activity in IgG4-RD, but also to differentiate other disorders.

W12-4

Initial corticosteroid therapy in IgG4-related kidney disease

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Conflict of interest: None

[Objectives] To examine the appropriate initial corticosteroid dose for treatment of IgG4-related kidney disease (RKD). [Methods] Forty-one patients with definite IgG4-RKD, in whom the eGFR before corticosteroid treatment had been less than 60 ml/min, were enrolled in this study. They were classified into two groups (initial prednisolone dose ≤30 mg daily, group L; ≥40 mg daily, group H), in whom we retrospectively examined the course of renal function after treatment. [Results] Group L included 22 patients, and group H 19 patients. There was no significant inter-group difference in patient age and pretreatment eGFR. In both groups, the pretreatment eGFR was significantly improved at 1 month after the start of treatment (27.9 to 40.2 ml/min in group L and 36.6 to 46.7 ml/min in group H), and there was no significant difference in the degree of improvement. Among 5 patients who had initially received prednisolone at ≤20 mg daily, renal function was improved in 3. However, renal function did not recover in one patient, and maintenance hemodialysis became necessary in the one remaining patient. [Conclusion] In IgG4-RKD, a high dose of corticosteroid is unnecessary for induction therapy, and a moderate dose (around 30 mg prednisolone daily in Japanese patients) is recommended.

W12-5

Involvement of macrophage and a proliferation-inducing ligand (APRIL) in IgG4-related inflammatory abdominal aortic aneurysm

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Conflict of interest: None

[Objectives] To evaluate the involvement of macrophage and a proliferation-inducing ligand (APRIL) in IgG4-related and non-IgG4-related inflammatory abdominal aortic aneurysm (IAAA). [Methods] We evaluated 12 IAAA patients whose lesions were obtained surgically. Clinical background, serum data, and histopathological findings including immunostaining of anti-macrophage antibody (anti-CD68 and CD163 antibodies), anti-membrane type APRIL antibody (Stalk-1), and anti-soluble APRIL antibody (Aprily-8) were analyzed. [Results] The patients were ten men and two women with an average age of 69.3 years. Five of them were diagnosed as IgG4-related IAAA based on high serum levels of IgG4 and abundant IgG4-bearing plasmacytic infiltration in the obtained specimens. In the surgical specimens of all patients, macrophage infiltration, membrane type and soluble APRIL expression were observed. APRIL expression was significantly more marked in IgG4-related IAAA than in non-IgG4-related IAAA. There was a significant positive correlation between the number of infiltrating IgG4-positive plasma cells and that of APRIL-producing cells. [Conclusions] Our data suggests that macrophage and APRIL in the affected lesions participate in the pathophysiology of IAAA, particularly, of IgG4-related IAAA.

W12-6

Clinical characteristics and course after corticosteroid therapy in IgG4-related aortitis/periaortitis and periarteritis: a retrospective multicenter study

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Conflict of interest: None

[Objectives] To clarify the clinical characteristics and course after corticosteroid (CS) therapy in IgG4-related aortitis/periaortitis and periarteritis **[Methods]** We retrospectively evaluated laboratory data, imaging findings, and the course after CS therapy in 40 patients with IgG4-related aortitis/periaortitis and periarteritis. **[Results]** The patients were mainly elderly (average age 66.4 years) with a marked male predominance. Subjective symptoms were scanty. Thirty-six patients were treated with CS, with the periaortic/periarterial lesions improving in most of them during the follow-up. Two (50.0%) of four patients with aneurysm or lumen enlargement of the affected lesions before CS therapy showed aneurysm enlargement after therapy, whereas none of 26 patients without lumen enlargement showed new aneurysm formation after therapy. **[Conclusions]** This retrospective multicenter study highlights two important points: the risk of aneurysm enlargement after CS therapy in patients with pre-existing lumen enlargement or aneurysm of the affected lesions, and the efficacy of CS therapy in preventing new aneurysm formation in patients without lumen enlargement. To confirm the safety of CS therapy in patients without lumen enlargement, a larger-scale prospective study is required.

W13-1

Treat to target strategy based management by shortening intervals of infliximab for rheumatoid arthritis patients

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Conflict of interest: None

[Objectives] To clarify efficacy and safety of treat to target (T2T) strategy based management by shortening intervals of infliximab (IFX) for rheumatoid arthritis (RA). [Methods] Among IFX received 390 consecutive RA patients from August 2009 until January 2013, 35 cases treated by T2T based management by shortening intervals of IFX (equal or less than 6 weeks) were enrolled and observed for 6 months. Efficacy and safety were statistically evaluated by clinical information. [Results] Classified total 35 cases (3 male, 32 female) with minimum interval, 7 cases were for 4 week-intervals, 12 for 5, and 16 for 6, respectively. At the point of shortening, average age were 56.6 years old. Average prednisolone, methotrexate, and IFX amount were 1.2 mg/day, 8.0 mg/week, and 289 mg/body. IFX continuation rate was 71% (25 of 35 cases) at 6 months. Reasons of 10 discontinuation cases include adverse events (6) no efficacy (1), and loss of follow up due to transfer (3). No severe adverse event requires admission were observed. Although average DAS28-CRP was 2.68 at the point of shortening, IFX continued cases achieved clinical remission (2.26) at 6 months. [Conclusion] Management by shortening intervals of IFX is considered as a useful option for achievement of remission.

W13-2

High rate of improvement in serum matrix metalloproteinase-3 levels at 4 weeks predict remission at 52 weeks in ra patients with adalimumab therapy

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Conflict of interest: None

[Objectives] To investigate whether serum MMP-3 is the predictor for remission in treatment for RA patients with biologics. [Methods] We analyzed 114 patients in TBC registry in continuation with adalimumab (ADA) therapy at 52 weeks. We divided into 2 groups based on the improvement of serum level of MMP-3 and CRP: high rate of improvement (MMP-HR group) and low rate of improvement (MMP-LR group) in serum MMP-3 levels at 4 weeks, and: CRP-HR group and CRP-LR group in serum CRP levels at 4 weeks. We evaluated the rate of remission at 24 and 52 weeks in HR group and LR group. [Results] The rate of remission at 24 and 52 weeks in MMP-HR group is 56% and 60%, and MMP-LR group is 32% and 37% respectively. The rate of remission at 24 and 52 weeks in MMP-HR group is significantly higher than in MMP-LR group. However, the rate of remission at 24 and 52 weeks had no significance in CRP-HR group and CRP-LR group. In patients continuing at 52 weeks, the best cut-off rate of improvement in MMP-3 at 4 weeks for determining remission at 52 weeks was 40% determined by ROC analysis (sensitivity: 47%, specificity: 83%, accuracy: 64%). [Conclusion] We considered that high rate of improvement in serum MMP-3 at 4 weeks can be useful for predicting the remission at 52 weeks in RA patients with ADA therapy.

W13-3

Analysis of long-term QOL in rheumatoid arthritis patients with AIMS2 – 3-year evaluation of biologic therapy –

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Conflict of interest: None

[Objectives] Our clinic has used AIMS2-based surveys of QOL in RA patients since 2011 to determine whether QOL is maintained long term when treatment goals are met and maintained with biologics (Bio). [Methods] Among RA patients maintaining clinical remission or low disease activity with Bio, those surveyed with AIMS2 continuously for 3 years were analyzed. [Results] Most of the 124 target patients were using etanercept, followed by infliximab, tocilizumab, adalimumab, abatacept, and golimumab. Yearly mean values were compared for each AIMS2 item. There were no major changes, and QOL was maintained. [Conclusions] QOL was confirmed to be maintained in patients with clinical remission or low disease activity on Bio. Nurses' proactive contact with RA patients through QOL surveys using AIMS2 etc. is one important factor in long-term maintenance of QOL because it makes it possible to detect abnormalities and changes in effectiveness of treatment early on so the necessary action can be taken

W13-4

Low-dose etanercept cannot control inflammatory synovitis in rheumatoid arthritis patient

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Conflict of interest: None

[Objectives] The aim of this study was to compare the ultrasonographic inflammatory synovitis between patients treated with standard- and low-dose Etanercept (ETN) for RA. [Methods] Patients with RA receiving standard- and low-dose ETN underwent musculoskeletal ultrasonography (US) at 34 synovial sites (30 joints). The GS (Gray scale) and PD (Power Doppler) signals were scored in each joint using a semi-quantitative scale from 0 to 3. Each sum total and the maximum of GSUS and PDUS scores were compared between two groups. [Results] Among 52 patients, we analyzed 11 (25 mg) and 15 (50 mg) patients in remission or low disease activity. Disease activity score-ESR and GSUS score showed no significant differences between groups. However, the sum of PDUS score and maximum PD score were significantly higher in the low-dose ETN group. [Conclusions] Low-dose ETN is not inferior to standard-dose ETN in terms of effects on clinical assessment. However, the effects of low-dose ETN may be inferior to the effects of standard-dose ETN in the synovial inflammation inhibiting effect evaluated ultrasonically. We consider that synovitis may not be suppressed sufficiently, and therefore joint destruction may progress, in RA patients receiving low-dose ETN.

W13-5

Transition of administration of infliximab with rheumatoid arthritis for ten years

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Conflict of interest: None

[Objectives] Examined the transition of patients' background, continuation rate, and dose increasing of infliximab (IFX) for ten years. [Methods] Targets were RA starting administration of IFX between 2003 to 2012. We grouped them by starting administration of IFX every two years, and examined the backgrounds and continuation rate by Kaplan-Meier method. Assessd increasing IFX dose and its efficacy. [Results] We administrated IFX 418 RA cases. The group of 2003-4: n=60, 2005-6: n=87, 2007-8: n =111, 2009-10: n=122, 2011-12: n=38. DAS28 has chlonologically decreased to 5.7, 5.5, 5.2, 4.8, 4.1, J-HAQ has 1.4, 1.4, 1.2, 1.0, 0.9. Concomitant MTX dose has increased from 7.8mg/week to 9.6mg/week, the rate of PSL has decreased from 88.1% to 48.6%, the amount was from 5.7mg/day to 2.9mg/day. Continuation rate of each group has not changed between 68.9% and 74.1% in one year, but 2003-4 has significantly been improved 27.8%, 2005-6 has 38.1%, 2007-8 has 42.7% in five years, 11.6% in ten years. The rate was 35.8% and the amount was 4.0mg/kg after increasing by full bottle, the rate was 12.7% the amount is 6.2mg/kg, after increasing by over bottle. DAS28 has significantly been improved from 4.1 to 3.8 in 8weeks after dose increasing. [Conclusion] Continuation rate of IFX was improved.

W13-6

Clinical research of efficacy for rheumatoid arthritis treated with half dose etanercept (CREATE study) in patients with moderate disease activity

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Fukuoka Biologics Study Group for Rheumatism

Conflict of interest: None

[Objectives] We studied the efficacy of half dose etanercept (ETN) on 26 biologics naive rheumatoid arthritis (RA) patients with moderate disease activity. [Methods] The women constituted 92.3% and median age was 57.8 years. We classified the RA patients with moderate disease activity into higher moderate disease activity group (H-MDA) and lower moderate disease activity (L-MDA) using a cut off level of DAS28-ESR 4.15. The patients with RA received subcutaneous injection of 25mg ETN every week. Clinical response through week 76 was assessed using DAS28-ESR. [Results] In L-MDA group, DAS28-ESR was 3.81±0.26 at enrollment, 2.38±0.79 at week 4, and 2.24±0.84 at week 76. The patients achieved DAS28-ESR remission (score<2.6) in 70.0% at week 4, and in 70.0% at week 76. On the other hand, DAS28-ESR was 4.64±0.27 at enrollment, 3.19±1.09 at week 4, and 2.14±0.85 at week 76 in H-MDA group. The patients achieved DAS28-ESR remission (score<2.6) in 33.3% at week 4, and in 58.0% at week 76. [Conclusion] In RA patients with L-MDA, 25mg dose of ETN every week yielded rapid significant improvement in signs/symptoms with safety, comparing with higher moderate disease activity group.

W14-1

Concomitant Methotrexate did not Affect Discontinuation Rate of Etanercept due to Ineffectiveness: Six-year Results from Japanese Multicenter Registry System

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Conflict of interest: None

[Objectives] Recent studies have highlighted drug immunogenicity as a mechanism behind treatment failure. Concomitant MTX can reduce the production of anti-drug anitibodies resulting in secondary failure. We studied the effect of concomitant MTX on the long-term adherence of etanercept (ETN) and adalimumab (ADA). [Methods] Eligible patients were registered in the TBC registry. RA patients previously unexposed to biologics were treated with ETN (n=560) or ADA (n=234). Drug discontinuation rates were calculated using Kaplan-Meier method using the end-point of inefficacy or adverse events (AEs). [Results] Among the ETN group, the discontinuation rate due to inefficacy were quite similar between the patients with concomitant MTX (n=385) and those without (n=175) (22.2 vs 24.5% at 6 years, p=0.936). Conversely among the ADA group, the patients with concomitant MTX demonstrated significantly lower discontinuation rate due to inefficacy (23.1 vs 36.2% at 4 years, p=0.014). The patients without MTX demonstrated significantly higher discontinuation rate due to AEs both in the ETN and ADA group. [Conclusion] It was quite interesting that the concomitant MTX did not improve the discontinuation rate due to inefficacy in the ETN group. Current data clearly showed the less immunogenicity of ETN.

W14-2

Hepatitis B virus (HBV)-DNA monitoring in occult HBV carrier patients with rheumatoid arthritis during methotrexate and/or biologics therapies

Shunta Kaneko, Yuko Takahashi, Hiroyuki Yamashita, Toshikazu Kano, Hiroshi Kaneko, Akio Mimori
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Conflict of interest: None

[Objectives] To estimate a frequency of hepatitis B virus (HBV) reactivation in RA patients during methotrexate (MTX) and/or biologics therapies. [Methods] Of our RA database, 503 patients had been examined for serum HBs- Ag and HBs-/HBc-antibodies. Infected patients were examined for serum HBV-DNA, and the DNA (+)/Ag (-) subjects (occult carrier) were monitored for the DNA during RA therapies. [Results] A total 109 (21.7 %) infected patients were identified in 503 RA patients. Of these, 8 patients were HB-Ag positive, and 1 (1.7 %) occult carriers were found in the 60 patients examined for serum HBV-DNA. The 8 carriers (the number of cases) had received, MTX (2), biologics (3), sulfasalazine (4), prednisolone (6), bucillamine (2) and tacrolimus (1). In 3 carriers, HBV-DNA was elevated during RA therapies, and the additional treatment by nucleoside analogs decreased the HBV-DNA without development of hepatitis. In the HBV-infected patients including occult carriers, no one developed hepatitis during MTX (a total observation 386 person years), biologics (135 person years), or other therapies. [Conclusion] In the HBV-infected non-carriers, reactivation risk by MTX or biologics therapy may be limited, and 3 of 8 carriers showed the reactivation before antivirus treatments.

W14-3

Evaluation of efficacy and safety of adalimumab on patients with rheumatoid arthritis: Two-year clinical outcome by orthopedic surgeons belonging to the multicenter study in Chiba

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Conflict of interest: Yes

[Objectives] Along with growing usage of biologic agents, orthopedic surgeons have been playing an important role in rheumatoid arthritis (RA) therapy. In 2011, we have established a study group of RA therapy by orthopedic surgeons in Chiba. In this study, we evaluated efficacy and safety of adalimumab (ADA) on RA patients treated at institutions belonging to this group. [Methods] Seventy-two patients with RA treated with ADA in the past 5 years were included in this study. [Results] Demographic characteristics of patients comprised mean age: 55 year-old, mean disease duration: 11.3 years, proportion of MTX use: 82%, PSL use: 61%, and biologics-naïve: 65%. Baseline disease characteristics included mean DAS28: 4.03 and rate of high disease activity: 46.1%. Fifty-two percent reached low disease activity or remission within the first 4 weeks after treatment with ADA, and 51.2% reached remission at 52 weeks. The 2-year survival rate was 66.7% with no severe adverse events. [Conclusion] RA patients treated by orthopedic surgeons in Chiba showed a favorable clinical response to ADA and an acceptable safety profile. In future studies, radiographic and functional outcomes from an orthopedic surgeon's view point should be evaluated in addition to the clinical outcome.

W14-4

Investigation of the pharmacokinetic equivalence, efficacy and safety of the biosimilar product, CT-P13, with its original drug, Infliximab

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Conflict of interest: Yes

[Objectives] To verify the pharmacokinetic (PK) equivalence of the biosimilar product, CT-P13, with its original drug, Remicade®, and compare their efficacy and safety in patients with active rheumatoid arthritis (RA) despite MTX therapy. [Methods] 104 RA patients were coadministered CT-P13 (C Arm; 51 pts) or Remicade® (R Arm; 53 pts), at 3 mg/kg, with MTX (6-16 mg/wk). The PK coprimary endpoints were the AUC_t (weeks 6-14) and C_{max} (week 6). [Results] At Week 14, the geometric mean ratios (90% CI) for the AUC_t and C_{max} of C Arm vs R Arm for anti-drug-antibody-negative patients were 111.62% (100.24-124.29%) and 104.09% (92.12-117.61%). These values met the predefined equivalence range of 80-125%, proving the drugs' PK equivalence. The Simple Disease Activity Indices at Week 54 were 11.00±10.70 and 17.59±14.53. Regarding joint destruction, the change (mean±SD) in the modified Total Sharp Score at Week 54 was 2.06±19.03 and 0.18±19.77. The change (mean±SD) in the Health Assessment Questionnaire score at Week 54 was -0.54±0.61 in C Arm and -0.32±0.49 in R Arm. Adverse events were similar in the arms. [Conclusion] CT-P13 showed PK equivalence with its original drug, Remicade®, in RA patients. The drugs showed similar efficacy and safety.

W14-5

Association between clinical factors and agreement levels of Treat-to-Target strategy in patients with rheumatoid arthritis

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Conflict of interest: None

【Objective】 To determine association between clinical factors and agreement levels of Treat-to-Target (T2T) in rheumatoid arthritis (RA)

patients.【Methods】In 320 RA patients (female 87.5%, mean age 63.8 years old, disease duration 15.5 years, DAS28 3.03, HAQ score 0.56, weekly dosage of MTX 7.28 mg, biologic (BIO) use 30.0%) registered to the KURAMA cohort in Kyoto University Hospital, we used Japanese T2T patients' version for questionnaire of T2T statement. We determined agreement levels of overarching principles (OP) or recommendation (RE) by rating 1 (no agreement) to 10 (full agreement) in each item. Then, association between clinical factor and OP (40 in total) or RE (=100) was studied.【Results】OP agreement level was inversely associated with HAQ score by univariate analysis (r = -0.199, p<0.05). RE agreement had negative association with DAS28 (r = -0.073), HAQ score (r = -0.208), age (r = -0.152) and disease duration (r = -0.182), and positive association with DAS28 remission, MTX and BIO use. By multivariate analysis, HAQ score and BIO use were significantly associated with high level of T2T-RE agreement.【Conclusion】In RA patients, OP and RE agreement levels inversely correlate to HAQ score. In addition, RE agreement has positive correlation to BIO use.

W14-6

Usefulness of Biweekly Administration of 25/50 mg Etanercept in the Elderly with Rheumatoid Arthritis who cannot receive MTX enough

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Conflict of interest: None

[Objectives] Many elderly patients cannot receive enough MTX because of greater decreases in hepatic and renal function, concomitant diseases, etc. Some pts with difficulty in receiving ETN due to financial reasons, self-injection difficulty and weekly clinic visit also exist. The usefulness of ETN in these pts given 25/50 mg every 2 weeks (Q2W) was evaluated. [Methods] Among pts treated with ETN at 25/50mg Q2W, RA pts aged ≥70 yrs with a chance for a follow-up survey for ≥2 yrs were evaluated. Changes in DAS28, SDAI, RF, MMP-3 were retrospectively analyzed. [Results] 11 pts whose mean age was 72.7 yrs were evaluated. Disease duration was 3.3 years. Concomitant MTX use was 81.8% at mean dose of 6.7mg/w. Mean DAS28-ESR, DAS28-CRS, and SDAI were 5.06, 4.33, and 21.06, respectively. Mean DAS28 and SDAI decreased significantly at week 104. DAS28-CRP remission rate was achieved by 45.5%, but SDAI remission was not obtained. Mean RF and MMP-3 also decreased. At week 312, all pts used ETN50 mg Q2W attained DAS28-CRP remission. [Conclusion] ETN25/50mg Q2W can be one of the therapeutic options for RA, considering each pt's condition in clinical settings.

W15-1

Efficacy and safety of tocilizumab in patients with rheumatoid arthritis who suffered from synovitis of larger joints

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Conflict of interest: None

【Objective】 To examine the efficacy and safety of tocilizumab in patients with rheumatoid arthritis (RA) who suffered from synovitis of larger joints. **【Methods】** We defined that RA who suffered from elbow, shoulder, knee and the hip joint as the larger joint type RA. Twenty-four RA patients who fulfilled the criteria of the larger joint type and were introduced Tocilizumab (TCZ) between 2008 to 2012 were evaluated efficacy and safety in 24 and 52 weeks. **【Results】** Of 24 patients, 16 patients were biologics naïve including 8 patients with methotrexate (MTX) treatment. Other 8 patients were used the anti-tumor necrosis factor blocker before TCZ use. Mean age was 60.9 years, and mean disease duration was 10.4 years. Baseline affected shoulder joint were 23, elbow joint were 23, knee joint were 23, hip joint were 0, wrist joint were 24, and ankle joint were 20. At 52 weeks, patients who suffered from larger joint were 6. Mean percent change in DAS 28 (ESR) and DAS28 (CRP) at 24 and 52 weeks were -3.08, -3.15, -3.46, -3.14, respectively. The Boolean remission was achieved in 17 patients at 52 weeks. One patient showed anaphylaxis and another patient had arthritis purulenta **【Conclusion】** These results suggested that TCZ is effective and safety in patients with the larger joint type RA.

W15-2

A 104-week prospective study on the effect on QOL and withdrawal of tocilizumab (TCZ) used as the first biologic: SAQRA study

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Conflict of interest: None

[Objectives] Investigation of QOL after 52 weeks of TCZ treatment and its withdrawal for 52 weeks in RA patients for MTX-IR. [Methods] TCZ was newly introduced, and the drug was withdrawn when remission on DAS28-ESR (DAS) was achieved after 52 weeks of administration. The evaluation items were DAS, HAQ, SF-36, and the continuation rate. [Patient background] The mean age was 60.9 years, and the duration of illness was 5.3 years. [Results] The efficacy at 52 weeks (24 patients) was: DAS28-ESR, 4.9 → 1.8 (P<0.0001, remission rate: 79%); HAQ, 0.92 → 0.55 (P=0.0029, remission rate: 73%); SF-36: PCS, 26.1 → 38.3 (P=0.0164); MCS, 54.4 → 49.1 (P=0.4022). The continuation rate was 92% (adverse event: 1, insufficient effect: 1). The drug was withdrawn at 52 weeks because of remission on DAS, and the 104-week study was completed in 9 patients. The withdrawal continuation rate was 89% (8/9: the disease recurred at 96 w in one). The efficacy was: DAS, 1.60 → 2.14; HAQ, 0.18 → 0.22; PCS, 40.6 →50.7; and MCS, 50.4 → 54.2 (P>0.05). [Conclusion] Only PCS was improved on SF-36, but marked efficacy could be achieved by the administration of TCZ as the first biologic in patients for MTX-IR, and the possibility of withdrawal of the drug in remission cases was suggested.

W15-3

Effects of Tocilizumab on Inflammatory Borne Destruction in Rheumatoid Arthritis

Masayasu Kitano[1], Sachie Kitano[1], Takeo Abe[1], Chie Ogita[1], Yuichi Yokoyama[1], Momo Ishizu[1], Tetsuya Furukawa[1], Takahiro Yoshikawa[1], Katsunori Tanaka[1], Miki Takata[1], Atsushi Saito[1], Aki Nishioka[1], Masahiro Sekiguchi[1], Naoto Azuma[1], Naoaki Hashimoto[2], Shinichiro Tsunoda[1], Kiyoshi Matsui[1], Tsuyoshi Iwasaki[3], Hajime Sano[1]
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Conflict of interest: Yes

[Objectives] To investigate the effect of tocilizumab on bone destruction in rheumatoid arthritis. [Methods] 44 patients with active RA were started on treatment with TCZ intravenously every 4 weeks. Circulating levels of MMP-3, NTx, osteocalcin, sRANKL, OPG, DKK-1, and osteopontin (OPN) were examined by ELISA at baseline and after 12 weeks. In addition, Δchanges of these parameters were analyzed by multivariate analysis. [Results] Average of MMP-3, NTx, DKK-1, and OPN levels at 12 weeks decreased from the baseline (345 vs 152ng/ml; p<0.01, 22.4 vs 19.5nmol BCE/l; p<0.01, 3030 vs 2317pg/ml; p<0.01, 106.4 vs 69.5pg/ml; p<0.01, respectively). Average of osteocalcin levels at 12 weeks increased from the baseline (7.45 vs 8.73ng/ml; p=0.029). Average of sRANKL levels did not change significantly. However, average of OPG levels at 12 weeks increased significantly from the baseline in remission group (4.53 vs 4.96 pmol/l; p<0.01). In results of multivariate analysis, Δchange of MMP-3 correlated with Δchange of OPN (r=0.40; p=0.016) and Δchange of CRP correlated with Δchange of OPN and DKK-1 (r=0.34; p=0.032, r=0.45; p<0.01, respectively). [Conclusion] These results suggest that TCZ may improve inflammatory bone destruction in RA through the regulation of OPN, DKK-1, and OPG expression.

W15-4

Retention rates of alternative biologic agents switched from Tocilizumab due to inadequate response or adverse events in patients with rheumatoid arthritis

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Conflict of interest: None

[Objectives] To compare retention rates of alternative biologic agents switched from Tocilizumab due to inadequate response or adverse events in rheumatoid arthritis (RA) [Methods] All patients who were treated with an alternative biologic agents after inadequate response to or adverse events associated with TCZ were included. We analyzed the reasons of switch and compared the characteristics and retension rates of the alternative biologic agents. [Results] Of all 372 patients treated with tocilizumab, a total of 45 patients were switched from tocilizumab to another biologic agent (34 of anti-TNF (18 of infliximab (IFX), 9 of etanercept (ETN), 4 of adalimumab (ADA), 2 of golimumab (GLM)), 12 of abatacept (ABT) and 1 of tofacitinib (TOF)). The median age of the patients was 59.6 years, 37 were female. 32 (73%) patients were positive for anti-cyclic citrullinated protein antibody. The median duration of TCZ treatment was 10.1 months. The drug retention rates were 55.5% with IFX, 44.4% with ETN, 75% with ADA, 50% with GLM, 30% with ABT, and 0% with TOF. The drug retention rates after inadequate response to TCZ were 71.4% with IFX, 0% with ETN, 75% with ADA, 50% with GLM, 40% with ABT, and 0% with TOF. [Conclusion] Retention rate after switching from TCZ was longer in ani-TNF compared with ABT and TOF.

W15-5

The efficacy and continuity of Tocilizumab treatment with rheumatoid arthritis for 24 months from TBC Registry

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Conflict of interest: None

[Objectives] To evaluate the efficacy and continuity of Tocilizumab (TCZ) treatment for 24 months by using Tsurumai Biologics Communication Registry (TBCR). [Methods] 222 patients with RA have been registrated into TBCR as TCZ users were included in this study. We compared two groups which are **TCZ** treatment with and without MTX. We assessed disease activity with use of DAS28-ESR and SDAI, retention rate of drug continuity with Kaplan-Meier method. [Results] In MTX (+) group and MTX (-) group, the mean age and disease duration of patients were 55.6, 61.0 y.o. and 11.4, 11.6 years, respectively. At the baseline, 6months, 12months, 24months, DAS28-ESR of MTX (+) group, were 5.5, 3.0, 2.7, 2.6, respectively. DAS28-ESR of MTX (-) group were 5.8, 3.4, 3.3, 3.3, respectively. In both groups, the disease activity improved significantly at each time. DAS28-ESR of MTX (+) group was significantly lower than that of MTX (-) group at 6, 12, 24 months. The continuation rates of TCZ treatment in both groups is not significant difference. In MTX (-) group, the discontinuation due to adverse event was significantly higher than in MTX (+) group. [Conclusion] DAS28-ESR in MTX (+) group was significantly improved than that of MTX (-) group at each time.

W15-6

Drug Safety and Survival of Tocilizumab in Comparison to TNF Inhibitors: Soft Tissue Infection Might Increase

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Conflict of interest: None

[Objectives] To compare the difference between TCZ and TNFi on drug survival time, safety and soft tissue infection rates. [Methods] We studied a cohort of rheumatoid arthritis (RA) patients in the Cohort of Arthritis Biologic Users at Kameda Institute (CABUKI) registry from Jan/2003 to Mar/2013. Drug survival estimates were analyzed with log rank test. We used multivariable-adjusted Cox regression model to adjust the confounding variable and compared the difference on safety. We also examined the rate of serious soft tissue infections (SSTIs) and soft tissue infections (STIs), which we analyzed with Fisher's exact test. [Results] We enrolled 305 patients who received TCZ (n=54) and TNFi (n=251). There was no significant difference in drug survival time (p=0.52). Event rates of SAEs did not significantly differ (HR=1.12, p=0.716). Event rates of adverse events (AEs) did not significantly differ (HR=1.31, p=0.231). Among AEs, STIs proportion was significantly different (p=0.013). Among SAEs, SSTIs proportion was not significantly different (p=0.687). [Conclusion] This study showed that the drug survival time and overall safety was comparable between TCZ and TNFi. Although it was not statistically significant in SSTIs group, STIs seem to be increased in TCZ users.

W16-1

Relationships among imaging, clinical, and functional assessments in patients given tocilizumab

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Conflict of interest: None

[Objectives] To investigate relationships among CDAI, imaging assessment (PDUS), and functional assessment in patients administered TCZ. [Methods] Participants comprised 48 patients with RA treated at one of four facilities in Kagoshima Prefecture who satisfied the selection criteria under the JCR guidelines and were given TCZ. Correlations among CDAI, HAQ, and joint ultrasound findings were investigated. [Results] Mean age at the time of treatment was 65.7 years and mean duration of illness of 11.1 years. 23 patients were biopharmaceutical-naïve, while 25 had switched from other drugs. Prior to administration, mean HAQ score was 1.1 and mean DAS–ESR28 was 5.14. Mean CDAI improved from 22.8 prior to starting TCZ administration to 12.4 after 6 months, while mean PDUS improved from 11.7 to 6.0 over the same period. A weak correlation (0.43; $p<0.01$) was observed between CDAI and PDUS prior to administration. A clear positive correlation (0.74; $p<0.001$) was observed for changes at 6 months after initiating TCZ administration. [Conclusion] Correlations were observed between degrees of clinical and functional improvement and degree of improvements on joint ultrasound and PDUS images after initiation of TCZ administration.

W16-2

In rheumatoid arthritis patients with an anti-tumor necrosis factor agent failure, which is better switching to tocilizumab or abatacept?

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Conflict of interest: None

[Background] Rheumatoid arthritis patients who discontinued anti-tumor necrosis factor agents (TNF d RA) may switch to tocilizumab (TCZ) or abatacept (ABC). It remains unclear which therapy is more benefit. [Objectives] To analyze the effectiveness of TCZ versus ABC on drug survival rate in TNF d RA. [Methods] A retrospective study was performed to compare TNF d RA treated with TCZ or an ABC. The primary end-point was drug survival rate. 63 received TCZ and 18 received ABC. [Statistical Analysis] To investigate the 24 month drug survival rate, Kaplan-Meier curves were constructed and compared between the groups with the log-rank test. Cox proportional hazards regression model was constructed to analyze 24 month drug survival rate. Covariates for our multivaliate model were selected by usisng a likelyhood ratio test. [Results] 24 month drug survival rate was significant higher in the TCZ group than the ABC group (79.4% vs 44.4%: $p<0.01$). According to the Cox proportional hazards model employing only one covariates, TCZ therapy was associated with a 70% reduction of 24 month drug discontinuation rate (versus ABC; HR=0.205; $p<0.01$) [Conclusion] We found a significant reduction of the drug discontinuation rate in TNF d RA who received TCZ compared with ABC

W16-3

Comparison of the efficacy and safety of Tocilizumab and Abatacept using propensity score matching method at 52 weeks. ~ The Tsurumai Biologics Communication registry ~

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Conflict of interest: None

[Objectives] These days, there are many reports of studies to compare biologics directly. The comparison between biologics directly will become more important in future. Prospective study is ideal, but difficult in clinical practice. Therefore, we have the propensity score matching method, which is a highly detailed retrospective analytical technique using the data which accumulated until now. [Methods] We investigated 381 RA patients who administrated TCZ or ABT in TBCR from April 2008 to September 2012. We compared the two groups using conventional adjusted logistic regression, as well as matching subjects across age, RA duration, biologic and MTX history, DAS28ESR, stage, class, and MMP-3 using a propensity score to adjust the patient background. [Results] In total, 170 patients (TCZ 85 patients, ABT 85 patients) were enrolled. The average of TCZ patient age, RA duration, rate of using biologics, CDAI was 61.9 years, 12.1 years, 47%, 23.2. That of ABT was 61.8 years, 11.3 years, 55%, 24.4 respectively. The low disease activity and remission rate of CDAI was 61%, 16% in the TCZ group and 41%, 11% in the ABT group at week 52. The rate of adverse events of the TCZ group was 5.9%, and that of the ABT group was 2.4%. [Conclusion] TCZ was more effective than ABT, and ABT was safer than TCZ.

W16-4

Clinical efficacy of abatacept, tocilizumab and etanercept in Japanese rheumatoid arthritis patients with inadequate response to anti-TNF monoclonal antibodies

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Conflict of interest: None

[Objectives] The aim of this study was to compare the efficacy and retention rates of three biologics (abatacept, tocilizumab and etanercept) after switching from first-course anti-TNF monoclonal antibody therapy. [Methods] We performed a retrospective multicenter study of 89 patients who underwent second-course biologic therapy for 52 weeks after switching from first-course anti-TNF monoclonal antibody therapy. [Results] Patients at baseline had a mean age of 58.7 years, mean disease duration of 9.8 years, and mean CDAI of 22.4. There was no significant difference between the three drugs, except in rheumatoid factor positivity. Retention rates for abatacept, tocilizumab and etanercept treatment at 52 weeks were 72.0%, 89.5% and 84.6%, respectively. The evaluation of CDAI indicated no significant difference at 52 weeks among the three drugs. [Conclusion] Our results show that patients treated with abatacept, tocilizumab and etanercept achieved a high response rate with no significant differences in drug retention rates and clinical efficacy. These drugs represent good therapeutic options for patients with RA who are refractory to anti-TNF monoclonal antibody therapy.

W16-5

Clinical outcome in patients with rheumatoid arthritis treated without methotrexate and switched to other biologic agents after etanercept failure - Comparison with abatacept and tocilizumab

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Conflict of interest: None

[Objective] Few studies have examined efficacy of second biologic agents after etanercept failure in patient with RA treated without methotrexate (MTX). In this study, we examine the efficacy of abatacept (ABT) in patients with RA treated without MTX after etanercept failure comparison with tocilizumab (TCZ). [Methods] Patients treated without concomitant MTX therapy and switched to ABT or TCZ after ETN failure for longer than 52 weeks were included, from the Tsurumai Biologics Communication Registry. We retrospectively reviewed the clinical data (DAS28-ESR, CDAI, and drug retention rate). [Results] Numbers of patients were 34/17 (TCZ/ABT). Mean age was 60/64.8 years old and mean disease duration was 9.7/15.9 years ($p=0.008$). Tacrolimus usage rates were 17.6/41.1% and prednisolone usage rate were 82.4/70.6%. Mean DAS28-ESR were 5.9/5.4 at baseline, and at 52 weeks, 3.6/4.2. Mean CDAI were 27.6/33.5 at baseline and 14.9/17.6 at 52 weeks. There was no difference between TCZ and ABT group in DAS28, CDAI at 52 weeks. Drug retention rate were 76.4/88% at 52 weeks. [Conclusion] These data provide additional support for the possible use of ABT in patients treated without MTX and switched to other biologic agents after ETN failure in routine care.

W16-6

Comparison of Tocilizumab and Abatacept for the treatment of Rheumatoid Arthritis

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Conflict of interest: Yes

[Objectives] To comepare the efficacy of Tocilizumab (TCZ) and Abatacept (ABT) for the treatment of rheumatoid arthritis. [Methods] A total of 128 and 97 patients were treated with TCZ and ABT, respectively. Disease activity was assessed usig the Clinical Disease Activity Index (CDAI). [Results] Improvement of CDAI at 1 year was significantly better in TCZ group (7.6 versus 11.4). This tendency was also found for the Bio-naive patients. There was no difference of efficacy between TCZ and ABT in Bionaive patients and in patients who were more than 65 years old. [Conclusion] ABT was suitable for Bionaive and elderly patients.

W17-1

The Involvement of Mast Cells in the Development of Lung Fibrosis via Modulating Pulmonary Fibroblast Immune Function

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Conflict of interest: None

[Background] Mast cells (MC) mediate a variety of inflammatory and fibrotic conditions, but their role in the development of lung fibrosis is unclear. [Methods] Bioptic material was obtained from the involved lung tissue of IPF and CTD-IP. We used immunohistochemistry to identify and quantify MCs, fibroblasts and myofibroblasts. Co-culture of human mast cell line 1 (HMC-1) with pulmonary fibroblasts was performed. Fibroblasts cultured with HMC-1 cells were cytospun and expression of α-smooth muscle actin (SMA), a marker of myofibroblast differentiation, was examined by immunohistochemistry. α-SMA gene expression in fibroblasts, and IL-6, TGF-β, and VEGF in HMC-1 cells and fibroblasts were evaluated by RT-qPCR. [Results] The number of MCs was increased during lung fibrosis. α-SMA mRNA and protein in fibroblasts during co-culture with MCs was up-regurated. In co-cultures of fibroblasts and HMC-1 cells, IL-6, TGF-β and VEGF gene expression was increased in the HMC-1 cells and the fibroblasts. [Conclusion] These findings suggest a novel role for MCs in the development of lung fibrosis via induction of myofibroblast differentiation. An amplification loop is generated between MCs and fibroblasts, enhancing production of pro-fibrotic and angiogenic factors.

W17-2

Examination about prognosis of our interstitial pneumonia (IP) patients associated with Rheumatoid arthritis (RA)

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Conflict of interest: None

[Objectives] We aim to know whether UIP (Usual interstitial peumonia) patients have poor prognosis than NSIP (Non-specific interstitial peumonia) patients among RA-IP patients. [Methods] We reviewed HRCT findings of RA-IP patients attended to our institute in January, 2008. HRCT findings are categorized as UIP pattern or NSIP pattern or other pattern. We observed these patients for five years. [Results] Total RA-IP patients were 59 with 27 males. Among them, RA-IP patients with UIP pattern were 18 with 11 males, those with NSIP pattern were 12 with 2 males, those with other pattern were 29 with 14 males. During five years, 8 RA-IP patients with UIP pattern were died. 1 RA-IP patients with NSIP pattern were died. 1 RA-IP patients with other pattern were died. Only 3 patients with UIP pattern were died due to IP worsening. [Conclusion] RA-IP patient with UIP pattern had apparently poor prognosis. But only 3 of 8 death of those patients were caused by IP worsening.

W17-3

KL-6: a serological biomarker for interstitial lung disease in patients with anti-aminoacyl-tRNA synthetase autoantibodies

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Conflict of interest: None

[Objectives] To investigate whether KL-6 could be used as a marker for interstitial lung disease (ILD) activity and treatment to target for ILD patients with anti-aminoacyl-tRNA synthetase (anti-ARS) autoantibodies. [Methods] Thirty four ILD patients with anti-ARS autoantibodies were included in a retrospective, cross-sectional analysis. Ninteen patients were followed for longitudinal evaluation. We investigated the variation of serum KL-6 levels and in relation to pulmonary function tests. [Results] We evaluate 34 cases of anti-ARS autoantibody positive ILD patients (Jo1:19, PL7:8, PL12:4, Jo+PL7:1, EJ:2) including 19 myositis. Serum levels of KL-6 were inversely correlated with percentages of forced expiratory volume in 1 s (FEV1), vital capacity (VC), forced VC and diffusing capacity of carbon monoxide (DLco). Changes in KL-6 levels showed a significant inverse correlation with changes in VC, FVC and FEV1. The patients whose %VC was more than 80% had significantly lower median KL-6 levels compared with those less than 80%: 463 U/mL (171-701) versus 1275 U/mL (788-2411). [Conclusion] The level of serum KL-6 is repeatedly measurable in ILD patients with anti-ARS autoantibodies and is a promising biomarker for use in clinical practice to assess a clinical response to a treatment.

W17-4

Theraputic treatment for nontuberculous mycobacterial infection complicated with RA in our hospital

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Conflict of interest: None

[Objectives] Nontuberculous mycobacterial (NTM) infection is one of the important diseases on the treatment for RA patients. We clarify diagnostic and therapeutic process in our hospital and to consider the pathology of the disease. [Methods] From January 2008 to October 2013, Among RA patiens with NTM, 28 patients were extracted with enough follow-up data. We clarify RA treatment, disease duration, NTM bacterial stain and medical treatment regimen and prognosis of NTM at the time of onset, and RA treatment (medicationand RA disease activity) and serum MAC antibody conc. [Results] Mean 69.1 year old, 2 male and 24 female patients were enrolled. 6 patients were treated with biologics11 with PSL and 17 with MTX at the time of onset. All patients were diagnosed with MAC, 15 patients were treated with aitibiotics and 8 patient have got worse on chest X-ray view. 11 patients were treated with PSL, 16 with MTX and 2 with biologics at the time of final research. Serum CRP was estimated 1.23 mg/dl, MMP-3 was 199.6 ng/dl, DAS 28 was 3.24, SDAI was 12.3 on average. Serum anti-MAC antibody concentration was measured with 12 patients at an average 2.99U/, and 58% patients were positive. [Conclusion] Prognosis were comparatively good in most patients and no patients died at this study period.

W17-5

Intravenous cyclophosphamide pulse therapy in patients with connective tissue diseases

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Conflict of interest: None

We divided patients who underwent intravenous cyclophosphamide

pulse therapy (IVCY) into 2 groups according to the main target organs, i.e, interstitial lung disease (ILD group) and other organs (non-ILD group), and compared the effectiveness and outcome. The ILD group included 44 patients, consisted of SSc 12, SjS 11, MPA 11, PM/DM 8, RA 7, and others 3. The non-ILD group included 35 patients, consisted of SSc 3, SjS 8, MPA 2, RA 3, MRA 3, SLE 16, GPA 3, EGPA 2, APS 3, and others 2. In the ILD group, the following drugs were used in combination with IVCY; PSL 44, M-PSL pulse 13, CyA 13, Tac 2, and IVIG 4. The rate of combination therapy was high (38.1%). In the ILD group, 28 patients improved but 16 died (death rate 36.3%). The main cause of death in the ILD group was exacerbation of ILD in 13 out of 16, and it is to be note that there were 2 ILD exacerbations induced by TNF blockers. In the non-ILD group, 5 out of 35 died (death rate 14.3%). The causes of death were infectious disease 3, cancer 1, and alveolar hemorrhage 1, respectively. In conclusions, ILD is an important prognostic factor for survival, and IVCY combined with other drugs is not still a sufficient therapy, resulting in encouraging search for new strategies.

W17-6

HRCT (high resolution CT) patterns of interstitial pneumonia (IP) patients associated with Rheumatoid arthritis (RA) of our institute

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Conflict of interest: None

[Objectives] We aim to know whether UIP (Usual interstitial pneumonia) is dominant to NSIP (Non-specific interstitial pneumonia) among RA-IP patients. [Methods] We reviewed HRCT findings and complication of other CVD (collagen vascular disease) of our RA-IP patients between 2008 and 2012. HRCT findings are categorized as UIP pattern or NSIP pattern or other pattern. [Results] Total RA-IP patients were 144 with 65 males. Among them, RA-IP patients with UIP pattern were 30 with 19 males, those with NSIP pattern were 28 with 4 males, those with other pattern were 86 with 42 males. 3 RA-IP patients with UIP pattern complicated other CVD. 10 RA-IP patients with NSIP pattern complicated other CVD. 12 RA-IP patients with other pattern complicated other CVD. [Conclusion] There is no difference between RA-IP patient number with UIP pattern and that with NSIP pattern. Concerning about RA without other CVD, RA-IP patient number with UIP pattern is superior to that with NSIP pattern.

W18-1

A novel mutation in the *PSTPIP1* gene in a patient with PAPA syndrome

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Conflict of interest: None

PAPA syndrome is an autoinflammatory disease linked to mutations in *PSTPIP1* gene. We reported a 22-year-old Japanese male who suffered from recurrent arthritis in knee and ankle joints, pyoderma gangrenosum, acne, and inflammatory bowel disease. We detected a novel heterozygous mutation in the *PSTPIP1* gene. To our knowledge, this is the third case of PAPA syndrome in Japan.

W18-2

Genotype-Phenotype Correlations in Japanese Patients with Familial Mediterranean Fever

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Conflict of interest: None

To investigate genotype-phenotype correlations, we distinguished 308 FMFpatients into two phenotypes: (1) the typical form of FMF, and (2) the incomplete form of FMF according to Tel-Hashomer's criteria. "Typical" FMF phenotype patients had a higher frequency of febrile episodes, a shorter duration of febrile attacks, more frequent thoracic pain, abdominal pain, a family history of FMF, and MEFV exon 10 mutations. Conversely, incomplete FMF phenotype patients had a lower frequency of fever episodes and more frequent arthritis in atypical distribution, myalgia, and MEFV exon 3 mutations. Multivariate analysis showed that the variable associated with typical FMF presentation was the presence of MEFV exon 10 mutations. "Typical" FMF phenotype frequencies were decreased in patients carrying two or single low penetrance mutations compared with those carrying two or single high penetrance mutations (M694I). Patients having more than two MEFV mutations displayed a younger disease onset and a higher prevalence of thoracic pain than those carrying single or no mutations. Thus, MEFV exon 10 mutations are associated with the more typical FMF phenotype. In contrast, more than half of the Japanese FMF patients without MEFV exon 10 mutations present with an incomplete FMF phenotype.

W18-3

MEFV and TNFRSF1A gene mutations in patients with inflammatory myopathy with abundant macrophages

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Conflict of interest: None

[Objectives] Inflammatory myopathy with abundant macrophages (IMAM) is characterized by diffuse infiltration of macrophages in fascia. We analysed MEFV and TNFRSF1A mutations in patients with IMAM. [Methods] Nine patients with IMAM were enrolled. Clinical characteristics and MEFV and TNFRSF1A were analysed. [Results] The patients with IMAM had myalgia, muscle weakness, arthralgia, fever and erythema. The thickening of fascia was observed in STIR images from MRI. In biopsied speciemens, a number of CD68+ macrophages were found apparently in the fascia. In genetic analysis, seven of nine patients had MEFV variants (P369S-R408Q, E148Q-L110P, G304R, R202R and E148Q) and one patient had TNFRSF1A mutation (C43R). [Conclusion] These results suggest that MEFV gene polymorphisms and TNRRSF1A mutations are susceptibility and modifier gene in IMAM.

W18-4

MEFV gene mutation and their clinical significance of patients with Adult onset Still's disease

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Conflict of interest: None

Objectives: Adult-onset Still's disease (AOSD) and Familial Mediterranean fever (FMF) share clinical features in many aspects. We studied the incidence and clinical characteristics of Mediterranean fever (MEFV) gene mutations in Japanese AOSD patients. **Methods:** The study included 48 AOSD patients and 75 healthy controls. In both groups, genomic DNA was genotyped using restriction fragment length polymorphism for MEFV gene mutations. Clinical features of AOSD patients with MEFV mutation were assessed. **Results:** MEFV gene mutations were found in 64.6% of AOSD patients. Allele frequencies in AOSD patients were E84K 2 (2.1%), L110P 7 (7.3%), E148Q 29 (30.2%), R202Q 4 (4.2%), P369S 5 (5.2%), R408Q 4 (4.2%), G634S 1 (1.0%) and M694I 2 (2.1%). Those of healthy controls were E84K 2 (1.3%), L110P 13 (8.7%), E148Q 35 (23.3%), R202Q 5 (3.3%), P369S 6 (4.0%) and R408Q 5 (3.3%). Exon 10 gene mutation was found only in AOSD patients. The frequency of joint pain and spontaneous remission was higher in AOSD patients with MEFV gene mutation than those without mutation. Colchicine was effective in 3 out of 6 patients with mutation. **Conclusions:** MEFV gene mutations might be associated with the development and/or modification of the clinical features of AOSD. Colchicine was effective in some AOSD patients.

W18-5

Mediterranean fever and gout are inflammasome-associated disease

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Conflict of interest: None

Objective: Four gout patients carry Mediterranean fever (MEFV) gene mutation. We examined the association between MEFV mutation and the development and/or clinical features of gout. **Description of Cases: [Case 1]** A 52 y/o female suffered from recurrent episodes of fever, abdominal pain and joint pain. She had tophus with recurrent attacks of gout. She and her daughter, both diagnosed with familial Mediterranean fever (FMF), shared the same MEFV mutation (E148Q and L110P). **[Case 2]** A 60 y/o male suffered from recurrent episodes of fever, chest pain, generalized myalgia and arthralgia. His synovial fluid contained monosodium urate (MSU). MEFV mutation (E148Q). Colchicine worked remarkably. **[Case 3]** A 49 y/o female developed attacks of gout and fever. No clinical features of FMF were found. MEFV mutation (G304R/G304R). She responded extremely well to colchicine therapy. **[Case 4]** A 72 y/o female suffered type 2 diabetes and nephrosclerosis. She had recurrent attacks of gout without FMF features. MEFV gene mutation (R202Q). **Conclusion:** It is suggested that MEFV gene mutation is associated with gout as follows; MSU in gout might trigger the activation of NALP3 inflammasome and production of IL-1β, and pyrin encoded by MEFV mutation cannot regulate the activation of NLRP3 inflammasome.

W18-6

Treatment with tocilizumab were effective for familial Mediterranean fever

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Conflict of interest: None

[Objectives] Four patient with familial Mediterranean fever (FMF) were treated with tocilizumab (TCZ). We examined the effect of this therapy. [Method] FMF was diagnosed based on diagnostic criteria by Migita K et al. of Task Force in the Ministry of Health Labor and Welfare. [Description of Cases] Case1: A 21 y/o female. Mediterranean fever (MEFV) mutation (M694I). She had typical FMF. She had recurrent attacks of FMF using prednisolone (PSL) and methotrexate. TCZ was effective. Case2: A 45 y/o female. MEFV mutation (E148Q/P369S). She had FMF variant. She had recurrent attacks of FMF using PSL and cyclosporin. TCZ was effective. Case3: A 28 y/o female. MEFV mutation (E148Q/P369S). She had FMF variant. She had attacks of FMF using colchicine and PSL. TCZ was effective. Case4: A 77 y/o male. MEFV mutation (E148Q). He had typical FMF. He responded extremely well to colchicine. But the symptoms relapsed using colchicine. TCZ was effective. [Conclusions] Colchicine is the established first-line therapy for FMF. However, this was not effective in 2 of 4 patients, and tocilizumab was effective for all patients. It is suggested that tocilizumab therapy might be second-line therapy for FMF.

W19-1

Expression of mitochondrial transcription factor A (TFAM) decreases in RA synovial cells

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Conflict of interest: Yes

[Objectives] Some reports showed that oxidative stress and decrease of apoptosis in synovial tissues play important roles in the disease etiology of RA. These factors are influenced by mitochondrial function. However, there are few study studies about the investigation of mitochondrial functions and mitochondrial transcription factors in RA. In this study, we investigated mitochondrial related factors in RA fibroblast-like synovial cells (FLS) compared with OA-FLS synovial cells. [Methods] RA and OA-FLS were obtained during knee surgery (n=8 each). We investigated mRNA expression of PGC-1a, NRF-1, TFAM, Lon protease and cycline D in RA and OA-FLS using realtime PCR. [Results] The expressions of NRF and TFAM in RA-FLS were significant lower than OA-FLS. On the other hand, the expression of PGC-1α and Lon protease were not significantly different between RA and OA-FLS. The expression of cycline D in RA-FLS was significantly increased than OA-FLS. [Conclusion] We showed that the mitochondrial related factors such as NRF-1 and TFAM were decreased in RA-FLS, which might be related to the increase of cycline D expression. These results may cause the decrease of the amount of mitochondria and the decrease of mitochondrial function in RA-FLS, and they might be related to the etiology of RA.

W19-2

Pathological changes in rheumatoid arthritis synovial tissues by biologics

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Conflict of interest: None

[Objectives] Various reports were made on actions of biological

drugs over pathological findings of RA synovial tissues. Specimens from RA patients undergoing surgeries before and after the use of drugs were observed using their pathological findings, to assess actions of such drugs. [Methods] Observation of specimens from 18 RA joints, evaluating inflammatory changes using the Rooney's system without fibrosis and proliferating blood vessels, examining the correlation between pathological findings when using drugs and the disease activity, and evaluating the latter with the CDAI. Were used Etanercept on 10 joints, Infliximab on 4, Tocilizumab on 2, Adalimumab on 1 and Abatacept on 1 join*t.* [Results] Before and after the use of drugs were significant as inflammatory scores improved from 21.8 to 6.4, with reduced synoviocyte hyperplasia, perivascular and diffuse infiltrates of lymphocytes, focal aggregates of lymphocytes in groups in remission or low after drug use. Not significant for moderate groups. [Conclusion] Biological drugs reduce inflammatory changes in both synovial lining cells and sublining layer. The study also suggests pathological findings on those sublining layers reflect a disease activity.

W19-3

Histologic and immunohistochemical evaluation of adverse reactions to metal debris following metal-on-metal total hip arthroplasty

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Conflict of interest: None

[Objectives] The pathologic term of ALVAL (aseptic lymphocyte-dominated vasculitis-associated lesion) has been used for adverse reactions to metal debris (ARMD) following metal-on-metal total hip arthroplasty (THA). We studied histologic and immunohistochemical evaluation of ARMD following large-diameter metal-on-metal THA. [Methods] Twelve hips (ten patients) were determined ALVAL score described by Campbell et al. The synovial-like tissue specimens in revised patients were examined by immunohistochemistry using antibodies to T lymphocytes (CD3) and B lymphocytes (CD20). A lymphocyte transformation test was performed in these patients. [Results] The mean ALVAL score was 7 points. Immunohistochemical study revealed that eight ARMD hips showed dominant CD20 positive B lymphocytes infiltration and four ARMD hips showed dominant CD3 positive T lymphocytes. Only one patient had a positive lymphocyte transformation test indicating lymphocyte proliferation to cobalt. [Conclusion] The present study suggested that T cell mediated type IV hypersensitivity might not be the dominant biological reaction involved in the occurrence of ARMD, but rather, the formation of tertiary lymphoid organs might be the contributor.

W19-4

Analysis of the Mechanism of Differentiation and Function of Osteoclast-like Cells Induced by Combination of Tumor Necrosis Factor α and Interleukin 6

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Conflict of interest: None

[Objectives] Local bone destruction associated with RA is partially controllable by biological agents targeting TNFα or IL-6. We elucidated the mechanism of differentiation and function of osteoclast-like cells (OLCs) induced by the combination of TNFα and IL-6. [Methods] We cultured osteoclast precursors from the femora of mice in the presence of M-CSF, TNFα, IL-6 and TNFα plus IL-6. The expression levels of c-Fos and NFATc1 were detected by Western blotting. The effects of anti-IL-1β antibody and JAK inhibitor were examined. The genetic ablation of STAT3 was also evaluated. These cytokines were administered into the supracalvariae in mice. [Results] The combination of TNFα and IL-6 induced TRAP-positive OLCs in an RANKL-independent manner. Stimulation with TNFα and IL-6 significantly induced the expression levels of c-Fos and NFATc1. The differentiation of OLCs was completely inhibited by JAK inhibitor but not anti-IL-1β antibody. We observed no difference in the induction of OLCs derived from STAT3-knockout mice and control mice. Bone resorption on the calvariae in mice was significantly increased, once the combination of TNFα and IL-6 was administered. [Conclusion] We have found a novel mechanism developing OLCs with the combination of TNFα and IL-6.

W19-5

Directly reprogrammed osteoblasts genetically engineered to produced interleukin-10 significantly suppress osteoclastgenesis

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Conflict of interest: None

[Objectives] Recent reports demonstrated that somatic cells such as fibroblasts can be directly converted into other cell types (ex. neurons and cardiomyocytes) by introducing critical transcription factors that regulate the differentiation of the corresponding cell lineages. We tried to induce IL-10-producing osteoblasts from fibroblasts as a potential therapeutic tool against the inflammation and bone destruction of rheumatoid arthritis. [Methods] Runx2 gene was transduced into mouse embryonic fibroblasts (MEFs), and the resultant cells were characterized by qRT-PCR, alkaline phosphatase staining, and alizarine red S staining. IL-10 gene was also transduced to some cells, and IL-10 production was measured by qRT-PCR and ELISA. The supernatant was added to a mouse macrophage cell line Raw264.7 cells that were induced to differentiate into osteoclasts by an addition of RANKL. [Results] Runx2-transduced MEFs massively produced bone matrix and induced calcium deposition. Co-transduction of IL-10 gene resulted in generation of osteoblasts that produced IL-10. The supernatant of the cells significantly suppressed osteoclast differentiation of Raw264.7. [Conclusion] IL-10-secreting osteoblasts were successfully generated from fibroblasts by direct reprogramming procedures.

W19-6

Inhibitory effects of FGF-8 and TNFα on BMP-induced osteoblast differentiation

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Conflict of interest: None

[Objectives, Methods] TNFα plays a predominant role in bone loss in arthritis. We earlier reported that TNFα inhibits BMP-induced osteoblast differentiation through JNK and NF-κB pathways. FGF-8 is known as a key regulator for limb development and cranial formation; however, the detailed mechanism of FGF-8 in osteoblasts remains to be elucidated. We here studied the effects of FGF-8 in relation to TNFα actions on BMP-induced osteoblastic differentiation. [Results] It was found that FGF-8 inhibited BMP-2-induced expression of osteoblast markers in a concentration-dependent manner. The efficacy of FGF-8 was smaller than that of TNFα in the experiments using myoblast C2C12, MC3T3-E1 and rat osteoblasts. Of note, the effects of FGF-8 on BMP-induced osteoblastic differentiation and Smad1/5/8 activation were enhanced by TNFα. FGF-8 had no influence on the expression of TNFRs, while FGF-8 increased the expression of ALK2/3 but reduced the expression of inhibitory Smad6/7. Moreover, the MEK inhibitor, but not JNK or NF-κB inhibitors, suppressed the effect of FGF-8 on BMP-induced osteoblast differentiation. [Conclusion] Thus, it was revealed that FGF-8 inhibits BMP-induced osteoblast differentiation via the ERK pathway and the effects were further enhanced by TNFα activity.

W20-1

Preliminary guidelines for the management of RA 2014 in Japan, from MHLW study group (1) Methods and the details

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Conflict of interest: Yes

[Objectives] To establish guidelines for the management of RA in the daily practice in Japan. [Methods] As a project of MHWL study group, a new guideline has been developed, using the newly proposed GRADE (Grading of Recommendations, Assessment, Development and Evaluation) method. [Results] According to the recommendation of GRADE method, evidences were evaluated as below. 1. Confidence in the estimates of effect: 88 clinical questions were evaluated by 10 members, by using the existing systematic reviews if available. If not available, a new systematic review was conducted. 2. The balance of desirable and undesirable outcomes of interest: clinical data of every drugs with indication for rheumatoid arthritis has been collected from the pharmaceutical companies. 3. Estimates of values and preferences: Questionnaire for the member of patients association and interview for the focus group was conducted. 4. Resource use: Annual cost was calculated. Finally, 38 recommendations were created, and a panel discussion was held among specialists of rheumatology, statistics and pharmacoeconomics, together with the representatives of patients association. Modified Delphi method was used for the consensus building. [Conclusion] After collecting the public comment, the guidelines will be published.

W20-2

Preliminary guidelines for the management of RA 2014 in Japan, from MHLW study group (2) MTX

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Conflict of interest: Yes

【Purpose】To establish guidelines for MTX use in the management of RA in the daily practice in Japan.【Methods】As a project of MHWL study group, new guidelines have been developed, using the newly proposed GRADE method. Clinical questions about MTX use were evaluated by using the existing systematic reviews if available. If not available, a new systematic review with other supportive evidences was conducted. Finally, recommendations indicating recommended strength as strong or weak were created. In a panel discussion held by a variety of specialists, modified Delphi method was used for the consensus building. I adopted 4 points or more as a recommendation at 5 points of perfect scores.【Results】Recommendations (recommended strength/agreement score) were as followed. 1. The MTX use to non MTX inadequate responders is recommended. (strong/5.0) 2. Additional DMARDs combination therapy to non MTX inadequate responders is recommended. (weak/4.17) 3. Both a single dose and divided dose of MTX are recommended. (weak/4.39) 4. The use of folic acid and folinic acid in RA patients receiving MTX is recommended. (weak/4.89) 5. The discontinuation of MTX use at perioperative period is not recommended. (weak/4.78)【Conclusion】Recommendations regarding MTX use for guidelines were determined.

W20-3

Preliminary guidelines for the management of RA 2014 in Japan, from MHLW study group (3) DMARDs

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Conflict of interest: None

[Objectives] To establish guidelines for DMARDs use in the management of RA in the daily practice in Japan. [Methods] As a project of MHWL study group, new guidelines have been developed, using the newly proposed GRADE method. For construction of evidence for this issue, we used the Cochrane library systematic reviews and conducted a new systematic review for other supportive evidences. Finally, recommendations with recommended strength as strong or weak were created. A panel discussion was held among specialists of rheumatology, statistics and pharmacoeconomy, together with the representatives of patients association. Modified Delphi method was used for the Occupational therapy

the consensus building. The recommendations with 4 or more on 5-point scale were adopted. [Results] Preliminary recommendations (recommended strength/agreement score) are as follows. Salazosulfapyridine is strongly recommended. Injectable gold, bucillamine and tacrolimus are weakly recommended. Leflunomide and iguratimod are weakly and conditionally recommended. Consensus points are 4.5, 4.3, 4.2, 4.2, 4.3, and 4.0, respectively. After collecting the public comment, the guidelines will be published. [Conclusion] Recommendations regarding DMARDs for the guidelines were determined.

W20-4

Preliminary guideline for the management of RA 2014 in Japan, from MHLW study group (4) Biologics

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Conflict of interest: None

[Objectives] To establish guidelines for biologics use in the management of RA in the daily practice in Japan. [Methods] As a project of MHWL study group, new guidelines have been developed, using the newly proposed GRADE method. SLRs about efficacy and safety in seven biologics, as well as discontinuation of biologics in perioperative period, were performed with Cochrane, Igaku-Chuo Zasshi and PubMed. Next, we proposed the statements with strength of recommendation (strong/weak), calculated consensus score (up to 5) by vote at panel session, and the statements with more than 4.0 were adopted. Comparative analyses between drugs were not performed due to different baseline characteristics. [Results] Preliminary statements (strength/consensus score) are as follows: 1. Use of biologics is recommended for RA patients with relevant disease activity, while requiring careful consideration of risk/benefit for each patient." (Strong/ IFX 4.95, ETN 4.95, TCZ 4.94, ADA 4.95, ABT 4.94, GLM 4.84, CZP 4.79, respectively) 2. Discontinuation of biologics in perioperative period is recommended. (Weak/ 4.59) [Conclusion] Preliminary recommendations regarding biologics for the guideline were determined. The guidelines will be officially released after further correction with public comments.

W20-5

Preliminary guidelines for the management of RA 2014 in Japan, from MHLW study group (5) Surgical treatment

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Conflict of interest: Yes

[Objectives] To determine recommendation statements regarding surgical treatments for the novel guidelines. [Methods] SLR was performed with the Cochrane library, Igaku-Chuo Zasshi and PubMed about efficacy, selection, and complications with a biological agent of surgical treatments to answer clinical questions. Next, we assessed quality of evidence, determined the statements with strength of recommendation, and calculated agreement score (up to 5) by vote at panel session. [Results] All of the surgical treatments raised in CQ were 'recommended', and in the comparisons between two procedures, both were recommended in any comparison. For complications, 'careful attention should be paid' was recommended in each of CQ. Agreement scores were; THA, 4.79±0.42; TKA, 4.84±0.37; TEA, 4.14±0.86; TSA/HA, 4.42±0.69; TAA, 4.33±0.77, and cement vs cementless in THA, 4.42±0.69; TSA vs HA in shoulder arthroplasty, 4.39±0.61; TAA vs arthrodesis in ankle, 4.21±0.80, respectively. In complications, Agreement scores were; SSI, 4.74±0.45; would healing delay, 4.74±0.45, respectively. [Conclusion] Recommendation regarding surgical treatment for the guidelines was determined.

W20-6

Preliminary guidelines for the management of RA 2014 in Japan, from MHLW study group (6) Rehabilitation

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Conflict of interest: Yes

[Objectives] To establish guidelines of rehabilitation including exercise, patient education, occupational therapy for the patients with rheumatoid arthritis in the daily practice in Japan. [Methods] As a project of MHWL study group, new guidelines have been developed, using the newly proposed GRADE (Grading of Recommendations, Assessment, Development and Evaluation) method. For construction of evidence for this issue, we used the Cochrane library systematic reviews and their update to 2012, a panel discussion was held among specialists of rheumatology, statistics and pharmacoeconomy, together with the representatives of patients association. Modified Delphi method was used for the consensus building. [Results] Preliminary recommendations for rehabilitation are as follows; Patient education, exercise, and occupational therapy are strongly recommended for the patients with rheumatoid arthritis. Temporal articular injection of glucocorticoid for the patients with adequate response to conventional and biological DMARDs is weakly recommended. Consensus points are 4.94, 4.95, 4.95, and 4,56, respectively. After collecting the public comment, the guidelines will be published. [Conclusion] These issues are very important for daily practice of RA.

W20-7

Preliminary guideline for the management of RA 2014 in Japan, from MHLW study group (7) Comorbidities

Hirahito Endo[1], Yuko Kaneko[2], Yutaka Kawahito[3], Toshihisa Kojima[4], Mitsumasa Kishimoto[5], Shintaro Hirata[6], Yohei Seto[7], Hiromu Ito[8], Keiichiro Nishida[9], Isao Matsushita[10], Kiichiro Tsutani[11], Ataru Igarashi[11], Naoyuki Kamatani[7], Mieko Hasegawa[12], Masayo Kojima[13], Nobuyuki Miyasaka[14], Hisashi Yamanaka[7]

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Conflict of interest: None

[Objectives] To establish a guideline for the management of RA with comorbidities or pregnancy in the daily practice in Japan. [Methods] As a project of MHWL study group, a new guideline has been developed, using the newly proposed GRADE (Grading of Recommendations, Assessment, Development and Evaluation) method. Evidence about DMARDs and biologics treatment for RA with comorbidities (respiratory, cardiovascular, renal, hepatic disorders, diabetes and autoimmune diseases, respectively) was evaluated. We also evaluate the recommendations for the use of DMARDs and biologics in RA patients with pregnancy and lactation. [Results] There are no high grade evidence for treatment of RA with several comorbidities and pregnancy. Treatment of DMARDs and biologics in RA patients with comorbidities should consider both the benefits and the risk. This grade of recommendation is strong. Treatment of DMARDs and biologics in RA with pregnancy and lactation should consider both of the benefit and the risk. This grade of recommendation is strong. Modified Delphi method was used for the consensus building. [Conclusion] Preliminary recommendation regarding DMARDs therapy in RA with comorbidities for the guideline was determined. After collecting the public comment, the guideline will be published.

W20-8

Preliminary guidelines for the management of RA 2014 in Japan, from MHLW study group (8) Patients' values and preferences; Findings from questionnaire survey and focus group

Masayo Kojima[1], Yutaka Kawahito[2], Yuko Kaneko[3], Mitsumasa Kishimoto[4], Shintaro Hirata[5], Yohei Seto[6], Hirahito Endo[7], Hiromu Ito[8], Toshihisa Kojima[9], Keiichiro Nishida[10], Isao Matsushita[11], Kiichiro Tsutani[12], Ataru Igarashi[12], Naoyuki Kamatani[6], Mieko Hasegawa[13], Nobuyuki Miyasaka[14], Hisashi Yamanaka[6]

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Conflict of interest: None

【Objectives】To explore the patients' values and preferences in the choice of therapies in RA.【Methods】We conducted a questionnaire survey to 2,222 patients randomly selected from the members of the Japan Rheumatism Friendship Association stratified by age and area. The study participants completed questionnaires with an open-ended question asking what they need from their doctors and/or medical care. A focus group with 5 RA patients was conducted successively to explorer the variance of patient values and preferences.【Results】Total of 1,470 patients returned the questionnaire. Logistic regression analysis revealed that having discussion about treatment goals with doctors was more likely to be associated with high satisfaction, comparing to explanation only (Odds Ratio, OR; 1.8, $p<0.001$) or no explanation (OR; 3.5, $p<0.001$). The results were unchanged even after controlling for confounders. Content analysis of the patients' needs found relatively small variance of patients' values. Focus group confirmed that any therapies involved safety and cost problems so that patients could accept them only after having appropriate explanation from doctors.【Conclusion】Questionnaire surveys and focus group are useful to collect information regarding patients' values and preferences.

W21-1

The Relationship Between Disease Activity, Disease Duration, and Physical Function

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Conflict of interest: None

[Objectives] In RA treatment, as well as clinical remission, to win the functional remission is also an important goal. The relationship between disease activity, disease duration, and physical function, were analyzed. [Methods] 512 cases of RA patients our hospital outpatient were intended. Physical function evaluation was evaluated and examined using HAQ, and disease activity DAS28-CRP. [Results] HAQ-DI was correlated with DAS28-CRP and disease duration, it was worse in accordance with them. Morbidity early example (<2 years), a strong correlation was observed in DAS28-CRP and HAQ-DI. Patient global assessment (patient VAS) had a strong correlation with the HAQ-DI in most of the compo-

nents of the DAS28-CRP. Meet the patient VAS under10mm it is 50.3% in the cases of the HAQ-DI <0.5, but only 16.0% in the cases of the HAQ-DI ≧ 0.5. [Conclusion] HAQ-DI is correlated with DAS28-CRP, in order to prevent the progression of dysfunction or gain of function remission, reducing the disease activity is important. In addition, HAQ-DI is also associated with patient VAS. There is a possibility to lower the VAS and HAQ by improving functional impairment, such as surgery, and lead to functional remission and clinical remission.

W21-2

Cost-effectiveness analysis of DMARDs and biolosics therapy (annual report from Ninja 2012)-The increase of DMARDs' cost is ending?-

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Conflict of interest: None

[Objectives] To evaluate the balance between the clinical effects of recent anti-rheumatic treatment and its cost by following up the annual change of them. [Method] The Data from RA patients registered in the large cohort database (NinJa; National database of rheumatic diseases by iR-net in Japan) in 2002-2012 was analyzed. They included disease activity, mHAQ, and dosage of DMARDs (biologics and others). The annual cost-effectiveness calculated from clinical index and the cost of DMARDs. [Results] The averages of DAS28, SDAI, and mHAQ were decreasing and the percentages of patients with low disease activity and patients with remission were increasing constantly. The annual cost of DMARDs was about 430,000 yen / patient in 2012. That was almost same in 2011. The cost of TCZ per registered patient decreased 16,000 yen. The rate of the cost of biologics for total DMARDs' cost was 75.4%. That increased slightly. ([The rate of the number of low activity patients to that of high activity patients] / cost) increased since 2009 and reached near the level in 2003 (pre-bio-era in Japan). [Conclusion] The increase of the DMARDs' cost almost stopped in 2012. The reason might be the price revision of TCZ. The cost-effectiveness of DMARDs was improving steadily.

W21-3

HAQ analysis using NinJa 2012data base

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Conflict of interest: None

[Objectives] To clarify the characteristics of HAQ and its items from the point of view of disease duration and disease activity of RA. [Methods] Analysis was performed using NinJa 2012 data base. [Results and Discussion] 1) HAQ score was on the almost same trend in the patients of disease duration under 10 years. 2) At the early stage of RA, the score of #4 "Get in and out of bed" seemed to have a association with disease activity, while at the late stage of RA, #11 "Take a bath" seemed to be correlated with disease duration. Discussion: We could show that patients activity was preserved during the early and middle disease duration (≦ 10y) under the good disease control. Questionnaire #4 seemed to have relation to activity-related HAQ (ACT-HAQ), whereas #11 to damage-related HAQ (DAM-HAQ).

W21-4

SDAI is inferior to DAS28 with respect to assessing large joints, the major player of physical disability: A Nationwide study based on the *NinJa* (National database of rheumatic diseases by IR-Net in JAPAN) 2012

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Conflict of interest: None

Objective: We have reported that HAQ was highly impacted by large joints at the annual meeting of JCR. We analyzed which composite measure, SDAI or DAS28 was better to assess large joints. ***Methods:*** Total joint indices were calculated as described previously.[1] Data of stage, HAQ-DI, SDAI, DAS28-CRP4 were extracted from *NinJa* database 2012. We compared HAQ, SDAI, and DAS28 between the two groups, group A: joint index >0 (presence of arthritis) in large joint region and joint index =0 (absence of arthritis) in small joint region, and group B: joint index =0 in large joint region and joint index >0 in small joint region. ***Results:*** In all stage, HAQ and DAS28 in group A were significantly higher than those in group B. In contrast, SDAI did not differ between the two groups in stage I, II and III. Only in final stage IV, patients in group A had significant high SDAI score than group B. ***Conclusion:*** Regarding the assessment of affected large joints which have great influence upon HAQ, SDAI was inferior to DAS28. ***Reference:*** 1. Nishiyama S, et al. Rheumatol Int. 2012:32;2569-71

W21-5

Survey on the understanding and practice of T2T for nurses engaged in medical treatment of the rheumatoid arthritis

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Conflict of interest: None

[Objectives] Importance of T2T has been proposed in the EULAR recommendations for nurses (Ns). **[Methods]** Carried out survey to Ns for awareness about T2T. **[Method]** Self-administered survey was carried out for understanding DAS28, T2T, patient guidance. Pearson chi-square was used for significant difference test. **[Results]** 103 Ns were enrolled (one male and Ave. one month and 5-year in RA medical). 19 Ns knew the concept of T2T exactly, 47 partially and 37 did not. In comparison with 37 Ns who do not know T2T, 66 Ns who knew T2T showed higher knowledge about DAS28. Experience of DAS calculation and the knowledge of T2T were mutually associated. Ns who understand T2T engaged in guidance of daily life, description of therapeutic agent and health care system. 126 Drs, 21 Ns, 8 patients carried out joint score, and Ns who do not know T2T showed a tendency to ask Dr to count. The benefits of direct measurement of joint score for Dr were knowledge enhancement and technical improvement, and for Ns resulted in the broadening of nursing care and DAS score before consultation. Considering the gap scoring between Dr and Ns, training was recommended. **[Conclusion]** This study indicates that understanding the concepts of T2T may increase the expertise and expand the area of nurse activity.

W21-6

A treat-to-target strategy in early rheumatoid arthritis in daily clinical practice

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Conflict of interest: None

[Objectives] Clinical remission is the therapeutic goal in rheumatoid arthritis (RA). The objective of this study was to implement and evaluate a treat-to-target strategy in early RA in daily clinical practice. [Methods] The study included 40 patients with early rheumatoid arthritis (RA) between April 2012 and March 2013. The patients were treated according to the American College of Rheumatology (ACR) recommendations up-

date in 2012. The primary outcome was the percentage of the patients who achieved a therapeutic goal within six month. Second outcome was time to remission [Results] Sixty percent of the patients achieved the therapeutic goal. At 3 months, 27.5% of the patients achieved remission and 37.5% achieved remission at 6 months. Sixteen patients were not achieved the goal. Six patients who were not achieved the goal were not implemented a treat-to-target strategy because of complications. [Conclusion] The implementation of this treat-to-target strategy according to ACR recommendations demonstrated that achieving remission in daily clinical practice is a realistic goal.

W22-1

Pathogenesis of intersitial lung disease accompanied with juvenile dermatomyositis

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Conflict of interest: None

[Objectives] Rapidly progressive Interstitial lung disease (RP-ILD) is an intractable and fetal complication of juvenile dermatomyositis (JDM) in Japan. The aim of this study was to reveal the pathogenesis of those disease. [Methods] We reviewed the findings of pulmonary pathology from autopsy from 5 patients with RP-ILD, and evaluated the results of blood examination from 31 patients with ILD (8 decased). ILD was identified on high-resolution computed tomography. [Results] 8 patients were diagnosed with RP-ILD, and 20 with chronic or asymptomatic ILD. The autopsy from all 5 patients showed diffuse alveolar damage pattern, such as diffuse distribution, alveolar organizinf fibrosis, alveolar septal thicking, alveolar fibrin and alveolar and tracheal hemmorrhage. Honeycombing was not seen. 19 of 24 patients had positive levels of anti-MDA5 antibodies, and the values of serum AST, ALT, LDH, ferittin and FDP-DD in the patients with RP-ILD were significantly higher than those in the patients with non RP-ILD. [Conclusion] These results suggests that the vasculits may play a roles in the pathogenesis of RP-ILD with JDM.

W22-2

Serum interleukin-18 as a diagnostic criterion of remission in systemic juvenile idiopathic arthritis

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Conflict of interest: None

[Objectives] To investigate whether serum IL-18 can be used as a marker to predict the prognosis of s-JIA and as a diagnostic criterion of remission in s-JIA. **[Methods]** We serially measured serum levels of IL-18 in fourteen patients with s-JIA until they had relapse or until they achieved remission. Serum levels of IL-18 were evaluated by commercial enzyme-linked immunosorbent assay. **[Results]** Seven out of fourteen patients had relapse of their disease during inactive phase within twelve months after disease onset (group A). The other seven patients achieved remission on medication (group B). Five out of these seven patients also achieved remission off medication. Longitudinal examination in group A patients clearly demonstrated sustained elevation of serum IL-18 over 1,000 pg/ml during inactive phase. On the other hand, longitudinal examination in group B patients showed serum IL-18 decreased to the normal levels less than 1,000 pg/ml within about six months. **[Conclusions]** Our results indicate that serum IL-18 level reflects the biological activities of immune system in s-JIA and might predict the prognosis of s-JIA. Serum IL-18 might be useful as a diagnostic laboratory criterion for clinical remission in s-JIA.

W22-3

The precedent symptoms of Behcet's disease (BD) in childhood to the diagnosis

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Conflict of interest: None

[Aim] To investigate (the precedent) symptoms of BD in childhood prior to fulfillment the diagnostic criteria after 16 years of age. [Methods] Eight BD patients (10.1%) out of 79, all who visited our hospital in recent 2 years (2009-2011), developed the symptoms of BD preceding under 16 year-old (y/o). Each doctor of these patients obtained informed consent to analyzed their HLA-A and B loci. [Results] The characteristics of the 8 were as follows: all fulfilled the Japanese and international criteria of BD; males, 37.5%; mean age (SD), 31.5 (9.0) y/o; oral aphthous ulcers (OU) and skin lesions, 100%; genital lesions, 75%; arthritis, 62.5%; ocular lesions, 50%; intestinal lesions, 25%; epidydimitis, 33.3% in the males; neural and vascular lesions, and positive pathergy test were absent. The precedent BD symptom under 16 y/o was only OU. All of others were over 15 y/o. Seven patients out of 8 were analyzed thier HLA. Eight alleles of HLA-A locus and 9 B were detected; however, no difference was detected between our patients and normal controls. Treatment was bellow: colchicine, 87.5%; NSAIDs, 62.5%; MTX, 12.5%; some stomach medicine, 87.5%: mucosal protestant (50%), H2-blocker (25%), PPI (25%); no PSL user. [Conclusion] The OU was the precedent symptoms of Behcet's disease to the onset.

W22-4

Characteristics of the infants born from mothers with autoimmune disorders

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Conflict of interest: None

[Objectives] Sufficient attentions are required for pregnancy complicated with autoimmune disorders. Characteristics of the newborn infants from mothers with autoimmune disorders were evaluated. [Methods] Clinical manifestations were assessed in 39 newborn infants from 37 mothers with autoimmune disororders visited Tokyo Women's Medical University Hospital from January 2011 to November 2013. [Results] Nineteen mothers had anti-Ro/SS-A, 5 had anti-La/SS-B antibodies. Twenty-one (56.8%) treated with oral glucocorticoid (GC) during pregnancy. The average gestational age (GA) at birth was 36.9 weeks and 14 of 37 had preterm birth. Average birth weight (BW) was 2,337g (508-3,676g) including 56.4% of low birth weight (LBW). The average GA and BW of babies whose mothers treated with GC was 36.0weeks, and 2,163g, suggesting that GC may be a factor which affects GA and BW. Auto-antibodies were recognized in 20 infants. Anti-Ro/SS-A in 17 and anti-La/SS-B in 3. No baby had complete heart block. Rash, thrombocytopenia, anemia developed in 1, 5, and 1 infant, respectively. [Conclusion] The probability of premature delivery and LBW infants were higher, and more remarkable in mothers treated with GC. Continued observation by pediatricians is important until auto-antibodies disappears.

W22-5

Discontinuation of Tocilizumab after Clinical Remission in Patients with Severe Systemic-onset Juvenile Idiopathic Arthritis

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Conflict of interest: None

[Objectives] The first line therapy for patients with systemic-onset juvenile idiopathic arthritis (s-JIA) has long been corticosteroids, and a half of them needed high-dose and long-term administration. Recently, tocilizumab (TCZ) made it possible to achieve remission even in the severe type of s-JIA. The purposes are to reveal the variables of discontinuation of TCZ and to find the predictors of flare. [Methods] We reviewed

the medical records of 23 patients with s-JIA who discontinued TCZ. [Results] Eleven patients were maintained remission after discontinuation of TCZ (groupR), and 12 flared (groupF). TCZ was introduced earlier in patients in groupR (the mean disease duration at the initiation of TCZ was 32 months) than in those in groupF (43 months). Patients of groupF had flare early (2-13 months). The flare was triggered by infection in 7 patients (URI 5, flu 1, varicella 1), by exercise in 2 and unknown in 3. Any laboratory data were't able to predict the flare, thus, other predictive markers will be investigated. [Conclusion] The earlier TCZ was introduced in the disease course, the better the patients' outcome was. The standardization of clinical and laboratory criteria to start withdrawal of TCZ and to reveal the risk of flare will be of value to manage the children with s-JIA.

W22-6

Early results from PRICURE registry and it's challenges for the future

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Conflict of interest: None

Performing quality clinical and translational research in pediatric rheumatic diseases (eg. Juvenile Idiopathic Arthritis, Child onset Systemic Lupus Erythematosus and Juvenile Dermatomyositis) had been difficult due the rarity of these diseases. Professor Takei, the former chairman of Pediatric Rheumatology Association of Japan, had ordered working group to make a new online registry system in 2012. Pediatric Rheumatology International Collaboration Unit Registry (PRICURE) initiated a multi-center observational cohort study to create a foundational clinical database for rheumatic diseases of childhood since the end of 2013. Initial data from PRICURE registry will be described here. The success of this registry rests on whether young researchers promote active clinical researches taking advantage of this database or not.

W23-1

The effect and safety of additional administration of tacrolimus in rheumatoid arthritis patients with an inadequate response to tocilizumab

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Conflict of interest: None

Objectives: Biologics for RA patients (Pts) are often discontinued due to inadequate responses (IRs) including primary and secondary ineffectiveness. The repetition of drug changes without careful consideration could cause multidrug-tolerance. There is no report about hopeful add-on treatment (AT) options for RA Pts with IR to TCZ. Tacrolimus (TAC) has been reported to be effective as AT in RA Pts with IR to the TNF-α inhibitor, but there is no report about the effects as AT with TCZ. Methods: 17 Pts (mean age 55 yrs, disease duration 10 yrs, TCZ dosing duration 2.5 yrs) who had shown an IR to TCZ were treated with TAC combination from 1/2012 until 11/2013. The effects and safety were evaluated at 2 months later. Results: At the onset, 1 Pt showed high, 10 Pts showed moderate, 6 Pts showed low in RA disease activity. The scores of CDAI at the onset, and after 2 months were 15.7, and 8.6, respectively. In the same fashion, the scores of DAS28-CRP were 3.12, and 2.35. The scores of MMP-3 were 229.6, and 69.4. They were significantly improved. 7 of 15 Pts achieved more than moderate response according to the EULAR improvement criteria. 2 Pts discontinued TAC due to IR or adverse effects (AEs). No severe AE was observed. Conclusion: TAC AT may be useful for RA Pts that show an IR to TCZ.

W23-2

The background of rheumatoid arthritis patients treated with tacrolimus

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Conflict of interest: None

Objectives: The background of RA patients treated with TAC had been evaluated. **Methods:** A total of 631 patients in our hospital from the NinJa database in 2012 were enrolled. A total of 72 patients (11.4%) treated with TAC had been evaluated. **Results:** The characteristics of patients treated with TAC were as follows: age:64.8±13.3, disease duration:9.8±8.8, SDAI:10.3±8.7, DAS28:3.6±1.2, rate of patients with lung disease:54.9%, TAC:100% (1.7±0.9mg), MTX:36.1% (6.9±2.8mg), biologic agent:22.2%, TAC monotherapy:15.3%, combination therapy:84.7%. The characteristics of patients (n=559 88.6%) treated without TAC were as follows: age:60.1±14.5, disease duration:9.2±7.0, SDAI:8.5±6.6, DAS28:3.2±1.2, MTX:68.3% (7.5±2.8mg), biologic agent:30.2%, monotherapy:49.0%, combination therapy:42.6%. **Discussion:** In comparison with patients treated without TAC, the background of patients treated with TAC was older, was longer disease duration, was higher disease activity, was lower use rate and dose of MTX, was lower use rate of biologic agent, was higher rate of combination therapy. **Conclusion:** These results suggested that TAC was used in patient could not receive MTX and biologic agent for complication and contraindication, in patient could not receive an adequate amount of MTX, in patient received combination therapy on intensification treatment.

W23-3

Efficacy of combination therapy with MTX and low dose tacrolimus for MTX refractory RA

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Conflict of interest: None

Background: MTX is an anchor drug for the treatment of RA. Biologics administration is recommended for MTX refractory RA patients with poor prognosis factors. However, there are some cases that could not induce biologics because of complication and economic matters. In these cases, combination therapy with DMARDs is recommended. Objectives: We clarify the efficacy of combination therapy of MTX and low dose TAC. Methods: We examined the MTX refractory RA patients who added on TAC retrospectively. We evaluated the efficacy with SDAI and DAS 28. Furthermore we examined the factors that have influence on the efficacy such as RA duration, disease activities at TAC add on, MTX dose and present of corticosteroid. Results: we analyzed 70 RA patients. As for RA activity, it was improved regardless of RA duration, combination with corticosteroid, dose of MTX and RA activation. Therefore, we confirmed the efficacy of combination therapy with MTX and low dose TAC. Conclusions: Our results indicate that the treatment of MTX combined with low dose TAC is useful for RA patients that have no TAC contradiction and are difficult to induce biologics.

W23-4

The Effectiveness of Induction Therapy for Rheumatoid Arthritis (RA) with Simultaneous Administration of Methotrexate (MTX) and Low-dose Tacrolimus (LD-Tac)

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Conflict of interest: None

[Objectives] In RA patients showing inadequate response to MTX, additional administration of LD-Tac was reported effective. In this study, we evaluate the effectiveness of induction therapy with simultaneous administration of MTX and LD-Tac from the initial stage of therapy. [Methods] 56 RA patients who have been treated with MTX alone or with LD-Tac were examined. We classified the patients into ①conventional group: mono-therapy induction of MTX and then with LD-Tac in patients with inadequate response to MTX, and ②simultaneous combination group: concomitant induction of MTX and LD-Tac. Observed and examined DAS28 in the two groups once in every 3-month for 1 year. [Results] The initial DAS28ESR were 4.39 in the conventional group and 4.71 in the simultaneous combination group. After 1 year, DAS28ESR was significantly improved in the simultaneous combination group (=1.8) in comparison with the conventional group (=2.72). Moreover, DAS28ESR in the simultaneous combination group was significantly low in comparison with the MTX plus LD-Tac group in conventional group after 1 year. [Conclusion] In the induction therapy with simultaneous administration of MTX and LD-Tac, remission is rapidly induced, and unlike the conventional group, the patients' conditions were improved continuously.

W23-5

Effectiveness and obstacles of the treat-to-target (T2T) strategy in Japan – data from The Epidemiological Study for T2T

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Conflict of interest: None

[Objectives] To elucidate effectiveness and obstacles of the T2T strategy in Japan. [Methods] We assessed clinical outcomes, implementation and impediments of the T2T strategy in rheumatoid arthritis patients with moderate to high disease activity. [Results] Of 197 cases (female 77%, mean age 61 y/o, mean disease duration 59 months), SDAI remission at week 12, 24, and 48 were achieved in 21%, 38%, and 49%, and low disease activity (LDA) in 47%, 43%, and 38%, respectively. HAQ remission rates were 56% and 60% at week 12 and 24. Adherence rates to T2T (remission achieved and maintained, remission predicted as achievable, treatment adjusted, LDA permitted) were 84% for week 0-24 and 88% for week 24-48. Among 77 cases whose treatment was not adjusted even with non-remission at week 12, the most common reason was physicians' prediction that remission would be achievable (45 cases). Of the 45 cases, 21 achieved remission at week 24. Reasons of non-adherence to T2T were difficulty in treatment intensification due to adverse events or comorbidities, lack of patients' consents, or no other appropriate treatment options, etc. [Conclusion] High SDAI and HAQ remission rates were achieved by implementing the T2T strategy in real clinical settings. Factors impeding the strategy were revealed.

W23-6

The annual hospitalization number for serious adverse events for high dose MTX monotherapy in Japanese patients with RA using NinJa 2012 cohort

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Conflict of interest: None

[Objectives] To evaluate serious adverse event by MTX dose dependent in patients with RA. [Methods] In 11940 Japanese RA patients registered with NinJa2012, 3,795 patients medicated MTX monotherapy without biological DMARDs and combination synthetic DMARDs were divided four groups by MTX dose once a weekly.; 1-5mg/week n=605, 6-7.5mg/week n=993, 8mg/week n=1016, over 8mg/week n=1181, respectively. We defined hospitalization for various infectious disease, interstitial pulmonary disease, pancytopenia, malignant lymphoma as serious adverse event and research annual hospitalization in each groups. Final, we compare the event number for 4 groups by Odds ratio. [Results] The annual hospitalization number were 11patients (1.8%) in 1-5mg group, 22patients (2.2%) in 6-7.5mg group, 30 patients (3.0%) in 8mg group, 21patients (1.8%) in over 8mg group. Incidence of serious adverse event of the whole NinJa 2012 cohort was 392patients (3.3%), and the OR with each group were 0.55, 0.67, 0.90, 0.56, respectively. [Conclusion] In this cohort, the annual hospitalization number for serious adverse events was not high. MTX monotherapy within 16mg/week in Japan is safe because Japanese doctors pay attention to age, a renal function, existing pulmonary disease and perform dose setting of MTX.

W24-1

Synoviocyte adipogenesis induced by Arterpilin-C and Magnolol

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Conflict of interest: None

[Objectives] Fibroblast-like synoviocyte (FLS) plays important roles in disease progression of rheumatoid arthritis (RA) by producing cytokines and proteases. We suggest that adipogenesis induction of FLS contribute to inhibiting cytokines and proteases production from FLS. Here, we used plant-derived natural products Arterpilin-C (ART) and Magnolol (MGN), which are reported to be ligands for PPARγ, to induce adipogenesis of FLS. [Methods] FLS were purchased from Articular Engineering. ART and MGN were refined from Brazilian green propolis and Magnolia Bark, respectively. FLS were cultured in dexamethasone containing medium with or without ART and MGN and the medium were exchanged every 3 days. The deposition of lipid in cells were evaluated by using Lipid Assay kit ™ (Cosmo Bio) or LipidTOX ™ (Molecular Probes). The protein expressions of PPARγ were determined by western blot. [Results] Both ART (30μM) and MGN (3μM) induced remarkable adipogenesis of FLS in the presence of dexamethasone. The minimum concentration of dexamethasone was 10^{-7}M for the differentiation. PPARγ is clearly induced by the addition of dexamethasone. [Conclusion] These data implicate that both natural PPARγ ligands may be useful in FLS adipogenesis induction therapy as a RA therapy.

W24-2

Cell cycle regulation therapy combined with cytokine blockade enhances anti-arthritic effects without increase of immune suppression

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Conflict of interest: None

[Objectives] Cytokine blockers to treat rheumatoid arthritis (RA) are to inhibit immune reactions involved in RA. However, they cannot induce complete remission in all patients. We revealed that cell cycle regulation by cyclin-dependent kinase (CDK) inhibitors exerted anti-arthritic effects by inhibiting synovial fibroblast proliferation. A new CDK4/6 inhibitor, palbociclib was reported to be well-tolerated and effective in clinical trials for breast cancer. We aim to reveal if palbociclib shows anti-arthritic effects and synergizes with cytokine blockers in preclinical studies. [Methods] Collagen (CII)-induced arthritis (CIA) of mice was treated with palbociclib, etanercept or anti-IL-6 receptor antibody alone, or with combinations of palbociclib and cytokine blockers. Clinical and radiographic scores, serum anti-CII antibodies and proliferative responses of lymph node cells to CII were quantified. [Results] Palbociclib and the cytokine blockers were effective in treating CIA. Furthermore, combinations of both enhanced the anti-arthritic effects, but did not affect the anti-CII antibody levels or T cell proliferative responses to CII. [Conclusion] A new CDK4/6 inhibitor exerted anti-arthritic effects and synergized with cytokine blockers without enhancing immune suppression.

W24-3

Effects of Janus kinase inhibitor tofacitinib on circulating serum amyloid A and interleukin-6 during treatment for rheumatoid arthritis

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Conflict of interest: None

The Janus kinase inhibitor tofacitinib is currently being investigated as a disease-modifying agent in rheumatoid arthritis (RA). We investigated the in vivo effects of tofacitinib treatment for 4 weeks on elevated circulating acute-phase serum amyloid (SAA) levels in 14 Japanese patients with RA. SAA levels fell from 110.5±118.5μg/ml (mean±standard deviations); at treatment initiation to 15.3±13.3μg/ml after 4 weeks treatment with tofacitinib. The reduction in SAA levels was greater in patients receiving tofacitinib plus methotrexate, compared with those receiving tofacitinib monotherapy. Tofacitinib was also associated with reduced serum interleukin (IL)-6, but had no effect on serum levels of soluble IL-6 receptor. Patients were divided into groups with adequate (normalization) and inadequate SAA responses (without normalization). Serum IL-6 levels were reduced more in the group with adequate SAA response compared with those with inadequate SAA response. These results suggest that tofacitinib down regulates the pro-inflammatory cytokine, IL-6, accompanied by reduced serum SAA levels in patients with active RA. The ability to regulate elevated serum IL-6 and SAA levels may explain the anti-inflammatory activity of tofacitinib.

W24-4

Clinical efficacy of add-on Iguratimod treatment in patients with rheumatoid arthritis receiving MTX treatment

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Conflict of interest: None

[Objectives] To evaluate the clinical efficacy of add-on Iguratimod (IGU) in patients with rheumatoid arthritis receiving MTX treatment. [Methods]We used IGU treating Japanese patients with active RA. The final study cohort of each 25 patients received continuous IGU treatment more than 24 weeks. We reviewed the methods about the improvement of DAS28-ESR and CDAI which was an index of disease activity of RA. [Results]The group of patients included 3 males and 22 females. The mean age was 61.3 ± 11.5 years; the mean disease duration was 9.1 ± 8.2 years; and the mean methotrexate dose was 9.6 ± 4.5 mg/week. Clinical findings related to RA were as follows: tender joint count, 4.8 ± 5.5; swollen joint count, 3.9 ± 3.1; CRP, 2.0 ± 2.5 mg/dL; ESR, 38.7 ± 20.3 mm/h; DAS28 (ESR), 4.59 ± 1.02; and CDAI, 16.6 ± 9.4. The mean DAS28 changed to 4.14 ± 0.95, 3.26 ± 0.95, 2.93± 1.21 at Week 4, 12, 24 ($p=0.007$, $p<0.001$, $p < 0.001$). The mean CDAI changed to 12.5 ± 8.2, 7.8 ± 5.7, 6.2± 6.3 at Week 4, 12, 24 ($p<0.001$, $p<0.001$, $p < 0.001$). [Conclusion] The RA patient that MTX is not as effective is effective for additional combination of IGU that it faced each other, and that additional combination of IGU could become one of the effective choices in RA treatment was suggested.

W24-5

Blockade of Insulin-like Growth Factor System as a New Therapeutic Target in Rheumatoid Arthritis

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Conflict of interest: None

[Objectives] We had previously reported the importance of connective tissue growth factor (CTGF) in RA. CTGF protein has a 4-module structure. In this study, we focused on the module-1, insulin-like growth factor binding protein (IGFBP). Further, we analyzed whether the pathophysiology of RA improved by blocking the related pathways. [Methods] IGFBP3 were identified from the serum of RA patients. Stimulation and suppression experiments were conducted using the synovial cells of RA patients and human umbilical vein endothelial cells (HUVEC). Further, the effects of IGF-1 and IGFBP3 on osteoclastogenesis were examined. [Results] IGFBP3 were significantly increased in the serum of RA patients. In addition, large fluctuations in the expressions of IGFBP3 were observed after TNFα stimulation of the synovial cells and after the administration of anti-IGF-1 receptor (IGF-1R) antibody. In HUVEC, increase of closslinking structure was observed after IGFBP3 stimulation and decrease of closslinking structure was observed after anti-IGF-1R antibody. Osteoclastogenesis was enhanced by the presence of IGF-I and IGFBP3 and inhibited by the presence of anti-IGF1 receptor antibody. [Conclusion] Anti- IGF-1R antibody was possibly identified as a new therapeutic target for RA.

W24-6

Monoclonal antibodies against intrinsically disordered regions of PAD4 reduce inflammatory polyarthritis in rheumatoid arthritis model, D1CC mouse

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Conflict of interest: None

[Objectives] Peptidylarginine deiminase 4 (PAD4) that catalyzes the conversion of protein arginine residues to citrulline residues in the presence of Ca^{2+} is likely to be involved in rheumatoid arthritis (RA), because

anti cyclic citrullinated protein antibodies against its catalytic modified peptides are associated with onset of RA disease progression. However, it is still not clear whether PAD4, in particular, its catalytic activity involves in onset of RA symptoms. [Methods] To reveal this, we created that anti PAD4 monoclonal antibodies recognized catalytic sites forming an intrinsically disordered region of PAD4. [Results] These anti PAD4 antibodies blocked PAD4 catalytic activity in vitro and were introduced by intraperitoneal administration in RA model mouse, called D1CC mouse, resulted in reduction of onset of inflammatory arthritis. [Conclusion] Our data indicates that anti PAD4 antibody reduces inflammatory arthritis in D1CC mouse when therapeutic approach focuses on a treatment at initial antigen recognition phase, before effector phase of RA disease. We therefore concluded that PAD4 played critical role in the pathogenesis of initial phase of RA.

W25-1

Longitudinal study of the effects of biological DMARDs on work productivity and activity impairment in rheumatoid arthritis patients in daily practice using the Institute of Rheumatology Rheumatoid Arthritis (IORRA) Cohort

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Conflict of interest: Yes

[Objective] To conduct a longitudinal study of the effects of biologics on work productivity and activity impairment in Japanese RA patients in daily practice. [Methods] RA patients who continued to participate in the IORRA and initiated biologics between 2011 and 2012 as well as who were paid workers were selected for the Bio group. For a control group, propensity-score matching was used from RA patients who had never used biologics before. Changes from baseline at mean 9 months in the scores of absenteeism (AB), presenteeism (PR), overall work impairment (OWI), and activity impairment (AI) in both groups were calculated using the WPAI. The effects of biologics on these scores were analyzed. [Results] Thirty-five patients were selected each for the Bio and the control group. The changes in AB/PR/OWI/AI scores were from 1.2%/32.0%/32.6%/32.0% at baseline to 3.2%/14.2%/16.9%/25.5% at mean 9 months in the Bio group and from 2.6%/32.9%/33.6%/29.0% at baseline to 3.9%/29.3%/29.6%/34.1% at mean 9 months in the control group. The introduction of biologics resulted in improvement in PR (p=0.01) and OWI (p=0.06) scores. [Conclusion] The introduction of biologics improved the work productivity in RA patients based on data from an observational cohort representing daily practice in Japan.

W25-2

The impact of immunogenicity on RA patients treated with infliximab

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Conflict of interest: Yes

[Objectives] To investigate the influence of antibodies (Abs) against infliximab (IFX) on the effectiveness in patients with rheumatoid arthritis (RA). [Methods] Fifty-seven patients treated with IFX between 2004 to 2013 were retrospectively examined. They were divided into anti-drug Ab (ADA)-positive or -negative groups. Serum levels of IFX and ADA were measured by ELISA and RIA, respectively (*Nat Rev Rheumatol*, 2013). Drug retention rate and risk factors for developing ADA were compared between the groups. [Results] Twenty-one patients (36.8 %) developed ADA, and serum trough levels of IFX in the same group were significantly lower than those from patients in ADA-negative group ($p < 0.0001$). There were no differences about clinical backgrounds including age, sex, disease duration, RA stage, initial DAS28 score, concomitant use of oral prednisolone and DMARDs, and MTX dosage. Compared with ADA-negative, ADA-positive patients had a higher cumulative drug withdrawal rate ($p = 0.047$). In ADA-positive group, however, patients treated with premedication with intravenous prednisolone (IV-PSL) had a significantly higher drug retention rate ($p = 0.0008$). [Conclusion] Development of ADA is associated with inefficacy of IFX for RA patients, which may be counteracted by premedication with IV-PSL.

W25-3

Clinical effect of adalimumab in Switch patients~Investigation of 39 Switch patients among 124 ADA patients ~

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Conflict of interest: None

[Objectives] Efficacy of adalimumab (ADA) Switch in RA patients non-responsive to biological (Bio) agents at the author's institution was investigated. [Methods] Of 124 RA patients introduced to ADA from May 2009 to October 2012, 39 switched to ADA due to responding poorly to Bio agents were studied. Mean age was 52 years, mean duration of illness 10 years, rate of concomitant MTX 95%, mean MTX dose 10.5 mg/week, and rate of concomitant PSL 18%. Pre-Bio treatment: IFX, ETN, ABT, TCZ, OCRE, GLM, and AIN457 for 13, 12, 6, 4, 2, 1, and 1 patients, respectively. Changes in DAS28, SDAI, and CDA were investigated at 4, 8, 12, 24, 36 and 52 weeks. [Results] At 52 weeks after the ADA Switch, DAS28 (CRP), SDAI, and CDAI remission rates were 62%, 56%, and 54%, respectively. EULAR good response rate was 46%. Changes in DAS28 (CRP) for the concomitant MTX ≥10 mg/week patients (≥10 group), and MTX <10 mg/week patients (<10 group) at 4, 8 and 52 weeks, showed significant decreases in the ≥10 group. [Conclusion] Changes in DAS28 (CRP) for ADA Switch patients responding poorly to MTX showed good responsivity for ADA plus MTX ≥10 mg/week. Treatment with an adequate dose of MTX (≥10 mg/week) with ADA is an effective treatment option for poor responders to Bio agents that can use MTX.

W25-4

Clinical effect and persistence of 100mg Golimumab (GLM) as 2nd line or later biological DMARDs (bDMARDs) in patients with rheumatoid arthritis (RA)

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Conflict of interest: None

[Objectives] To clarify effect and persistence of GLM in patients (pts) with RA with prior bDMARDs use. [Methods] Among 64 pts initiated GLM in our department, 35 pts with prior bDMARDs use and 24 weeks observed with 100mg GLM were subjected. DAS28ESR, SDAI, HAQ, persistence at 24 weeks were analyzed with LOCF imputation, and stratified by prior bDMARDs (1 or ≧2), MTX or conventional synthetic (cs) DMARDs use, ACPA, reason for withdrawal. [Results] Baseline characteristics (mean) were; age 60 yrs, female 86%, duration 136 months, Stage I+II 37%, DAS28ESR 5.56, SDAI 26.9, HAQ 1.59, MTX 42%, csDMARDs (MTX, TAC, SASP) 82%, ACPA+ 82%. Prior bDMARDs; 1 in 20 (57%), ≧2 in 15 (43%). At 24 weeks, DAS28 4.28 ± 1.39, SDAI 14.3 ± 9.5; REM 5 (14%) in both; LDA 8 (23%) by DAS28, 15 (42%), HAQ 1.51 ± 0.94; HAQ-REM 5 (17%). Significance was not identified in any assumed stratification. Persistence in 24 pts (68%) and reason for withdrawal were, AE 5 (45%), LOE 5 (45%), other 1 (9%). AEs tend to appear at earlier period, whereas LOE increased later. Duration, Class, DAS28, HAQ, csDMARDs, and ACPA were identified as baseline factors to affect persistence. [Conclusion] We clarified clinical effect and persistence of GLM in our RA patients with prior bDMARDs use. Further investigation is required.

W25-5

Retrospective analysis of safety and efficacy of the treatment with biologic agents in elderly patients with rheumatoid arthritis

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Conflict of interest: None

Objective: Regarding the treatment of elderly RA patients, no guideline exists for the use of biologic agents. This study aimed to clarify the safety efficacy of the treatment with biologic agents in elderly RA patients. **Methods**: We retrospectively assessed hospital records of RA patients over the age of 70 years from January 2006 to August 2013. Patients were classified into groups of treatment of biologic agents (n=58, observation period 3.7y) or non-biologic agents (n=220, observation period 3.9y). The incidence of serious infections requiring hospitalization was examined. In addition, risk factors of serious infections in elderly patients were analyzed. **Results**: Rates of MTX use (82.7% vs 77.7%), PSL use (44.8% vs 40.4%) and pulmonary complication (39.6% vs 27.7%) were not significantly different between biologic agents group and non-biologic agents group. Furthermore, the incidence of serious infections was not significantly different between two groups (20.7% vs 18.6%). Serious infections were significantly associated with PSL use (OR 6.1; CI 95%, 3.1-12.1, p=0.0001). **Conclusion**: Our study indicates that biologic agents can be used safely in elderly RA patients, but PSL use is an important risk factor for serious infections regardless of use of biologic agents.

W25-6

Sustain biologic free remission after adalimumab treatment in RA patients

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Conflict of interest: Yes

[Objectives] To examine the condition that get to maintain biologic free remission after adalimumab (ADA) treatment in RA. [Methods] RA patients who passed a year ADA treatment were enrolled. Patients were divided into two groups based on achieved biologic free remission (Group A) or not achieved (Group B). Baseline characteristics and clinical responses were examined between group A and B. [Results] A mean DAS28-CRP score of group A decreased from 3.8 to 1.3 at started ADA free. A mean period of ADA treatment in group A was 20 months. A sustain remission rate was 100% at 6 months after withdraw. Group A was significantly lower women's rate and shorter disease duration than group B. ROC analysis indicated that the cut-off point of disease duration at baseline was 9 months. Clinical activities such as DAS28-CRP, CDAI and SDAI of baseline were no difference between the two groups, but RF was significantly lower in group A. Clinical responses were no difference between the two groups, but serological factor such as MMP-3 and RF were significantly lower in group A at a year. [Conclusion] The disease activity after withdrawal ADA could be controlled. Given disease duration is short and RF and/or MMP-3 decrease during ADA treatment, it is considered possible to sustain bio-free remission.

W26-1

What is the utility of routine ANA testing in predicting development of biological DMARD-induced lupus/vasculitis in patients with rheumatoid arthritis?

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Conflict of interest: None

Objective: Anti-TNF therapy is often associated with newly developed autoimmune diseases. We determine the clinical significance of ANA in patients with rheumatoid arthritis (RA) receiving TNF inhibitor (TNFi). Methods: Patients with first TNFi use since 2005 were identified in University of Leeds and Yokohama city university. Serial autoantibody profiles, treatments, and adverse events were evaluated. Results: In Leeds, 454 patients were identified. Infliximab was associated with higher ANA seroconversion rates (31.2%) compared with etanercept (11.8%) and adalimumab (16.1%) ($p<0.001$). Median therapy duration was 10.9 months. Positive anti-dsDNA was noted in 6 patients (median 2.0 years). One patient developed lupus. An association between seroconversion and secondary non-response to TNFi was observed. In Yokohama, 90 patients were identified. ANA seroconversion rates were 40.8%, 20.6% and 14.3% in infliximab etanercept and adalimumab, respectively. Two patients developed lupus. Three of 4 patients having infusion reaction to infliximab showed ANA seroconversion. Lupus patients were successfully managed with rituximab and abatacept. Conclusion: ANA seroconversion was associated with anti-TNF-induced lupus in only a minority, secondary non-response to the agent, and drug allergy.

W26-2

A prospective study of the influence of biologic agents on the standardized incidence ratio (SIR) of tuberculosis (TB) in patients with RA by *NinJa* cohort data for 10 years

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Conflict of interest: None

[Objectives] To evaluate the incidence of biologic agents on the standardized incidence ratio (SIR) of tuberculosis (TB) in patients with rheumatoid arthritis (RA) prospectively. [Methods] We calculated the standardized incidence ratio (SIR) of TB from the clinical data on National Database of Rheumatic Disease by iR-net in Japan (NinJa) prospectively from 41 facilities for 10 years. [Results] Among 67,104 RA patients registered from 2003 to 2012, 52 patients developed TB and the SIR of TB was 3.55 (95%CI: 2.59-4.52. 5 patients (9.6%) were treated with biologic agents. The SIR of TB in RA patients treated with biologic agents was 2.64 (0.33-4.95), and the SIR of TB in patients treated without biologic agents was 3.50 (2.50-4.50). [Conclusion] On a downward trend in the incidence of TB in RA patients and the loss of an increase the incidence of TB in RA with biologics administration was found by our prospective study for 10 years.

W26-3

Assessment of factors predicting remission in rheumatoid arthritis patients (RA) with Adalimumab (ADA) and 8mg/w of MTX combination therapy

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Conflict of interest: None

[Objectives] We previously reported at JCR 2012 that the high retention rate can be achieved by ADA with≧10mg/w MTX treatment for RA patients. Here we assessed factors to predict patients who can achieve sufficient clinical responses by ADA + MTX (8mg/w). [Methods] RA patients treated with ADA + MTX (8mg/w) (n=41) for 1 year were divided into two groups who achieved DAS28-CRP remission (n=19, remission group) or not (n=22, non-remission group), and compared their baseline characteristics. [Results] The baselines of DAS28-CRP in the remission

and non-remission groups were 3.81±1.26 and 4.93±1.90, respectively, and this difference was statistically significant. The DAS28-CRP cutoff value to achieve remission was analyzed by receiver operating characteristic analysis, and the value was identified as 4.7. When looked at the remission rate in patients who had DAS28-CRP ≤4.7 at the initiation of ADA treatment in the combination with MTX (8mg/w), 70% of the patients achieved remission 1 year after, while only 23.8% met the remission in the patients with DAS28-CRP > 4.7 (p<0.005). [Conclusion] Analysis on the patients treated with ADA + 8mg/w MTX identified 70% of patients whose baseline DAS28-CRP is below 4.7 have potential to achieve remission in 1 year with ADA + MTX 8mg/w.

W26-4

Safety of adalimumab in Japanese rheumatoid arthritis patients: postmarketing surveillance report of 7,740 patients

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Conflict of interest: None

[Objectives] To determine the adverse drug reaction (ADR) profile of adalimumab (ADA), and to identify factors associated with its safety in Japanese rheumatoid arthritis (RA) patients (pts). [Methods] Postmarketing surveillance of 7, 740 pts was performed. All pts received ADA 40 mg every other week for 24 weeks and were followed for safety for 28 weeks. Assessments were made for all adverse events (AEs), serious AEs, ADRs, and serious ADRs. [Results] The overall frequency of ADRs was 24.0%, highest for skin and subcutaneous tissue disorders (7.2%), and with serious ADRs reported in 4.5% of pts. There were 0.2% of malignancy, 0.1% of tuberculosis, and < 0.1% of cardiac failure. 767 pts discontinued treatment because of AEs. Age, pulmonary disease history or comorbidity, co-existing diabetes mellitus, concomitant methotrexate >8 mg/week and concomitant glucocorticoids >5 mg/day were risk factors for infections. The estimated standardized mortality rates associated with the use of ADA was 0.89. [Conclusion] The overall safety profile of ADA was comparable to those of other biologic agents. No unexpected ADRs, which would affect the overall safety of ADA were observed. There was no notable risk of death linked to use of ADA.

W26-5

Efficacy and Safety of Etanercept Monotherapy in Women with Rheumatoid Arthritis Having the Desire to Bear Children

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Conflict of interest: None

[Objectives] Efficacy and safety of etanercept (ETN) monotherapy were evaluated clinically in women with rheumatoid arthritis (RA) desiring to bear children. [Methods] ETN monotherapy was applied to women with RA having the desire to have children. ENT was discontinued at the time when a patient was found to be pregnant. ETN was used again if symptoms relapsed after child delivery. Changes in disease activity, course after pregnancy, neonatal growth and so on were analyzed retrospectively in these cases. [Results] Of the 10 patients, 8 delivered children, 1 is still pregnant and 1 experienced abortion. Mean DAS28-CRP sore decreased significantly in women having received ETN treatment before child delivery and retreatment after delivery. No adverse event was seen, and there was no problem with neonatal growth, etc. Of the 10 patients, 2 became pregnant twice (1 case leading to child delivery twice and the other case leading to child delivery after the first pregnancy and abortion after the second pregnancy). [Conclusion] Women with RA desiring to have children are indicated for positive treatment with biological agents as needed. ETN monotherapy was shown to be safe if discontinued upon diagnosis of pregnancy.

W26-6

New application for assessment of synovial histology treated with biologics in patients with rheumatoid arthritis: the role of IH score

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Conflict of interest: None

[Objectives] We established Immunohistological (IH) score, a new scorning system for immunohistology of synovium in RA. [Methods] 21 patients treated with anti-TNF blockade with mean age of 60.8 years, mean disease duration of 9.1 years, mean DAS28 (CRP) of 4.19, 16 infliximab and 5 golimumab were analyzed Rooney score and IH score of TNF-α and IL-6. The IH score was used for the semiquantitative analysis by using a visual analogue scale (VAS) ranging from 0 to 5 points as follows: grade 0, 0%; grade 1, 0% to ≤5%; grade 2, >5% to ≤20%; grade 3, >20% to ≤40%; grade 4, >40% to ≤60%; grade 5, >60% to ≤100%. Three-field light microscopy was used at ×200 magnification at the superficial, interstitial, and perivascular layers. The sum of the IH grades in the three fields was used for the IH score of the synovial samples. [Results] The κ values of IH score were 0.885 for inter observer and 0.899 for intra observer. Mean Rooney score and IH score (TNF-α) and IH score (IL-6) were 23.58, 6.24 and 8.4 respectively. DAS28 (CRP) was correlated with Rooney score and IH score (TNF-α), however not with IH score (IL-6). Larsen grade was correlated with IH score (TNF-α) reversely. [Conclusion] IH score is useful for immunohistological assessment of synovium with relation to disease activity in RA.

W27-1

The length of drug holidays from anti-TNF biologics with adding tacrolimus in rheumatoid arthritis patients who had ever relapsed after withdrawal of anti-TNF biologics

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Conflict of interest: Yes

[Objectives] To assess the length of remission after withdrawal of anti-TNF biologics (TNFB) with adding tacrolomus (TAC) in RA patients who had ever relapsed after the withdrawal of TNFB. [Patients] Patients who received TNFB for treating active RA despite treatment with MTX and discontinued TNFB after achieving remission but had relapsed and discontinued TNFB again after achieving remission and adding TAC were analyzed. [Results] Five patients could be analyzed, all are females with a mean age of 43 years and a mean symptom duration of 15 months and were treated with MTX with a mean weekly dose of 13.5 mg at the onset of TNFB. RF and ACPA were all positive. The mean duration of the treatment with TNFB at the time of the first discontinuation of TNFB was 26 months. There are 6 episodes of the drug holidays from TNFB and the mean duration of them was 17 weeks. The mean daily dose of TAC were 2 mg and the mean trough level of TAC was 5.2 ng/ml. In all patients, no episodes of RA relapse and reinstitution of TNFB were observed after adding TAC. The mean duration of drug holiday from TNFB after adding TAC were 65 weeks. [Conclusions] Even in patients who had relapsed after discontinuation of TNFB, long-term drug holiday from TNFB may be possible after adding TAC.

W27-2

Comparison of Clinical Results and Persistence Rate Between Low and Standard Dose Etanercept in My Hospital

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Conflict of interest: None

[Objectives] 25mg/w Etanercept usage has been replied to the needs for reduction of medical espense and frequency of visit to hospital, al-

though 50mg/w is regular dose. The long term clinical results and persistence rate depending on two usage of ETN were investigated. [Methods] 236 RA patients (50mg/w 84 patients, 25mg/w 152patients) were participated from August, 2005 to April, 2013. Clinical results were evaluated by DAS28-CRP and SDAI, and persistence rates were estimated by Kaplan-Meier analysis. [Results] The back ground factors were investigated between 25mg/w and 50mg/w groups. There are no significant difference in age, disease duration treatment periods, sex, and MTX dosage. There were significant difference in PSL dosage, MMP-3 in initial time, initial DAS-CRP, and Bio naive ratio. 25mg/w and 50mg/w groups were compared by Kaplan-Meier method, there was no signicant difference in persistence rate with log-rank and Wilcoxon test. Because of background factors were significantly different, persistence rate was reexmined by adjusting background factors with propensity score. But, there was no significant difference in persistence rate. [Conclusion] The treatment of ETN 25mg/w seemed good in clinical results and long-term persistence rate compared to 50mg/w.

W27-3

Effects of Biological Agents on Upper Cervical Spine Lesions in Patients with Rheumatoid arthritis

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Conflict of interest: None

We evaluated radiographic change in the upper cervical spine lesions of 38 RA patients receiving continuous biological therapy at least 2 years. During the average follow-up period of 5.4 years, 20 Patients who had no cervical lesions at the initiation of biological therapy did not show the development of new cervical lesions. On the other hand, in 6 of the 18 patients with preexisting cervical lesions the lesions progressed. We conclude that biological agents were capable of preventing the development of new cervical spine lesions in RA patients, however they did not prevent the progression completely in RA patients with preexisting cervical spine lesions.

W27-4

Early response in tender joint count and low baseline rheumatoid factor are associated with sustained remission after withdrawal of etanercept in rheumatoid arthritis patients

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Conflict of interest: Yes

[Objective] To investigate factors associated with sustained remission after withdrawal of etanercept (ETN) in RA patients who had had inadequate response to MTX but had achieved remission with MTX and ETN. [Methods] Fifteen patients could be analyzed, 9 had sustained remission more than 1 year after withdrawal of ETN (Group 1), 6 had a relapse within 1 year after withdrawal of ETN (Group 2). Baseline characteristics, treatments, and the area under the curve (AUC) of the rate of improvement of clinical indicators for every twelve weeks from the onset of ETN were compared between groups. [Results] Age, symptom duration, titer of anti-CCP, and duration of ETN therapy were not significantly different between 2 groups. Group 1 had tendencies toward having higher tender or swollen joint count, DAS28, SDAI and having lower MTX dose than Group 2. RF titers at baseline were significantly lower and the AUC of the rate of improvement of tender joint count from base line to 24th weeks were significantly larger in Group 1, and Group 1 had tendencies toward having larger AUC of the rate of improvement of physician's global assessment, compared to Group 2. [Conclusion] Early response in tender joint count and low baseline RF are associated with sustained remission after withdrawal of ETN.

W27-5

Improvement in Activities of Daily Living for Patients with Rheumatoid Arthritis Receiving Treatment with Golimumab by a Multicenter Study

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Conflict of interest: None

[Objectives] To describe improvement of ADL of patients with Rheumatoid Arthritis (RA) receiving treatment with Golimumab (GLM) in Gunma RA Network (GRN). [Methods] We studied 44 patients (male; 4, female; 40) with RA that we could evaluate by HAQ-DI for 6 months after giving GLM in the hospitals of GRN. Patients with RA were 63 years old on average and had mean disease duration of 10 years. 73% of patients used MTX concomitantly, 8.6mg/week on average and 39% of patients used PSL, 4.4mg/day on average. 32 patients took GLM 50mg/4weeks, and 12 patients took GLM 100mg/4weeks. Patients underwent serum marker (CRP, ESR, MMP-3), disease activity score (DAS28-ESR, SDAI, CDAI) and HAQ-DI at pre-administration, 1 month, 3 months, 6 months. [Results] Serum markers except for CRP at 3 months improved in every points compared to before administration. Disease activity score except for CDAI at 6 months improved too. And HAQ-DI at every point revealed better than pre medication. WWe divided RA patients into 2 groups. Among the patients with RA under 10 years, HAQ-DI was better at 1 month. But it was not better than those with it over 10 years. [Conclusion] RA patients taking GLM yielded improvement in their ADL early. But their ADL was not better in patients with long duration of RA.

W27-6

Efficacy of golimumab in patients with rheumatoid arthritis in multicenter study

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Conflict of interest: None

[Objectives] The aim of this study was to assess clinical outcome in rheumatoid arthritis (RA) patients being treated with golimumab (GLM). [Methods] The subject was 78 RA patients being treated with GLM; 31 patients were bio-naïve patients and 76% were receiving concomitant MTX. At baseline, after 1, 3, 6, 9 and 12 months, the following parameters were investigated: CRP, ESR, MMP-3, DAS28-ESR, DAS28-CRP, CDAI, SDAI, drug survival rate of GLM. [Results] After 1, 3, 6, 9 and 12 months, each of these scores: DAS28-ESR, DAS28-CRP, CDAI and SDAI improved significantly than that of baseline. After 6 months, MMP-3 also improved significantly than that of baseline. Drug survival rate at 12 months was 80%. [Conclusion] These results suggest that patients who receive GLM can achieve improvement in disease activity soon.

W28-1

Comparison of angiogenesis-related factor levels in patients with rheumatoid arthritis between abatacept and tocilizumab-administered groups

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Conflict of interest: Yes

Objective: We have previously demonstrated that the serum vascular growth factor (VEGF) level is significant correlated with disease activity in rheumatoid arthritis (RA) patients. We evaluated RA disease activity before and after administration of abatacept (ABT) and tocilizumab (TCZ), and examined whether the administration affects the serum angiogenesis-related factor levels. Methods: We evaluated disease activity (DAS-28, SDAI, mHAQ), and measured the levels of serum VEGF, angiopoetin-1, and angiopoetin-2 before and after the administration. Power Doppler ultrasonography was also performed in the 28-joints per patient to evaluate disease activity using blood flow scoring system. We statistically analyzed the relationship between the levels of angiogenesis-related factors and disease activity. Results: The mean ages of ABT and TCZ groups were 56 and 59 years, respectively. In both groups, DAS-28, SDAI, mHAQ and blood flow score were decreased 6 months after the administration. Although the VEGF level was significantly lower after the administration in both groups compared to before that, ABT decreased the VEGF level more slowly compared to TCZ. Conclusions: Our date suggested that ABT decreased the VEGF level as with TCZ.

W28-2

Abatacept therapy altered the expression ratios of transcription factors that regulate helper T cell differentiation

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Conflict of interest: None

[Objectives] Abatacept (ABT) modulates T cell activation and shows anti-rheumatic activity in RA patients. Recently, it has been shown that Treg cells and Th17 cells were decreased in the peripheral blood of RA patients by ABT theapy. We investigated the expression of transcription factors that regulates helper T cell differentiation. [Methods] RNA was extracted from peripheral blood at baseline and after 4w, 12w, and 24w of ABT therapy, from 9 RA patients. The expression levels of T-bet, GATA-3, Foxp3 and Ror-γt was measured by real-time PCR. Relative expression levels were expressed as the ratios of two genes, and the changes of the ratios before and after ABT therapy were examined. [Results] Mean DAS28ESR was 4.83, and 6 patients showed moderate or good response to ABT therapy. The ratio of Foxp3 / Ror-γt expression decreased after ABT therapy, but other ratios showed no significant tendency. No clear relationship between the changes of the ratios and clinical effects were observed. [Conclusion] The expression ratio of Foxp3 / Ror-γt in the peripheral blood decreased by ABT therapy.

W28-3

The efficacy and safety of abatacept (ABA) in Japanese biological naïve patients with rheumatoid arthritis (RA) for 48 weeks; Data from ABROAD study

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Conflict of interest: Yes

[Objectives] To assess the efficacy and safety of abatacept (ABA) in biological naïve rheumatoid arthritis (RA) patients for 48 weeks. [Methods] We evaluated 156 RA patients (mean age; 61.8 yrs) enrolled in the ABROAD study for 48 weeks. Clinical remission (SDAI≦3.3) was measured at week 24 and 48. We also compared the efficacy of ABA between in young and old patients (above 65 yrs) with or without MTX. [Results] SDAI remission rate at week 24 and 48 was 15.4% and 23.7%, respectively. The mean SDAI score at week 0 and 48 in old or young patients was 25.5→11.4 or 24.0→10.1, respectively. At week 4, SDAI score were significantly reduced from baseline in both old patients with or without MTX. The reductions of DAS28CRP and SDAI from baseline to at week 48 were not different between old patients with or without MTX. [Conclusion] The efficacy of ABA treatment is increased at week 48 comparing at week 24. The efficacy of ABA treatment is the same in both old and young patients and in old patients with and without MTX. These results suggest that ABA is suitable biological DMARDs for old RA patients who cannot use MTX.

W28-4

Predicting factors of efficacy of abatacept in biologic naïve patients with rheumatoid arthritis; Data form ABROAD STUDY

Yutaka Kawahito[1], Takao Fujii[2], Akira Yokota[2], Hideo Hashimoto[2], Kiyoshi Matsui[2], Kenji Miki[2], Masayasu Kitano[2], Naoki Shimmyo[2], Aihiro Yamamoto[2], Koichiro Ohmura[2], Takanori Kuroiwa[2], Toshihiko Hidaka[2], Ichiro Yoshii[2], Masahiro Sekiguchi[2], Norihiro Nishimoto[2], Tsuneyo Mimori[2], Hajime Sano[2]
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Conflict of interest: Yes

【Purpose】To determine the predicting factors of efficacy of abatacept (ABT) in biologic naïve rheumatoid arthritis (RA) patients.【Methods】We examined 179 biologics-naïve RA patients (female = 85.5 %, mean age = 62.5yr) in the ABROAD study (Abatacept Research Outcomes as a first-line biological Agent in the real worlD) in collaboration with 46 institutions in western Japan. We measured SDAI at week 0, 4, and 24 after treatment. To evaluate the response to ABT, we used validated response definitions (50/70/85% improvement) for SDAI, which are correlated with ACR (20/50/70 improvement) response. To determine the most predictive cutoff point, the minimum p-value method was used.【Results】SDAI remission at 24 week was achieved in 13% of our patients. SDAI 50%, 70%, and 85% improvement rate at week 24 were 71%, 39%, 16%, respectively. In multivariate analysis, very high-positive ACPA (≧99 IU/mL) (OR 3.58, p=0.01), 70% improvement of CRP at week 4 (OR 2.5, p=0.03), short disease duration (<1 year) (OR 6.06, p=0.008), were significantly associated with SDAI 50/70/85% response, respectively.【Conclusion】We clarified predictors of SDAI 50/70/85% response to ABT. This analysis is on the way and we will perform more detailed examination.

W28-5

The comparison of effectiveness of abatacept and anti-TNF inhibitor for the patients with rheumatoid arthritis by ultrasonography

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Conflict of interest: None

[Objectives] The aim of this study was to assess the effectiveness of abatacept (ABT) compared to tumor necrosis factor inhibitors (TNFi) for rheumatoid arthritis (RA) treatment. [Methods] This study included RA patients treated with ABT (n=45) or TNFi (n=89). They underwent musculoskeletal ultrasonography (US) at 26 synovial sites (22 joints). The GS (Gray scale) and PD (Power Doppler) signals were scored in each joint. We compared DAS-CRP and the sums of GSUS and PDUS scores between two groups. [Results] TNFi group showed significant lower DAS score compared to baseline at 2 months. However, the improvement of DAS from baseline in ABT group was not significant at 2 months. Although TNFi group showed lower DAS score than ABT group at 6 and 8 months, there was no significant difference between two groups ay 12 months. The sums of GSUS and PDUS scores at 6 and12 months were lower than baseline in both groups, and showed no significant difference

between two groups. [Conclusions] The clinical effect revelation of ABT was slow compared to TNFi. However, ABT treatment caught up with TNFi in 12 months. And also the effect of ABT was not inferior to TNFi in ultrasonographic assessment.

W28-6

Experimentation about serum cytokines and subsets of peripheral blood mononuclear cells in rheumatoid arthritis patients treated with abatacept

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Conflict of interest: Yes

OBJECTIVE: To examine the mechanism of abatacept (ABT) for RA patients by serum cytokines and subsets of peripheral blood mononuclear cells (PBMC) and their activation markers. **METHODS:** 9 serum pro-inflammatory cytokines and PBMC subsets of T, B, NK cells and monocytes including activation markers were quantified using high sensitive ELISA system and flow cytometry at a baseline, Week 2, 12 and 24 of the treatment with ABT in 51 RA patients who had not been treated with any biologics. The relations between the cytokines, cell surface markers and clinical data were analyzed. **RESULTS:** The mean age was 65.8 years, with the mean disease duration of 8.6 years. Mean DAS28-ESR was 5.3 at a baseline. The numbers of HLA-DR+CD4, OX40+CD4, HLA-DR+Th1, HLA-DR+Th2, HLA-DR+Th17, regulatory T cells (Treg) and HLA-DR+Treg were significantly decreased at Week 24. The ratio of surface expression of CD69 in monocytes also decreased. Changes of the ratios of HLA-DR expression in CD14+CD16+ monocytes were statistically correlated with those of DAS28-ESR and serum IL-6 levels. **CONCLUSIONS:** The activation of CD4+T cells including Treg totally decreased in bio-naive RA patients treated with ABT and especially the activation of non-classical monocytes and IL-6 were related to the effectiveness of ABT.

W29-1

Prognostic factors and therapeutic response prediction by the treatment with Abatacept in patients with rheumatoid arthritis. The ALTAIR next study

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Conflict of interest: None

[Objectives] To determine the prognostic factors affecting clinical outcomes by the treatment with Abatacept (ABT) in RA patients. [Methods] 108 patients with rheumatoid arthritis were treated with abatacept for 52 weeks in routine clinical practice. [Results] At Week 52, 25% of patients achieved clinical remission (SDAI<3.3), while functional remission (HAQ≦0.5) and Structural remission (ΔmTSS<0.5) were achieved in 31% and 63% of patients respectively. 15% of patients achieved comprehensive disease remission (CDR), which was defined as SDAI≦3.3, HAQ≦0.5, ΔmTSS ≦0.5, while 20% of patients achieved comprehensive disease control (CDC), which was defined as SDAI≦11.0, HAQ≦0.5, ΔmTSS ≦0.5. RF was the independent prognostic factor for SDAI at 52 weeks (cutoff value; RF >125IU/ml at baseline). The prognostic factors predicting functional and structural remission were HAQ and CRP (HAQ≦1.0 and CRP≦1.4mg/dl), whereas age was the predictive of CDC achievement (cutoff value; age <48) by logistic regression analysis. Improvement of HAQ at 2weeks was the only independent variable for SDAI at 52 weeks (cutoff value; ΔHAQ <-0.125). [Conclusion] ABT enables personalized treatment according to the patient's specific disease state and early improvement of HAQ can predict the efficacy of ABT.

W29-2

The application possibility of urinary pentosidine for the marker of early therapeutic response of abatacept in patients with rheumatoid arthritis

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Conflict of interest: None

[Objectives] We studied the application possibility of urinary pentosidine for the marker of early therapeutic response of abatacept in patients with rheumatoid arthritis. [Methods] Urinary PEN was measured using HPLC in 53 patients with RA receiving ABT. We assessed the disease activity of RA by CRP and DAS28-CRP at baseline, 3M, 6M, and 12M after initial ABT therapy. We defined the high disease activity group (High: high and moderate disease activity group) and the low disease activity group (Low: remission and low disease activity group) at 12M after baseline. we assessed the differences of PEN between the continued group of ABT therapy (n=47) and the switched group with another therapy (n=6) after 12M. [Results] PEN showed a weak correlation with age (r=0.36) and CRP (r=0.30) at baseline. In the total group, PEN showed significantly lower level at 6M. High showed significant higher level of PEN and Low showed significant lower level of PEN at 12M. The continued group showed significant lower level of PEN at 3M. On the other hand, switched group showed the no difference of PEN in this study period. [Conclusion] PEN reflects the therapeutic effect of ABT in patients with RA. PEN may be the marker of early therapeutic response of abatacept in patients with RA.

W29-3

Long term retention rates of abatacept: Results from the Japanese multicenter registry system, effect of concomitant methotrexate and previous biologics history

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Conflict of interest: None

[Objectives] Abatacept (ABT) has been available for rheumatoid arthritis (RA) patients since 2010 in Japan. The long-term clinical results of ABT therapy in Japanese are still unknown. We evaluated two-year adherence of ABT and studied the factors affecting long term retention rate of ABT in this study. [Methods] 376 RA patients treated with ABT were included, from the Japanese multicenter registry system for RA patients with biologics (TBCR). We calculated retention rates using Kaplan-Meier methods; the endpoints were insufficient efficacy or adverse events resulted in ABT discontinuation. [Results] Overall retention rate was

77.5%. Bio-naïve patients demonstrated higher rate than switch patients (86.0% vs 69.6%, p=0.005). Among the switch group, the patients without concomitant MTX demonstrated significantly higher discontinuation rate due to secondary failure compared to those with more than 8mg/week MTX (87.0% vs 100%, p=0.039), while the patients with lower dose MTX (~6mg/week) had comparable discontinuation rate (91.2%) to those without MTX. [Conclusion] ABT demonstrated good retention for two years. Current data clearly demonstrated that the bio-switch group, a heterogeneous patients group, would require sufficient MTX usage for long term stabilization of RA activity.

W29-4

The efficacy of Abatacept combined with Methotrexate or not for patients of Rheumatoid arthritis from multicenter study TBC

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Conflict of interest: None

We evaluated efficacy of Abatacept (ABT) combined with Methotrexate (MTX) or not for patients of Rheumatoid arthritis. These results are derived from multicenter study from TBC. Efficacy was evaluated based on DAS28-CRP, SDAI, as well as retention rate, and safety at 52 weeks in 256 RA patients. The retention rate at 52 weeks period was 71.0% in combined group, 66.7% in not combined group. Average of DAS28-CRP improved 4.42±1.20 to 3.01±1.25 in combined group, 4.54±1.36 to 3.28±1.42 in not combined group after 52 weeks later. Average of SDAI improved 24.0±13.4 to 12.0±9.9 in combined group, 25.9±15.2 to 14.6±13.3 in not combined group. In each analysis, there was no difference in effectiveness of concomitant MTX. Adverse events occurred in 38 cases in combined group, 29 cases in not combined group. In analysis of patients whose disease activity was high at starting ABT treatment, average of DAS28-CRP improved 5.94±0.72 to 4.06±1.30 in combined group, 5.89±0.70 to 3.99±1.66 in not combined group. There was also no difference in effectiveness between these 2 groups.

W29-5

Long-term Clinical Efficacy and Safety of Abatacept in Rheumatoid Arthritis: Results from the Japanese Multicenter Registry (TBCR)

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Conflict of interest: None

[Objectives] Abatacept (ABT), a selective T-cell co-stimulation modulator, is a new biologic drug and has been available for rheumatoid arthritis (RA) patients since 2010 in Japan. The long-term clinical results of ABT therapy in Japanese are still unknown. [Methods] 254 RA patients treated with ABT for longer than 52 weeks were included, from the 376 patients with ABT therapy in the Tsurumai Biologic Communication Registry (TBCR). We retrospectively reviewed the clinical data. [Results] Mean age was 64.5 years and mean disease duration was 12.0 years. 48.8% of patients were taking concomitant methotrexate in mean dose of 7.3 mg/week. 132 patients were biologics naïve and 122 patients had previous biologics history. Mean DAS28-CRP before abatacept therapy was 4.5. Drug retention rate was 78.7% at 52 weeks. Each composite measure index significantly decreased at 4 weeks, between 4 and 24 weeks, and 24 and 52 weeks. [Conclusion] ABT demonstrated good clinical efficacy and retention for 52 weeks. The important point in our current data is that ABT therapy showed significantly increasing efficacy even after 24 weeks from initiation. Long-term continuing ABT therapy would be beneficial for the patients without any other treatment options except for ABT.

W29-6

Correlation with a dose per body weight of the abatacept intravenous-injection and clinical efficacy in patients with rheumatoid arthritis

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Conflict of interest: Yes

[Objectives] Correlation of ABTiv dose per weight and efficacy is considered. [Methods] 28 ABTiv RA patients, age: 64.3 years old, the sex ratio (male: female): 9:19, weight: 52.9kg, disease duration: 12.0 years, Steinbrocker class1/2/3/4:0/19/8/1, Steinbrocker stage I/II/III/IV: 4/6/4/14, DAS28-ESR: 4.35, SDAI: 19.63, MMP-3 (male / female): 166.5/123.4 ng/ml, vdH-mTSS (ES/JSN): 119.3 (84.9/34.5), HAQ-DI: 1.40, BIO naive/switch: 11/17, MTX combined use/nothing: 12 (7.17 mg/w)/16, PSL combined use/nothing: 20 (4.73 mg)/8. A dose per weight of each case, and correlation with clinical index and an adverse event appearance by 52 week is investigated by the LOCF method, respectively. [Results] A 52-week persistence rate was 71.4%. The correlation coefficient (p value) with each index is ΔDAS28-ESR: -0.4.20 (p= 0.026), ΔDAS28-CRP: -0.397 (p=0.037), ΔCDAI: -0.504 (p=0.006), ΔSDAI: -0.475 (p= 0.011), ΔMMP3: -0.374 (p= 0.0502), ΔmTSS: -0.525 (p= 0.004), and: ΔHAQ-0.090 (p= 0.650). The increase in dosage dependence was not observed by the adverse event appearance ratio. [Conclusion] Significant correlation was observed by the improvement of a dose of ABT and a clinical indicator. It was 10.49 mg/kg when the cutoff value of the ABTiv dose was computed by ΔDAS28-ESR>=1.2 considered as effective change.

W30-1

Modulation of T cell CD80/CD86 co-stimulatory signal does not alter ACPA titer in the course of 48-week treatment of rheumatoid arthritis

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Conflict of interest: Yes

[Objectives] Anti-cyclic citrullinated peptide antibodies (ACPA) is highly specific for rheumatoid arthritis (RA). ACPA production seems to depend on antigen-specific CD4+ helper T cell activation. Abatacept (ABA) is a biological agent suppressing T cell activation via inhibition of CD28 binding to CD80/CD86 ligands. This study aims to clarify how 48 weeks ABA treatment affects T cell activation and ACPA production in RA patients. [Methods] PBMCs were obtained from 30 patients enrolled in ABROAD study at baseline, 24 and 48 weeks of ABA treatment. The proportion of CD25+ in CD4+ T cells were analyzed with flow cytometory. The ACPA titer was measured with EliA CCP kit. [Results] Twenty-five patients (83.3%) were ACPA (+) (>4.5 U/mL). DAS28-CRP and SDAI were significantly reduced at 24 and 48 weeks compared with those at baseline. The CD25+ cell proportions in CD4+ T cells were also reduced at 24 and 48 weeks (13.9±5.4% at baseline; 6.6±5.8% at 24

weeks, $p<0.0001$; 6.1±3.1% at 48 weeks, $p<0.0001$). However, ACPA titer was not significantly changed at 24 and 48 weeks compared with those at baseline. [Conclusion] 48-week inhibition of T cell co-stimulation reduced disease activities and CD25+ cell proportions in CD4+ T cells but not ACPA titer in ACPA (+) RA patients.

W30-2

Effects of CTLA4-Ig on human monocytes

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Conflict of interest: None

[Objectives] We explored the effects of abatacept (CTLA4-Ig) on function of monocytes. [Methods] Monocytes from healthy donors were cultured in the presence of staphylococcal enterotoxin B (SEB) with pharmacologically attainable concentrations of abatacept or control IgG-Fc. The expression of CD80 and CD86 and the induction of apoptosis of monocytes were measured by flow cytometry. The expression of CD80 and CD86 mRNA was determined by quantitative RT-PCR. [Results] Abatacept promoted apoptosis of SEB-stimulated monocytes. The induction of apoptosis of monocytes by these biological agents were reversed by addition of IgG, but not IgG-F $(ab')_2$ fragmants. Furthermore, abatacept significantly suppressed the expression of CD80, but not that of CD86 at protein levels. Finally, abatacept significantly suppressed the expression of mRNA for CD80 of monocytes stimulated with SEB, but not that of CD86. [Conclusion] These results demonstrate that one of the mechanisms of action of abatacept involves the induction of apoptosis of monocytes, which involves interaction with Fc receptor on monocytes. Moreover, the data also demonstrate that abatacept selectively suppress the expression of CD80 at mRNA levels.

W30-3

Multicenter prospective trial for rheumatoid arthritis using abatacept in Japanese patients, an investigator-initiated study (Mt. Fuji study)

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Conflict of interest: None

[Objective] To study clinical usefulness of abatacept in RA patients in Shizuoka Rheumatism Network. [Methods] 101 cases that completed the study for 12 months were subjected. The mean age was 61.9 year-old (range 32~84), male:female=19:82, mean disease duration was 9.5 years (3m~45y). 42 were Bio-Naïve, and 59 were Bio-Switched. 76 were on MTX, 25 were not. Mean MTX dosage was 8.8 mg/week. [Results] 73 cases continued abatacept for 12 months (72%). At 12 months, DAS28-CRP were 2.52±1.16 in Bio-Naïve, and 3.26±1.38 in Bio-Switched. HAQ-DI were 0.572±0.575 in Bio-Naïve, and 0.929±0.802 in Bio-Switched. DAS28-CRP and HAQ-DI were significantly improved in Naïve compared to Switched ($p<0.01$). Similarly, DAS28-CRP were 2.79±1.32 in MTX+, and 3.46±1.29 in MTX-. HAQ-DI were 0.707±0.718 in MTX+, and 0.977±0.745 in MTX-. DAS28-CRP and HAQ-DI were significantly improved in MTX+ compared to MTX- ($p<0.01$). ΔmTSS was significantly improved from 4.94 at 0M to -0.14 at 12M ($p<0.01$). Serum TNFα level was not changed, whereas IL-6 level was significantly decreased from 39.4 to 17.8pg/ml ($p<0.01$) at 12M. [Conclusions] These findings suggest that abatacept is more effective in patients with MTX as well as in Bio-naïve patients. Abatacept has a significant ability to suppress radiographic change.

W30-4

The influence of the treatment with abatacept (ABT) in Bio-Naïve RA patients complicated with pulmonary involvement

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Conflict of interest: None

[Objectives] It is very difficult to choose the drug for rheumatoid arthritis (RA) patients who have pulmonary involvement, such as interstitial lung disease and airway disease. The purpose of this study is to determine the influence of ABT in RA patients complicated with pulmonary involvement [Methods] 38 patients with RA that completed the study for 24 weeks were subjected. The mean age: 58.97±14.09 years old, male: female= 8:30, mean disease duration: 6.85±7.80 years, stage I(14)/II(10)/III(7)/IV(7), mean PSL dosage: 3.89±3.35mg/day, mean methotrexate (MTX) dosage: 5.37±3.78mg/week, DAS28-CRP: 4.24±1.33, SDAI: 24.01±12.32. 8 patients (21%) have a pulmonary involvement. We evaluate the continuation rate and disease activity after 24 weeks of ABT treatment. [Results] The continuation rate was 100% in patient with pulmonary involvement group and 96.6% in patient without pulmonary involvement group at 24 week. After 24 weeks of ABT treatment, DAS28-CRP and SDAI decreased significantly from the baseline in patient with or without pulmonary involvement ($p<0.01$). [Conclusion] ABT could be safe and useful drug to treat RA with pulmonary involvement.

W30-5

Favorable outcome by low-dose abatacept in Japanse patients with active rheumatoid arthritis

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Conflict of interest: None

[Objectives] In the previous phase IIb dose-findings trial, almost equally effectiveness was observed between 2mg/kgBW and 10mg/kgBW of abatacept (ABT) for treatment of rheumatoid arthritis (RA) among Japanese. We examined the efficacy, safety and tolerability of low-dose ABT (250mg) among Japanese patients who had active RA and inadequate response to other DMARDs. [Methods] This trial was 52-week single center prospective study. The registered consecutive 86 Japanese patients with active RA. CDAI, HAQ score and safety were evaluated at 52 weeks after administration of 250mg ABT. [Results] 86 patients (85% were female) with active RA were included the study. At the enrollment, the median age was 61.9 and the median disease duration was 84 months. The average body weight was 51.2 kg. At week 52, 64% of the enrolled patients completed the study. Low-dose ABT therapy lead to significant improvement in CDAI (from 25.8±11.6 to 7.9±7.5) and HAQ score (from 1.12±0.85 to 0.44±0.59). 14 patients needed to increase ABT to 500mg. Of these, 11 patients reached to low disease activity. There were no serious adverse events observed during the study. [Conclusion] Low-dose of ABT might be sufficient for the treatment of active RA in our patient population, especially in that with lower body weight.

W30-6

Efficacy and tolerance of abatacept in patients with rheumatoid arthritis for 96 weeks

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Conflict of interest: Yes

[Objectives] To evaluate efficacy and tolerance of abatacept (ABT) for 96 weeks in patients with rheumatoid arthritis (RA). [Methods] Twenty five RA patients treated with ABT for 96 weeks in our department are included in this study. Mean age was 56.6 years old, mean disease duration was 7.8 years, and 18 patients were treated with methotrexate (MTX). Seven patients had no history of biological agents use. Efficacy was evaluated based on DAS28-CRP, SDAI, and Boolean remission criteria. [Results] Mean DAS28-CRP was 3.97/2.87/2.76/2.63 (baseline/24 weeks/48weeks/96weeks), and mean SDAI was 27.1/15.3/14.0/12.9 respectively. The efficacy of ABT emerged by 24 weeks, and the efficacy was sustained until 96 weeks. Contributing factors for effectiveness were no previous biologics use and short disease duration. Remission rate at 96 weeks was 20/16% (SDAI/Boolean criteria). Drug survival rate was 84/72% (48weeks/96weeks). Infections were the most common adverse events. There was no case that ABT was discontinued due to adverse events. [Conclusion] This study indicated that ABT can provide sustained efficacy and consistent safety for 96 weeks. The predictors for good response were no previous biologics use and short disease duration.

W31-1

Disease activity and the effects of rehabilitation (rehab) in Rheumatoid Arthritis (RA)

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Conflict of interest: None

[Objectives] Since 1987, our hospital has admitted RA patients for rehab and education program to maintain/improve ADL (Activities of Daily Living)/QOL (Quality of Life). Investigate 1) change in QOL indices Face Scale (FS), Visual Analogue Scale (VAS), and modified Health Assessment Questionnaire (mHAQ), 2) effect of disease activity and duration on QOL gains from rehab. [Methods] We analyzed the changes of measures that are FS, VAS, mHAQ, and C-reactive protein (CRP) level around the program among 99 patients who hadn't changed medication between 2003 and 2013. We classified them by the disease activity and duration. [Results] The group of low disease activity reached to functional remission, but high activity group didn't reach. The group of under 10 years duration reached to clinical remission, but over 10 years group didn't. [Conclusion] If your patient has been controlled as clinical remission or low disease activity by medicine, we suggest that rehab should be started as early as possible. So it will be achieved the functional remission which got difficultly only by the medication.

W31-2

The effect of home-based exercise on physical function in rheumatoid arthritis

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Conflict of interest: None

[Objectives] The purpose of this study was to investigate the effect of home-based exercise on physical functions in rheumatoid arthritis (RA). [Methods] Seven patients diagnosed with RA participated in the study. Home exercise program was prescribed for an 8-week. Exercise program consists of isokinetic strengthening exercises for bilateral knee extensors, hip abductors, ankle plantar flexors, elbow flexors with the resistance training using elastic band. The main outcome measures were limb muscle strengths of (knee extensors, hip abductors, leg extensors, elbow flexors), timed up and go test, five-repetition sit-to-stand (STS) test, one leg standing time, health-related QOL (SF-36). All subjects were assessed at baseline, post-intervention, and at 4 month follow-up. [Results] Lower limb muscle strengths (hip abductors and leg extensors strengths) post-intervention and at 4 month follow-up were significantly increased compared with baseline. STS test were trended to improve after intervention, lasting at least 4 months after post-intervention. [Conclusion] The results of the present study suggest that home-based exercise in patient with RA had beneficial effects improving lower limb muscle strengths and physical performance, and remained effective for several months after intervention.

W31-3

Study of music therapy for self-efficacy of patients with rheumatoid arthritis

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Conflict of interest: Yes

[Objectives] We previously reported that music therapy improves general health condition, pain, and anxiety of patients with rheumatoid arthritis (RA) attending to the patient class. In this study we investigated the effect of music therapy for the self-efficacy of patients with RA. **[Methods]** Music therapy was conducted by a music therapist, a pianist, hospital staffs, and healthcare students. Six Japanese songs were sung with a piano accompaniment and 3 of 6 were played with chime bars (a sort of hand bells) by the participants. General health condition, pain, and state anxiety were surveyed by self-rating questionnaire including 10cm VAS, face pain rating scale, and General Self-Efficacy Scale (GSES). **[Results]** Twenty-four patients with RA (22 females and 2 males) participated. mHAQ of the attendee was 0.51±0.63. VAS was improved significantly from 3.3±2.3 to 2.2±1.8, face scale was improved significantly from 5.4±4.0 to 3.5±2.3 by music therapy. In contrast, GSES was improved from 7.6±4.5 to 8.2±4.5 insignificantly. All the attendees were well or approximately satisfied for music therapy and in favor of playing music. **[Conclusion]** Music therapy improves physical and psychological conditions of patients with RA, however further research is necessary for the effect on self-efficacy.

W31-4

Patient-reported disease activity using a smartphone in rheumatoid arthritis - a longitudinal, comparative study with evaluation by physicians -

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Conflict of interest: Yes

[Objectives] To investigate the accordance and discordance between patient-reported disease activity using smartphone and disease activities evaluated by physicians in patients with rheumatoid arthritis. [Methods] Ten patients were recruited. Of these, 7 patients (2 males, 5 females) completed the study, and those data were analyzed. The averages of age and the duration of the disease were 55.0 and 10.9 years. Patient-reported disease activity (PtDAS) was calculated from a self-assessed tender joint count, mHAQ, and a parameter in gait analysis by an accelerometer in smartphone and was assessed in daily basis. We compared PtDAS with DAS28-CRP (PhDAS) evaluated by a physician in monthly visits. [Results] The average of PhDAS was 2.73 (0.99~4.68) at the beginning of

the study, and 3.21 (1.00~6.17) at the end of the study. The average of the difference of the PtDAS and PhDAS was 1.08±1.08 (0.08~5.83). The overall trends of the two DAS were similar, but the difference tended to be bigger when flare-up, sudden change, or more symptoms in upper extremities. [Conclusion] Patient-reported disease activity using smartphone was well accorded with DAS evaluated by a physician. However, sudden changes or more symptoms in the upper extremities cause discordance between the two.

W31-5

Efficacy of a wrist hand orthosis with heat retaining material in winter

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Conflict of interest: Yes

[Purpose] The wrist joint in rheumatoid arthritis is most likely to be injured, and the joint easily causes pain in activities of daily living. A wrist hand orthosis is effective for sharp pain relief and for improvement in ADL. We developed the wrist supporter with heat retaining material increasing heat retaining effect, and evaluated the effect on ADL improvement and sharp pain relief. [Method] Ten rheumatoid arthritis patients with sharp pain in the wrist joint were participated in this study. Grip and pinch strength were measured and body surface temperature was observed by thermography before and after wearing the supporter, and as a one month follow-up, they were evaluated again by sharp pain VAS-DASH-HAQ. [Result] The grip and pinch strength increased an average of 1.5 times and 1.2 times respectively, and the rise of body surface temperature was observed in thermography. At the one month follow-up, the improvement of VAS/DASH-HAQ was confirmed. [Conclusion] We developed the wrist supporter using the heat retaining material, and it showed improvement in ADL. We would like to investigate whether this research is applicable in hot environment as well.

W31-6

Usefulness of range of motion (ROM) exercise after arthroplasty for rheumatoid forefoot deformities by an offset shortening osteotomy

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Conflict of interest: None

[Objectives] To verify the usefulness of passive ROM exercise by a physical therapy for MTP joint after an offset shortening osteotomy in patients with rheumatoid arthritis (RA). [Method] 13 RA patients were enrolled in this study. 7 patients were performed passive ROM exercise by physical therapists (group; ROMex) and 6 patients were not performed (group; non ROMex). All patients had an operation on the forefoot that included an offset shortening osteotomy of the metatarsal bone of the lateral toes. At the same time, all patients were underwent modified scarf osteotomy in the first metatarsophalangeal joint. ROM exercise was started at 3 weeks after the operation and continued for 2 weeks. We assessed ROM of MTP (II-V) joints and JSSF (lesser toe) scale at 3 months after the operation in those two groups respectively. [Result] The average ROM of MTP (II-V) joints was flexion/extension; 7.5±6.8°/27.7±9.8° in the ROMex group, on the other hand, flexion/extension; 9.8±6.0°/12.1±6.7° in the non ROMex group. JSSF score were 80.1±6.1/77.3±10.3 in the group of ROMex/non ROMex, respectively. [Conclusion] This study suggests that passive ROM exercise by physical therapists was useful after an operation on the forefoot in RA patients.

W32-1

Questionnaire survey for the patients with rheumatoid arthritis 10 years after upper-extemity surgery

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Conflict of interest: None

[Objectives] To investigate a long-lasting effect of upper-extremity surgery on the patients with RA, a questinnaire survey was performed. [Methods] A questionnaire was sent to 87 RA patients who underwent upper-extremity surgery between January 2002 and December 2003. It inquired present condition of the surgically treated site, satisfaction level, and reasons of satisfying or not. [Results] Avaiable reply was obtained from 68 patients (78%, mean age at surgery 57.5), 86 sites (shoulder:1, elbow:18, wrist:39, thumb:13, fingers:15). Disease activity was moderate at the time of surgery, and it was low at present. About the usefulness, 85.2% of the patients answered “better” than preoperative condition. In satisfaction level, 86.8% answered “most satisfying” or “satisfying”. Its level was relatively high in the wrist (92%) and the fingers (93%) compared to the elbow (78%) and the thumb (77%). The most frequent reason of satisfying was “pain relief” in all sites. The reason of unsatisfying was “decrease in power” in the elbow, the thumb and the fingers, and “decrease in motion” in the wrist. In the thumb and the fingers, “improved appearance” was a frequent reason of satisfying. [Conclusion] A long-lasting favorable effect of the upper-extremity surgery was expected on the patients.

W32-2

Improvement of DASH score after upper extremity surgeries in patients with rheumatoid arthritis

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Conflict of interest: None

[Objectives] We aimed to investigate the influence of each joint of rheumatoid upper extremity surgeries on the disability of arm, shoulder, and hand (DASH) score. [Methods] 53 patients were available for this study. Average age (years old) was 59.8, mean disease duration (year) was 18.7, and mean follow-up period (month) was 17.9, respectively. There are 15 elbow, 23 wrist, and 14 hand procedures. All patients were assessed Visual Analog Scale (VAS) for pain, Health Assessment Questionnaire – Disability Index (HAQ-DI), DAS28-CRP, and DASH score pre-and post-operatively. [Results] There are significant differences in VAS for pain, DAS28-CRP, and DASH score between pre- and post-operatively. DASH score were improved in elbow (51.9±18.3 to 34.8±19.7), wrist (39.8±22.5 to 31.3±24.8), and hand procedure (41.8±18.2 to 34.9±17.9). All procedures were improved in doing heavy household chores, washing or blowing one’s hair, and feeling less capable, less confident, and less useful. [Conclusion] Elbow, wrist, and hand procedure was improved in rough and large motion, pain, and fine motion, respectively. Upper extremity surgeries give improvement of pain and function for patients with rheumatoid arthritis.

W32-3

An Evaluation of patient’s subjective satisfaction, Hand20, DASH score and the clinical results of silastic implant arthroplasty of the metacarpophalangeal for the rheumatoid hand

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Conflict of interest: None

[Objectives] We have reviewed the pre- and post-operative clinical results, the patient's satisfaction, Hand20, Disability of the arm, shoulder and hand (DASH) score of silastic implant arthroplasty of the metacarpophalangearl (MCP) joints for the rheumatoid hand. [Methods] A total of 132 AVANTA implants were inserted in 39 hands of 33 patients. The mean age of patients at the surgery was 61.4±10.8 years, the average disease duration was 21.2±10.4 years and the average follow-up period was 24.1±14.4 months. The clinical evaluations included the ulnar deviation, the range of motion of MCP joint, satisfaction-related VAS (function, cosmetic and pain), Hand20, and DASH. [Results] The mean pre- and post-operative ulnar deviation was 23.8±17.8°, 9.9±8.5° ($p<0.01$), extension of MCP joint was -45.8±32°, -16.5±16.8° ($p<0.01$), flexion of MCP joint was 76.3±19.6°, 63.5±19.6° ($p<0.01$), Hand20 was 54.5±22.1, 38.6±21.7 ($p<0.01$), and DASH score was 44.3±18.7, 34.8±17.7 ($p<0.01$), respectively. The post-operative satisfaction-related VAS was 28.7±19.4. [Conclusion] The hand function was improved with better movement for the arc of motion towards the extension after silastic implant arthroplasty. The improvement might be correctively estimated by evaluation by Hand20 and DASH.

W32-4

Clinical result of MP joint arthropasty of RA

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Conflict of interest: None

[Objectives] Rheumatoid arthritis (RA) often results in deformities at the matacarpophalangeal (MP) joint. Patients with severe deformities can be treated by silicone MP joint arthroplasty. The objective of the study is to identify the level of functional recovery after MP joint arthroplasty. [Methods] Evaluation was made on ten hands in ten cases, which treated in our department from 2007 to 2011. There were all women whose age at the time of surgery ranged from 50 to 76 years. All patients underwent the Swanson implant arthroplasty. We evaluated hand function at baseline and follow-up including pain, grip strength, range of motion of hand and DASH score. [Results] No postoperative complications, such as infection. Finger joint flexion angle compared to the preoperative mean had decreased to about 80%, but had improved extension. Grip strength is average 10% increase and the DASH score before surgery from 62.4 in the final survey at 48.9 had improved. [Conclusion] Silicone implant MP joint arthroplasty for RA improves hand function.

W32-5

Total finger arthroplasty for the MP joint deformity on RA hand

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Conflict of interest: None

[Objectives] We evaluated clinical outcome of the total finger arthroplasty (TFA) of the metacarpophalangeal (MP) joint in RA patients. [Methods] Sixteen patients (3 men and 13 women) mean aged 61 years old with 23 hands (right: 14, left 9) and 66 fingers (20 index fingers, 19 long fingers, 14 ring fingers, and 13 small fingers) suffered by hand MP joint deformity by RA underwent replacement of the MP joint with prosthesis from 2002 to 2009. Method: We used MP joint prosthesis made by ME System Co. Ltd. Metacarpal component was made of titanium and it comprised an articular ball, a calcar and stem. Proximal phalangeal component comprised an HDP socket and stem, and titanium envelope. Every titanium part was fixed to bone with PMMA cement. [Results] The mean follow-up period was 78 months. The MP active motion angle (extension/flexion: preop., postop.) was -25/57, -13/52 on index finger, -22/65, -24/57 on long finger, -33/64, -26/59 on ring finger, or -26/65, -12/46 on small finger. Total active motion (preop. /postop.) was 126/109 on index finger, 163/141 on long finger, 126/124 on ring finger, or 131/130 0n small finger. Grip strength or pinch strength (preop. / postop.) was 4kg/5kg or 1kg/1kg. [Conclusion] A finger prosthesis was satisfactory for replacement of the MP joint.

W32-6

Proximal interphalangeal Joint arthroplasty in Patient with Rheumatoid Arthritis

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Conflict of interest: None

Retrospective study on outcomes of arthroplasty for finger proximal interphalangeal (PIP) joints with functional disorders was made in patients with rheumatoid arthritis. A total of 52 joints in 36 hands in 31 patients were evaluated. Mean age at operation was 58.5 years (33-76 years). Mean follow-up period was 6.1 years (range, 1 to 8 years). Operative technique included 27 soft tissue reconstruction (extenser) alone, 12 silicon implant reconstruction, and 2 fusion in boutnniere deformity (41 joints in 24 cases). Sugeries were performed in 7 patients of swan-neck deformity. Patients were evaluated in terms of the range of motion, the degree of satisfaction for cases of boutnniere deformity. In patients with soft tissue reconstruction, the mean preoperative range of motion (extension / flexion) was -36.1 and 89.3, and the postoperative one was -16.5 and 74.4. In patients with implant reconstruction, the mean preoperative range of motion was -47.7 and 65.8, and the postoperative one was -16.1 and 43.5. Arthroplasty seemes to be useful mehod for boutnniere deformity in rheumatoid hand.

W33-1

Changes in bone mineral density of the lumber spine over three years in newly diagnosed patients with rheumatoid arthritis

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Conflict of interest: None

[Objectives] To investigate changes in bone mineral density (BMD) of the lumber spine over three years in newly diagnosed patients with rheumatoid arthritis (RA). [Methods] In 54 newly diagnosed RA patients, BMD of lumbar spine was measured using dual-energy X-ray absorptiometry at the diagnosis of RA and after 3 years. The relationship of the decrease in BMD over 3 years to the demographic characteristics, disease activity of RA, and drugs used were examined. [Results] The subjects were 84% of female. The mean age and the median disease duration were 62-year-old and 4 months. At the diagnosis of RA, the mean BMD and T-score were 1.05±0.55cm/m3 and -0.70±1.5, and at 3 year, 1.03±0.63cm/m3 and -0.78±1.5, respectively. The mean change in BMD over 3 years was -1.6%. The BMD at 3 year was significantly decreased in patients with positive anti-CCP antibody and bone erosions or oedema in MRI at the diagnosis of RA. Patients whose BMD was decreased more than 1% were worse in DAS28 at 1 year. Any treatment was not significantly related. [Conclusion] In RA, anti-CCP positivity, bone erosions or oedema in MRI at the diagnosis of RA, and high values of DAS28 were the prognostic factors of decrease in BMD.

W33-2

Anti-TNF agents increase bone mineral density in rheumatoid arthritis patients for three years

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Conflict of interest: None

[Objectives] Loss of bone mass in patients with rheumatoid arthritis (RA) causes decreases in activities of daily living. The purpose of this study is to exxamine the effect of anti-TNF agents on bone mineral density (BMD) in RA patients. [Methods] In 247 patients with RA (mean age, 62 years; mean duration of RA, 12 years), BMD was measured for three years and the annual rate of change was assessed. Anti-TNF agents

were administered to 103 patients (infliximab: 32 cases; etanercept: 63 cases; adalimumab: 8 cases). To determine factors affecting changes in BMD in RA patients, a multiple regression analysis was performed. Explanatory variables included anti-TNF agents, Body Mass Index, existence of a menopause, amount of steroids, amount of MTX, bisphosphonate, compression fractures in thoracolumber vertebrae, level of CRP, level of anti-CCP antibody, serum osteocalcin, urinary NTX, HAQ score, and having working or not. [Results] The result showed that anti-TNF agents and bisphosphonate were significantly associated with increase in BMD at both femoral neck and lumber spine. [Conclusion] Anti-TNF agents increase bone mineral density in rheumatoid arthritis patients for three years.

W33-3

Retrospective study on the usefulness of teriparatide for the prevention of steroid-induced osteoporosis in patients with collagen diseases

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Conflict of interest: None

[Objectives] To investigate the usefulness of teriparatide (TP) in patients with collagen diseases (CD) receiving steroids. [Methods] We retrospectively reviewed the medical records of 46 CD patients (male 5, female 41) receiving steroid therapy and were prescribed TP from April 2011 to November 2012. [Results] Mean age was 68.4 years old. RA 25, SLE 6, PM/DM 5, scleroderma 4, Sjogren 1, PMR 2, vasculitis 2, adult onset Still's disease 1. Thirtyfour patients had a history of fragile fracture. Clinical features at starting TP; the mean period of steroid therapy 129.5 months, the mean steroid (prednisolone) dose 6.1 mg/day, the mean YAM value of lumbar BMD 72.4% (n=39). Previous therapy for osteoporosis; bisphosphonate 31 (with vitamine D, 16), SERM 5 (with vitamine D, 3), vitamine D alone 3. Mean YAM value of lumbar BMD significantly elevated to 79.2% (n=18) after one year. New vertebral fracture developed in 3 cases, but non-vertebral fractures were not seen. Four cases stopped TP due to adverse reactions (myalgia 2, arthralgia 1, boredom 1). [Conclusion] In elderly patients with CDs receiving steroids, lumbar BMD significantly elevated by treatment with TP.

W33-4

Influence of the combination of biological agents and teriparatide (Forteo) on osteoporosis and the change of bone turnover markers in patients with rheumatoid arthritis

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Conflict of interest: None

[Objectives] Biological preparation (Bio) and teriparatide (TPTD) are drugs that gives a strong influence on bone metabolism. We evaluated the case that receiving TPTD for the osteoporosis (OP) of the rheumatoid arthritis (RA). [Methods] 23 cases that the object gave TPTD for 24 months (m). 9cases treated with both Bio and TPTD (Bio-G) and 14cases treated with only TPTD (Non-G). The examination item is evaluation at the whole and compared patient background, growth rate of lumbar spine BMD (LS-BMD), total hip BMD (TH-BMD), BTM (BAP, P1NP, NTX, TRACP-5b) between two groups. [Results] All were female. Mean age was 71years old. RA duration was 19years. The rate of concomitant prednisolone was 74%. LS-BMD increase was significantly higher in Non-G in 6m (2.3%vs8.9%), 12m (6.9%vs13.3%). There was not the significant difference between two groups in 24m (11.9%vs13.2%). TH-BMD was was significantly higher in Non-G in 12m (1.5%vs5.3%). There was no significant difference in the rate of increase BTM, but tended to be large Bio-G than in the Non-G. [Conclusion] TPTD treatment for OP of RA were good results regardless of the combination Bio. BMD growth rate was large in Non-G at first, and Bio-G showed a tendency to catch up.

W33-5

Efficacy of once-weekly teriparatide for glucocorticoid-induced osteoporosis patients with collagen diseases

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Conflict of interest: None

[Background] Treatment of glucocorticoid-induced osteoporosis (GIOP) is very important for rheumatologists, because GIOP patients are at very high risk of fractures. They should be treated immediately with a powerful drug for fracture prevention. Daily teriparatide, PTH agent, injections have demonstrated anti-fracture efficacy with a bone anabolic mechanism. Recently, once-weekly teriparatide provided both rapid and powerful anti-fracture efficacy. This drug is expected to be effective for GIOP, but it has not been reported. [Method] GIOP patients with collagen diseases at our department, who were used PSL 2.5mg or above for at least 6 months and were started the treatment with once-weekly teriparatide, were registered into our study. We measured BMD, NTx, BAP, Ca and FRAX at baseline and 6 months later. Some patients had been measured at 12 months and 18 months after starting this drug. [Result] 13 GIOP patients with collagen diseases were registered into this study. Three patients stopped the therapy before 6 months, 10 were completed for 6 months. New fracture had not been observed. [Conclusion] Our study shows that once-weekly teriparatide is effective for GIOP patients with collagen diseases.

W33-6

The prednisolone use is a risk factor for falls and fracture in RA patients –the third year results of the TOMORROW study-

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Conflict of interest: None

[Objectives] Patients with rheumatoid arthritis (RA) who have muscle weakness and stiff or painful joints might be at increased risk of falling and fracture. The present study prospectively determines the incidence of falls, fractures and their risk factors in patients with RA who participated in the TOMORROW study that was started in 2010. [Methods] We evaluated anthropometric parameters, BMD, disease activity and the occurrence of falls and fractures for a period of three years in 202 patients with RA and 202 age- and sex-matched healthy volunteers (Vo). [Results] There is no difference in incidence of falls/fractures between RA (37/9.4%) and Vo (30/7.4%) during three years. RA patients had significantly more frequent number of falls (2.5 times) than that of Vo (1.7 times) ($p=0.03$). After adjusting for risk factors, multiple regression analysis identified that incidence of falls and use of prednisolone (PLS) were associated with fractures in RA (fall: odds, 12.35, $p<0.001$, PLS: 4.58, $p=0.004$). In RA patients, amount of PLS appeared to be related o number of falls after adjusting for risk factors. ($\beta=0.214$, $P=0.027$). [Conclusion] Multiple fallers in RA patients were higher than in Vo during three years. In RA patients, use of PLS appeared to be related to falls and fractures.

W34-1

Validity and Reliability of the Japanese version of LupusQoL©: Assessment of Disease-Specific Health-Related Quality of Life in Systemic Lupus Erytematosus (SLE)

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Conflict of interest: None

[Objectives] The LupusQoL© is the most widely used SLE disease-specific HRQoL questionnaires worldwide. The purpose of the present study was to translate and adapt the LupusQoL to Japanese and further investigate its validity and reliability. **[Methods]** The English version of the LupusQoL was translated, back-translated and culturally adapted to Japanese. Japanese SLE patients were asked to complete the LupusQoL and other related demographic questionnaires such as the SF-36 (generic HRQoL measure) and physicians were asked to complete the SLICC/ACR Damage Index (SDI) and the SLE Disease Activity Index 2000 (SLEDAI-2K). **[Results]** A total of 266 patients and 30 physicians participated. 97.5% were women; the median age and disease duration were 43.5 and 10 years, respectively. Median SLEDAI-2K and SDI scores were 2 and 1, respectively. Each domain of LupusQoL score significantly correlated with SDI score and the scores of corresponding domain of SF-36, but not with SLEDAI-2K score. The LupusQoL demonstrated acceptable internal consistency, with Cronbach's α of 0.86-0.89. The intraclass correlation coefficients were mostly 0.85-0.89, which means good test–retest reliability. **[Conclusion]** We have successfully translated, adapted and validated the Japanese version of the LupusQoL.

W34-2

Features and risk factors for atherosclerosis in systemic lupus erythematosus

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Conflict of interest: None

[Objectives] To clarify the characteristics and risk factors for atherosclerosis in systemic lupus erythematosus (SLE) patients. [Methods] Sixty-four patients with SLE (20-60 years old, female 58) examined by carotid ultrasonography (CUS) and ankle bronchial index (ABI) at our hospital from April, 2012 to October, 2013 were included. Clinical and laboratory data, classical atherosclerotic factors, antiphospholipid antibodies (aPL) and treatments were obtained from medical records and cross-sectionally analyzed. [Results] The median age and mean disease duration were 42 years old and 12.6 years, respectively. Twenty-four patients (37.5%) had aPL. By CUS analysis, intima-media thickness >1.1 mm was observed in one patient (1.6%) and atherosclerotic plaques in thirty-nine (60.9%). ABI < 0.9 was found in two patients (3.1%). Multiple logistic regression analysis showed that age > 40 (OR 9.59, 95%C.I. 2.63-35.0) and phosphatidylserine-dependent anti-prothrombin antibody-IgG (aPS/PT-IgG) (OR 8.27, 95%C.I. 1.34-51.2) represented risk factors for atherosclerosis. Other factors were not related to carotid plaques. [Conclusion] This study suggests that SLE patients have high prevalence of carotid plaques. Older age and the presence of aPS/PT-IgG are associated with carotid plaques in SLE.

W34-3

The effectiveness of tacrolimus for minor flares of SLE

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Conflict of interest: None

[Objectives] We assess the effectiveness of tacrolimus (TAC) for minor flares of SLE. [Methods] The minor flare was defined as an increase in SLEDAI, which remained between 3 to 11. We recruited 15 patients who treated with add-on medication with TAC for the minor flares (TAC group). As a control, sex, age, and dose of glucocorticoids (GCs) and SLEDAI at flare matched 15 patients administered increased dose of GCs for minor flare were also recruited (GC group). All patients were maintained remission for 3 months before the flares with GCs (≦10mg/day) and/or immunosuppressants except calcineurin inhibitors. [Results] The clinical characteristics of baseline were comparable between the two groups. After 12 months, SLEDAI was improved to the level before the flares in 73% in TAC group and 67% in GC group. There was no significant difference in SLEDAI at 12 months between the two groups. Two patients in both groups developed flares. TAC discontinued in only 1 patient because of fatigue. The normalization rate for anti-ds-DNA antibody levels was higher in TAC group than GC group (60% vs 0 %, p=0.028). [Conclusion] Our study suggested that the effectiveness of TAC for the treatment of SLE with minor flares was not inferior to GC without increasing frequency of adverse effects

W34-4

Treatment of refractory SLE with combination of tacrolimus and mizoribine

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Conflict of interest: Yes

[Objectives] We have focused on multitarget therapy with combination of prednisone, tacrolimus and mizoribine as induction or additional therapy for refractory SLE. The aim of this study is to evaluate efficacy and safety of multitarget therapy for SLE. [Methods] Twenty six patients treated with multitarget therapy in our department since April 2009 were involved. They were divided into two groups; (A) 10 patients who were initially treated with this therapy as induction, and (B) 16 patients who were additionally treated with this therapy due to difficulty in reducing prednisone dose. We evaluated efficacy and safety of this therapy respectively. [Results] (A) Five of 10 patients had lupus nephritis. Complete nephritis remission rate at 6 months was 80%. Five patients not suffered from nephritis had cytopenia, skin rash, arthritis, and hypocomplementemia. All of these patients improved their symptoms or blood examination data. There were 3 severe adverse events. (B) Fourteen of 16 patients showed improvement of clinical findings, decrease of the autoantibodies, and elevation of complements. We can reduce the dose of prednisone without flare in 13 patients. There was no severe adverse event. [Conclusion] Multitarget therapy is very effective for refractory SLE.

W34-5

Efficacy of mycophenolate mofetil for lupus nephritis

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Conflict of interest: None

[Objectives] Mycophenolate mofetil (MMF) is known as useful for lupus nephritis. However, available trials are yet for Japanese patients. [Methods] Patients who visited to our center, were diagnosed with lupus nephritis (World Health Organization Class III, IV, V, and IV +V), and treated with MMF for over one year were included. Changes in urinary protein excretion rate, serum C3 and C4 levels, and anti-double-stranded (ds)-DNA antibody titer, at prior to, 3 month, 6 month and 1 year after MMF introduction were examined. [Results] A total of 8 patients (5 females and 3 males, 38±12 years) had MMF, after steroid therapy. As for a complete remission, 3, 4 and 5 patients got it 3 months, 6 months, and 1 year after the introduction, respectively. The urinary protein excretion rate prior to MMF introduction was 3.6 (0.4~7), and decreased to 1.2

(0.1~2.5), 1.0 (0.1~1.8) and 0.25 (0.2~0.4) (p=0.02). The serum C3/C4 levels were 60.5/11.4 (12 ~83/21~80.5) and increased to 89/19 (50~122/11.7~30.4), 103/31 (93~155/ 21~93) and 131/3.7 (103~160/6.6~21.8)mg/dL (p=0.005/0.004). The serum anti-ds-DNA antibody titers were 25.5 (0~20) and decreased to 5 (0~20), 0 (0~10) and <10IU/mL (p=0.03). Each parameter improved significantly. [Conclusion] MMF therapy would be effective and safe for lupus nephritis.

W34-6

Prognosis of proliferative lupus nephritis including silent lupus nephritis: A retrospective study

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Conflict of interest: None

[Objectives] We previously reported that silent lupus nephritis (SLN) with proliferative lupus nephritis (LN) was occasionally seen but their renal outcome was favorable. We further investigated the characteristics and prognosis of proliferative LN including overt LN (OLN) and SLN. **[Methods]** We retrospectively studied patients with OLN and SLN (n = 54 and 10, respectively) who had biopsy-proven ISN/RPS class III/IV LN. A LN remission was defined by no proteinuria or occult hematuria and normal renal function. **[Results]** Median follow-up period was 72 months. A remission was attained in 35 patients (65%) of OLN, and all SLN patients maintained remission. Renal flare was observed in 13 patients (37%) out of 35 OLN patients who once achieved remission during the follow-up period. Median time to flare was 22 months and median daily dose of prednisolone at flare was 11 mg. In multivariate analysis, urinary protein (mg/day) was the only pre-treatment factor that was significantly associated with remission (OR 1.00, $p<0.01$) among OLN or OLN+SLN patients. There was no significant difference about pre-treatment clinical backgrounds or labo data between OLN patients with and without flare. **[Conclusion]** In proliferative lupus nephritis, urinary protein was the most powerful prognostic factor.

W35-1

The expression of P-glycoprotein on $CD4^+CD69^+$ cells and its relevance to proliferative lupus nephritis and treatment-resistance in systemic lupus erythematosus

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Conflict of interest: None

[Objectives] P-glycoprotein (P-gp) expression on activated lymphocytes is associated with active efflux of intracellular drugs, resulting in drug resistance in SLE. CD69 is an early inducible lymphocyte activation receptor detected in infiltrated lymphocytes. We have investigated the relevance of $CD4^+CD69^+P\text{-}gp^+$cells to clinical features. [Methods] Immunohistochemistry and flow cytometry were performed using $CD4^+$cells. [Results] The expression of P-gp and CD69 on peripheral $CD4^+$cells was increased in SLE patients (n=116), compared to healthy volunteers (n=10). P-gp expression on $CD4^+CD69^+$cells correlated with only SLEDAI, but not BILAG and specific involvement such as serositis, NPSLE and lupus nephritis (LN). P-gp expression on $CD4^+CD69^+$cells were increased in corticosteroid (CS)-low responders and in proliferative LN (pLN). Furthermore, $CD4^+CD69^+P\text{-}gp^+$cells were significantly expanded in Cs-low responders with pLN. pLN with expansion of peripheral $CD4^+CD69^+P\text{-}gp^+$cells showed accumulation of $CD4^+P\text{-}gp^+$cells in the renal interstitial tissue. Treatment with MTX and IV-CY resulted in reduction of $CD4^+CD69^+P\text{-}gp^+$cells, clinical remission and tapering of CS. [Conclusion] $CD4^+CD69^+P\text{-}gp^+$cells might infiltrate in kidney, resulting in tissue damage and treatment-resistance.

W35-2

The clinical characteristics of four patients with protein-losing enteropathy in systemic lupus erythematosus

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Conflict of interest: None

[Objective] We examined the clinical characteristics of the systemic lupus erythematosus (SLE) patients with protein losing enteropathy (PLE). [Methods] Four SLE patients with PLE who were hospitalized in the Tokyo University Hospital between October 1st, 2012 and September 30th, 2013 were retrospectively reviewed by their clinical records. They were diagnosed as PLE by 99mTc-labeled human serum albumin scintigraphy. [Results] All patients were female. Their mean age was 58.3±4.6 years; the mean time to development of PLE after the diagnosis of SLE was 14.1±11.0 years; the mean serum albumin level was 2.5±0.63 g/dl. The concomitant disorders were nephritis in two patients and serositis in one patient. Three patients showed leg edema and two showed ascites. No case showed intestinal symptoms, such as diarrhea or abdominal pain. Protein leakage was detected at the small bowel in one patient and the colon in three patients. In all patients, there was no abnormal appearance by colonoscopy. All patients were treated by steroid with immunosuppuressants; AZP, MMF, CyA and somatostatin analogue with MMF. In two patients the serum albumin levels were improved. [Conclusion] PLE should be considered in SLE patients with low serum albumin level without intestinal symptoms.

W35-3

Characteristics of protein-losing enteropathy (PLE) associated with systemic lupus erythematosus (SLE): case series report

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Conflict of interest: None

[Introduction] Protein-losing enteropathy (PLE) is characterized by an excessive loss of serum proteins into the gastrointestinal tract, resulting in hypoproteinemia and occasionally complicated with SLE. We report recent 2 cases with PLE with SLE. **[Case 1]** A woman had serum ANA, anti-Sm antibodies, hypocomplementemia and hypoalbuminemia. She was diagnosed with PLE with SLE by use of Tc-99m albumin scintigraphy. High dose steroids ameliorated her symptoms and hypoalbuminemia. 7 years later, hypoalbuminemia recurred and scintigraphy revealed the recurrence of PLE. The dose of steroid was re-increased and she recovered again. **[Case 2]** A man had serum ANA, anti-Sm antibodies, hypocomplementemia and hypoalbuminemia. He was also diagnosed with PLE with SLE by scintigraphy. In addition, the gastric tissue biopsy showed interstitial infiltration of imflammatory cells and deposit of complements and immunogloblins around capillary walls. High dose steroids ameliorated his hypoalbuminemia and abnormal findings of scintigraphy. **[Clinical Significance]** The 2 cases agree with the literature. Specifically, PLE usually develops as the first manifestations of SLE, is not associated with anti-dsDNA antibodies, and well respond to steroids, and Tc-99m albumin scintigraphy is useful for its diagnosis.

W35-4

Interstitial pneumonitis in systemic lupus erythematosis

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Conflict of interest: None

Background: Systemic lupus erythematosis (SLE) has a lower comorbidity with interstitial lung disease (ILD) than other collagen diseas-

es. SLE-ILD progressing within a few weeks is called acute lupus pneumonitis (ALP); the other is called chronic ILD, which has two types: residual ILD after ALP and ILD that has progressed subclinically. **Methods:** Patients with SLE-ILD admitted in our department from 2005 to 2013 were identified and their clinical characteristics were studied. **Results:** Out of 250 SLE patients identified, 17 (6.8%) had SLE-ILD. The SLE-ILD group was significantly older (57.7 vs. 44.4 years) and had more male patients (47.1% vs. 13.3%). SLE-ILD was treated with steroid (prednisolone 1mg/kg ± steroid pulse) plus immunosuppressive agents if needed. During the follow-up, one patient suffered an exacerbation and the others had a good prognosis. In 8 patients, SLE-ILD occurred simultaneously with SLE. In 13 patients, SLE-ILD occurred on SLE exacerbation. Four patients showed multiple small nodular shadows at the lung base on high-resolution computed tomography (HRCT), which is specific for ALP. Others showed NSIP (7/17), UIP (3/17), or OP (3/17) pattern in HRCT, respectively. **Conclusions:** SLE-ILD often occurs rapidly with SLE exacerbation and has a good prognosis.

W35-5

Serological findings and response to treatment in patients with acute lupus hemophagocytic syndrome

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Conflict of interest: None

Objectives: To clarify the association of serological findings with response to treatment in patients with acute lupus hemophagocytic syndrome (ALHS). Methods: We retrospectively investigated 7 patients with ALHS, who admitted to our department between 2005 and 2013. Results: 1) The mean age at the onset of ALHS was 41.3±21.8 years. All the patients were female. ALHS was the initial manifestation of systemic lupus erythematosus in 5 cases. 2) Anti-DNA antibody; 86.7±132.9IU/ml, ferritin; 15491.4±12665μg/l at baseline. Significant negative correlation between anti-DNA antibody and ferritin was found (Spearman R=-0.943, p=0.0048). 3) Bone marrow aspiration was conducted in all the cases and revealed hemophagocytosis in 5 cases. 4) Prednisolone was initiated in all the patients. Then we added cyclosporine (CsA) in three patients, intravenous cyclophosphamide in one patient and rituximab in another patient. 5) Six patients survived and one patient died. Although the three patients who received CsA showed high levels of ferritin (26291.3 ±6483.7μg/l) and steroid resistance, CsA was effective in these cases. Conclusion: Although ALHS patients with high ferritin levels had low titers of anti-DNA antibody and steroid resistance, they might respond to CsA.

W35-6

The risk factors of aseptic necrosis of the femoral head (ANF) in Systemic Lupus Erythematosus : Case Control Study

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Conflict of interest: None

(objectives) Although high-dose corticosteroid therapy, alcohol intake and SLE is regarded as risk factors for ANF. Several studies suggested that statin, anti-platelet agent and bisphosphonates reduced the risk of ANF in SLE. The purpose of this study was to clarify the risk factor on ANF in SLE. (Methods) We conducted a hospital-based case control study of 10 SLE with ANF and 10 matched controls. The demographic (BMI, smoking history, alcohol intake), clinical (CNS involvement, renal involvement, skin involvement, lung involvement, arthritis, serositis, cytopenia), laboratory (anti-SSA ab, anti-SSB ab, anti-Sm ab, anti-RNP ab, anti-CL IgG ab, anti-CL-β2GP1 ab, LAC (dRVVT)) and management (max dose of corticosteroid, steroid pulse therapy, statine, anti-platelet, bisphosphonates) characteristics of these two groups of patients were recorded according to predefined protocol and compared. We use Student's t-test test, Welch's t-test and Fisher's exact test. (Results) The steroid pulse therapy was positively associated with ANF. ANF trended to develop less frequency in serositis. (Conclusion) The steroid pulse therapy may be associated to ANF.

W36-1

Skewed helper T cell responses to IL-12 family cytokines in patients with Behcet's disease (BD)

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Conflict of interest: None

[Objectives] We have presented evidences that high frequency of helper T (Th) 17 cells and overactivity of Th cells against both IL-12 and IL-23 in patients with BD. Recently, some researchers revealed that IL-12, IL-23, IL-27 and IL-35 are heterodimeric and share the subunits, and named them IL-12 family cytokines. This investigation was designed to study the functional differences of IL-12 family cytokines in Th cell differentiation between BD and normal controls. [Methods] We cultured Th cells with IL-12 family cytokines and evaluated cytokine production and gene expression of the cells obtained from patients with BD (n=5) and NC (n=4). [Results] In patients with BD, high frequency of Th17 cells was observed in the presence of IL-23 and anti-IL-23 (p19) compared to NC ($p<0.05$). On the contrary, frequency of Th1 cells was significantly low in the presence of IL-23, IL-35, anti-IL-23 and a JAK inhibitor (P6) in patients with BD compared to NC ($p<0.05$). IFNγ mRNA in two patients with BD was relatively high in case of IL-12, IL-23 and IL-35 stimulation but the average value showed no significant difference between BD and NC. [Conclusion] These results suggest that skewed Th cell differentiation in patients with BD against IL-12 family cytokines is assessed by in vitro experiments.

W36-2

Analysis of anti-claudin1 antibody in Behçet's disease

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Conflict of interest: None

[Objectives] Behçet's disease (BD) is considered at the crossroads of autoinflammatory syndrome and autoimmune disease. A few autoantibodies were reporetd in patients with BD. We try to identify autoantibodies in BD and assess anti-claudin-1 antibody [Methods] We assess titers and function of anti-claudin1-antibody identified by protein microarray. The values were measured by ELISA and compared between BD group and healthy control group. The function was assessed with formation of monolayer with epithelial cell line, Caco2 cell. [Results] Serum titers of anti-claudin1-antibody were elevated in 27 patients with BD compared to 22 controls (10.3 [2.7, 18.0] AU/ml and 2.6 [0.7, 8.3] AU/ml). Association between titers and clinical manifestations showed a positive correlation (14% in low titer group and 23% in high titer group for erythema nodosum, 41% and 59% for oral aphtha). Addition of anti-claudin1-antibody reduced transepithelial electric resistance in Caco2 cell (283 [184, 652] ohm with antibody and 3036 [1306, 4203] ohm without antibody), suggesting interference cell adhesion. [Conclusion] Anti-claudin1-antibody may be characteristic of BD.

W36-3

HLA-B51 and HLA-A26 locus were related to the development and ocular lesions of Behcet's disease, respectively

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Conflict of interest: None

[Objectives] To investigate the relationships between the development or symptoms of BD and HLA-A/B loci. [Methods] Sixty-nine patients fulfilled the Japanese criteria of BD visited our hospital from January 2009 to December 2011, were enrolled. Each doctor of these patients obtained informed consent, and HLA-A/B loci were analyzed with PCR-rSSO method. [Results] The characteristics of the patients were as follows: 18 males and 51 females; mean age (SD: quartile), 41 (13.3: 31, 41, 53) years old; ocular lesions was 30%; oral aphthous ulcers, 97%; genital lesions, 78%; skin lesions, 94%; arthritis, 55%; intestinal lesions, 25%; neural lesion, 7%; vascular lesions, 4%; epidydimitis, 11% (in 18 males); positive pathergy test, 2%. Moreover, 17% were the complete type comparing 83% were the incomplete type. The HLA-B51 (p=0.04, OR: 1.7, 95% CI: 1.0-2.7) was strongly associated with development of BD based on our case-control study. The locus HLA-A26 (p=0.02, OR: 4.1, 95% CI: 1.4-12.4) was significantly correlated with ocular lesions of BD. [Conclusion] HLA-B51 and HLA-A26 locus were related to the development and ocular lesions of Behcet's disease, respectively.

W36-4

Roles of Th22 in the pathogenic control of Behcet's disease (BD)

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Conflict of interest: None

[Objectives] Th22 is a novel helper T-cell subset characterized by the production of IL-22 without IL-17 expression. IL-22 is involved in a suppression of excessive inflammation. The aim is to clarify roles of Th22 in the control of BD pathogenesis. [Methods] This study enrolled 23 patients with BD and 13 healthy controls. Levels of plasma IL-17, IL-22, and lipocalin-2, a molecule under control of IL-22, were measured by enzyme immunoassay. Proportions (%) of Th22 in circulating CD4+ T cells were examined using flow cytometry by expression of chemokine receptors. [Results] IL-22 levels were lower in patients with active BD than in those with inactive BD or controls (P = 0.02). Levels of IL-22 and IL-17 tended to be positively correlated in active BD, but negatively correlated in inactive BD, suggesting predominant Th22 response in inactive BD. This was confirmed by increased proportion of Th22 in inactive BD, compared with active BD or controls (P = 0.03). Serial analysis in 4 patients with active BD revealed an increased proportion of Th22 along with improvement of disease status. Finally, lipocalin-2 was positively correlated with IL-22 in inactive BD. [Conclusion] Up-regulated Th22 in patients with inactive BD may be involved in negative regulation of the pathogenic process.

W36-5

Antibody toward infliximab modulates efficacy and safety in Behçet's disease

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Conflict of interest: None

[Objectives] We investigate infliximab (IFX) trough levels and antibody toward IFX (ATI) in Behçet's disease (BD) patients receiving IFX along with the clinical efficacy and safety. [Methods] IFX trough level and ATI were determined by ELISA in sera from 129 BD patients receiving IFX, including 25 intestinal BD and 6 neuro-BD. [Results] IFX trough level was 5.6 + 6.4 mg/ml in the sera from 5 to 8 wk of administration interval, but it was it was undetectable (less than 0.1 mg/ml) in 22 patients including 14 patients (11.1%) having ATI. ATI was also found in 3 of 7 patients who discontinued IFX therapy. Infusion reaction (IR) was found in 9 of 17 ATI positive patients, which was significantly more frequent than ATI negative ones (P<0.001). Concurrent use of methotrexate and corticosteroids significantly suppressed ATI. In our hospital, 6 had IR, 4 had ocular attacks, and 6 had extraocular manifestations in 7 ATI positive patients, including 3 patients who discontinued IFX. IFX was detectable after shortening administration intervals in 2 patients, leading to recovery of efficacy. [Conclusion] Decreased IFX trough level, which is associated with positive ATI, IR and reduced efficacy, is circumvented by concurrent use of immunosuppressants and shortening administration intervals.

W36-6

Study on the safety and efficacy of infliximab, an anti-TNF-αantibody, in 21 patients with refractory intestinal Behcet's disease

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Conflict of interest: None

[Objectives] Intestinal Behcet's disease (BD) is an intractable condition of BD which can affects mortality and morbidity. In the present study, safety and efficacy of 3-years-treatment with an anti-TNF-α antibody Infliximab (IFX) on refractory intestinal BD were estimated. [Methods] IFX was administered to 21 intestinal BD patients. The healing rate of intestinal ulceration on colonoscopy was used as the primary efficacy endpoint. The secondary endpoint used was the ameliorating effect based on the "Disease Activity Index for Intestinal Behçet's disease" (DAIBD), and the dose of corticosteroid (CS) tapered. [Results] The retention rate was 85.7 %. No severe adverse effects were observed during observation period. The healing rate of intestinal ulceration on colonoscopy was 66.7% and average DAIBD score decreased significantly from 73.3 to 21.4 (1 year), 11.1 (2 year), 11.7 (3 year). The dose of concomitant CS was reduced significantly from 14.2 mg/day to 2.5 (1 year), 1.5 (2 years), 1.3 mg/dl (3 year). [Conclusion] IFX treatment is highly effective in the treatment of intestinal BDin cases of refractory intestinal BD, and that it demonstrates excellent tolerability. IFX therapy has been shown to be effective treatment strategies for intestinal BD.

W37-1

Anti-ribosomal P Protein Antibodies Exacerbate Long-term Prognosis in Patients with Diffuse Psychiatric/Neuropsychological Syndromes in Systemic Lupus Erythematous

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Conflict of interest: None

[Objectives] The aim of this study is to clarify the effects of various autoantibodies including anti-ribosomal P protein antibody (anti-P) on the overall mortality in patients with diffuse psychiatric/neuropsychological syndromes in systemic lupus erythematous (diffuse NPSLE). [Methods] Fifty-eight patients with diffuse NPSLE who had been admitted from 1992 to 2012 were exhaustively collected. The relationship of various serum autoantibodies with overall mortality was analyzed. [Results] Of 58 patients, 12 patients [20.7%] died during the observation periods (2322 ± 2250 days [mean ± SD]). The 5-year, 10-year and 15-year mortality rates were 17.9%, 22.0% and 30.7%, respectively. The overall mortality was neither correlated with age nor with the duration of SLE at the onset of diffuse NPSLE. Among various autoantibodies in the sera, the presence of anti-P, but not that of anti-DNA, anti-Sm or anti-phospholipid antibodies at the onset of diffuse NPSLE, significantly increased the odds ratio for death (p=0.0447). Moreover, the survival rate was lower in patients with positive anti-P than those with negative anti-P at the onset (p=0.0711). [Conclusion] These results indicate that the presence of anti-

P in the sera is a significant risk factor for the poor prognosis of diffuse NPSLE.

W37-2

Anti microtube associated protein 2 antibody in cerebrospinal fluid is a novel diagnostic biomarker for Neuropsychiatric systemic lupus erythematosus

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Conflict of interest: None

[Objectives] Anti microtube associated protein 2 (MAP-2) antibody has been reported to be found in sera with SLE patients especially having neuropsychiatric manifestations. In some cases, it is hard to diagnose NPSLE because clinicians have to exclude clinically many other diseases such as viral infection or steroid psychosis. Therefore, novel diagnostic biomarkers have been expected to be established. Herein, we conducted this study to clarify that anti-MAP-2 antibody in cerebrospinal fluid can be used for a diagnostic biomarker of NPSLE. [Methods] Anti-MAP-2 antibody, anti-ribosomal P antibody, and IL-6 was measured by ELISA in cerebrospinal fluid with NPSLE patients (n=24) and non NPSLE patients (n=18). [Results] Prevalence of anti-MAP-2 antibody was 33.3% (8/24) in NPSLE patients. None of patients with non NPSLE (0/18) reacted with MAP-2. Prevalence of anti-ribosomal P antibody and IL-6 concentration were significantly higher in cerebrospinal fluid of NPSLE patients with anti MAP-2 antibody. [Conclusion] Anti-MAP-2 antibody in cerebrospinal fluid was recognized in 33.3% patients with NPSLE and it was highly specific for NPSLE. We propose that anti-MAP-2 antibody in cerebrospinal fluid is a novel diagnostic biomarker for NPSLE.

W37-3

Examination of clinical and imaging findings of Neuropsychiatric SLE (NPSLE) in our hospital

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Conflict of interest: None

[Objectives] Various symptoms of NPSLE sometimes confuse the diagnosis. We analyzed clinical and imaging findings of NPSLE in our hospital. [Methods] The patients diagnosed SLE in our hospital were extracted from 2005 to October, 2013. SLEDAI, CSF examination (cell counts, protein, IgG index, IL-6 value), MRI, and SPECT were examined among NPSLE patients. [Results] Among 89 SLE patients 32 patients developed central-nerves condition. Fifteen patients (9 aseptic meningitis, 3 CVD, 2 convulsive seizures, 1 cognitive dysfunction) was diagnosed as NPSLE. Non-NPSLE was 17 patients (8 CVD, 5 steroid psychosis, 3 CNS infection, 1 SIADH). SLEDAI was 19.7±1.7, and CSF protein; 75.9±8.7 mg/dl and the cell counts were 18.9±5.9/mm3. CSF IL-6 level (n= 13) was 574±290 pg/ml. In SPECT (n= 12), 3 patients were normal. The diffuse or local hypoperfusion of cortex was seen at another 9 patients. At head MRI (n= 13), 8 patients were normal, 4 cytotoxic pattern and 1 vasogenic edema pattern. [Conclusion] It is suggested that CSF protein, cell counts, and IL-6 value were useful to diagnosis of NPSLE. Although patients show the normal head MRI, abnormalities are revealed in CSF and SPECT examination. Co-examination by CSF, MRI and SPECT can be useful.

W37-4

Cerebral blood flow scintigraphy findings (CBFS) in SLE

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Conflict of interest: None

[Objects] To evaluate the clinical significance of the CBFS in SLE patients. [Methods] The medical records of 62 SLE patients (14 male, 48 female) who admitted to our hospital from January 1st 2007 to August 31st 2013 and had the CBFS were analyzed retrospectively. [Results] Mean age was 44.4 and mean spinal fluid IL-6 level was 218.2 pg/mL. Clinically neuropsychiatric symptoms were seen in 34 cases (psychiatric disorder 18, convulsion 15, peripheral neuropathy 4, optic fundus change 3, cerebrovascular disease 3, headache 3, cranial nerve dysfunction 1, spinal cord disease 1). Other patients had symptoms such as fever and/or findings suggestive of NPSLE such as elevation of spinal fluid IL-6 level. 14cases had normal CBFS findings. Integrated decrease of CBFS was seen in 40 cases (21 frontal lobe, 14 temporal lobe, 13 occipital lobe, 9 parietal lobe, 7 cerebral hemisphere, 6 striatum, 3 cerebellar hemisphere) and integrated increase of CBFS was seen only in stiatum in 8 patients. There were no association between the degree of integration and symptoms, exam finding, and treatment. [Conclusion] When SLE patients had symptoms such as fever, immune disorders such as autoantibody, CBFS abnormality was observed even in the absence of neuropsychiatric symptoms, which might be asymptomatic NPSLE.

W37-5

Elevated cerebrospinal fluid levels of progranulin and their diagnostic reliability in patients with NPSLE

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Conflict of interest: None

[Objectives] Recently, it has been reported that progranulin (PGRN) is a soluble cofactor for TLR9 signaling. We reported that serum PGRN is associated with SLE global activity and may have a role in the pathogenesis via increased IL-6 production. The aim of this study was to evaluate cerebrospinal fluid (CSF) levels of PGRN and their diagnostic reliability in patients with NPSLE. [Methods] CSF levels of PGRN and IL-6 were measured by ELISA in patients with NPSLE (n=18) and non-NPSLE (n=9), inflammatory controls (n=10), non-inflammatory controls (n=8). In patients with SLE, we assessed the correlation between the CSF PGRN levels and established disease-activity indexes. Moreover, we evaluated the sensitivity and specificity of CSF PGRN and IL-6 levels, brain wave, head MRI, SPECT for diagnosis of NPSLE. [Results] CSF PGRN levels were significantly higher in NPSLE patients than those in non-NPSLE patients and non-inflammatory controls. They were significantly correlated with CSF IL-6 levels, but not with general disease activities. The sensitivity and specificity of CSF PGRN levels for diagnosis of NPSLE were 55.6% and 88.9%, respectively, at the cut-off value of 4.7ng/ml. [Conclusion] CSF PGRN levels are elevated in patients with NPSLE and may be a useful measure in diagnosing NPSLE.

W37-6

Therapeutic outcomes of neuropsychiatric systemic lupus erythematosus

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Conflict of interest: None

[Objectives] Neuropsychiatric systemic lupus erythematosus (NPSLE) involves serious organ disorder with variety of symptoms. Despite advances in the understanding of the immunopathogenic and clinical aspects of SLE, NPSLE remains a diagnostic and therapeutic challenge. The purpose of this study is to understand the immunopathogenic and clinical aspects of NPSLE. [Methods] We analyzed the laboratory data, symptoms, treatment regimen, and therapeutic outcome one year after treatment, and the prognostic factors of 23 NPSLE patients and 27 cytokine profiles in pre-treatment samples of their cerebrospinal fluid (CSF). [Results] The responders at one year post-treatment were six patients; their age at NPSLE onset was 27.3±9.75 yrs versus 38.4±10.6 yrs in the non-responders (p=0.0354). Patients with > 2 NPSLE symptom types had poorer outcomes (p=0.0369). CSF Interleukin (IL)-8 levels were higher in the non-responders (p=0.0191). The therapeutic response was better in the non-tacrolimus-treated (p=0.0086) and rituximab-treated patients (p=0.0113). [Conclusion] Younger, single-symptom NPSLE patients had better therapeutic outcomes. B-cell depletion treatment may provide better NPSLE outcomes.

W38-1

Association of the Hypoxia Inducible Factor 1A (*HIF1A*) gene polymorphisms with systemic sclerosis (SSc) in Japanese population

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Conflict of interest: None

[Objectives] SSc was characterized by fibrosis and peripheral circulatory insufficiency. HIF1α is guided in a hypoxic condition and works as a transcription factor. Wipff et al reported that *HIF1A* polymorphism rs12434438 was associated with SSc development in European Caucasian. In this study, we investigated the association between *HIF1A* gene polymorphisms and SSc development in Japanese population. [Methods] Case control study was performed in 289 Japanese SSc patients and healthy matched controls. Four SNPs (rs11549465, rs11549467, rs1957757, rs12434438) of *HIF1A* gene were genotyped using the Taqman probe. Association between these SNPs and disease development was analyzed. Association between these SNPs and clinical symptoms, disease type, complications, and disease unique autoantibodies in SSc patients were also analyzed. [Results] Any associations between those SNPs and susceptibility to SSc were not found. However, the frequency of rs12434438 was significantly higher in SSc patients who developed pulmonary arterial hypertension (PAH) compared with that in SSc without PAH ($p<0.05$). [Conclusion] Although *HIF1A* polymorphisms was not associated with SSc development in Japanese population, the association between rs12434438 and PAH development in Japanese SSc patients was found.

W38-2

The regulatory role of γΔNKT cells in systemic sclerosis patients with interstitial pneumonia

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Conflict of interest: None

[Objectives] Interstitial pneumonia (IP) is a serious complication in systemic sclerosis (SSc). However, the exact mechanism of IP remains elusive. The purpose of this study is to clarify the role of γΔNKT cells in SSc patients with IP. [Methods] 1) The proportion of γΔNKT cells in PBMCs from SSc patients (n=35) and healthy controls (HC, n=22) was analyzed by flow cytometry. 2) In SSc patients with IP, the correlation between proportion of γΔNKT cells in PBMCs and serum KL-6 levels was analyzed. 3) Cytokine and chemokine secretion assay using γΔNKT cells from SSc patients and HC were performed. 4) The effect of culture supernatant of γΔNKT cells on fibroblast proliferation was evaluated. [Results] 1) The proportion of γΔNKT cells was significantly higher in IP-negatives SSc patients (mean±SEM, 1.03±0.32%) than IP-positive SSc patients (0.28±0.07%, $p<0.05$) and HC (0.23±0.09%, $p<0.05$). 2) The proportion of γΔNKT cells correlated negatively with serum KL-6 values ($r=-0.464$, $p<0.05$). 3) Upregulation of CCL3 and downregulation of IFN-γ production were noted in γΔNKT cells from IP-positive SSc patients. 4) Fibroblast proliferation was promoted with culture supernatant derived from SSc patients. [Conclusion] γΔNKT cells might play a regulatory role in the pathogenesis of IP in SSc patients.

W38-3

Utility in the assessment of lactulose breath test in the determination of Small Intestinal Bacterial Overgrowth in Systemic Scleroderma

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Conflict of interest: None

[Objectives] Small intestinal bacterial overgrowth (SIBO) caused by intestinal diminished peristalsis is common complication in the patients with Systemic Scleroderma (SSc). However, the diagnosis of SIBO remains issues for physicians. The lactulose breath test has been developed to test for bacterial overgrowth in the small intestine, based on bacterial metabolism of carbohydrates to hydrogen and methane gases. Originally, lactulose is broken down by resident bacterial flora in the colon, the gas levels rise earlier in SIBO patients resulting from fermentation by bacteria increased abnormally in the small intestine. [Methods] We tried the lactulose breath test to six patients with SSc. [Results] In the patients without gastrointestinal symptoms or marked intestinal gases by abdominal X-ray, hydrogen gas levels in the breath stayed in low concentration. In the patients with gastrointestinal symptoms and marked intestinal gas images, the gas levels at the start of tests were higher and increased early, diagnosed with SIBO. They showed improvement of symptoms in all patients by the oral antibiotics. [Conclusion] It has been suggested that the lactulose breath test is useful in determining the therapeutic strategy and diagnosis of SIBO in SSc patients.

W38-4

Validity and utility of new ACR/EULAR classification criteria for systemic sclerosis

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Conflict of interest: None

[Objectives] We evaluate the validity and utility of the 2013 American College of Rheumatology (ACR) classification criteria for systemic sclerosis (SSc) [Methods] Study design: Cross sectional study. The consecutive 1309 patients visited our department between August 2013 and October. Of these, sclerosis and diagnosed as SSc, MCTD, SLE, and UCTD were enrolled to our database. We use The 2013 ACR/EULAR classification criteria for SSc, The 1980 ARA classification criteria for SSc and the 2003 Ministry of Health and Welfarein (MHWL) in our clinical practice, and compare the validity and utility. [Results] In 234 patients, new ACR/EULAR criteria was 56 people (23.9%), 1980ARA criteria was 25 (10.7%), 2003 MHLW criteria was 60 (25.6%). Both criteria had low false-positive rate, but the new ACR/EULAR criteria tended to be higher than 2003 MHLW criteria, and the sensitivity showed the tended to be higher than 2003 Ministry of Health, Labour and Welfare diagnostic criteria. [Conclusion] New ACR/EULAR SSc classification criteria is considered to be beneficial in clinical scleroderma. it will consider the promotion of understanding the pathogenesis of particular.

W38-5

Screening of early pulmonary hypertension using exercise Doppler echocardiography in patients with connective tissue diseases

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Conflict of interest: None

[Objectives] We introduced a formula for estimating mean pulmonary arterial pressure (mPAP) using exercise Doppler echocardiography for connective tissue diseases (CTD) patients who need need right heart catheterization (RHC) *(Yamasaki Y, EULAR 2013)*. Here we extended numbers of the validation cohort. **[Methods]** A total of 231 CTD patients suspected PH were performed Doppler echocardiography before / after exercise with the Master's double two-step. Thirty-two of 68 patients (47%) who had >45mmHg of tricuspid regurgitation pressure gradient (TRPG) just after the exercise agreed to undergo RHC (derivation cohort). We validated with the additional 25 patients. **[Results]** Of 32 patients, 5 (16%) had PH. TRPG at 3 minutes after the exercise explained 53% of the variability in the mPAP ($r^2 = 0.5305$, $P < 0.0001$). The formula we derived was **[estimated mPAP = 0.551+0.384 x TRPG (post 3 minutes)].** Applying the formula to the validation cohort gave a good correlation (Spearman r =0.6051, p =0.0014). In receiver operating characteristic, the area under the curve was 0.885. Using an estimated threshold of 16.5 mmHg for PH, the sensitivity / specificity were 86% / 78%. **[Conclusion]** The provided formula using exercise Doppler echocardiography would help the selection of candidate patients for RHC.

W38-6

Analysis of Nail fold capillary changes and response by therapy in patients with systemic sclerosis

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Conflict of interest: None

To determained the effect of usefulness about nail fold capillary changes analysis we examine the capillaroscopic change by nail fold activity score used by dermoscopy. [Methods] 72 SSc patients, mean age 58±14 years old, disease duration 9.4±7.5 year, dcSSc/lcSSc 26/46, Nail fold capillary changes were nail fold capillary activity score (NFcA); nail fold bleeding, nail fold capillary enlargement, score from 0 to 2 all fingers, tatal maximum score 40 using dermascope (Dermlyte). These NFcA score was compared with 42 other diseases (RA, SLE, Raynaud's disease etc.). Moreover 12 SSc patients during therapy followed up the NFcA every 2 weeks for 24 weeks. [Methods] NFcA (mean 6.8±6.0 (0-22)) in patients with 72 was patients counter-correlated with disease duration. Sensitivity of NFcA detected ROC analysis was cut off point over 3.5. Other index, MRSS (10.1±8.4), age did not detected significant relationship between NFcA. High NFcA in patients with dcSSc significantly decreased by Steroids and immnosupressive therapy (IVCY). [Conclusion] Analysis of Nail fold capillary changes is a useful tool for diagnosis and evaluation of therapeutic effects in patients with SSc.

W39-1

Peripheral blood eosinophil number is high in systemic sclerosis compared with other connective tissue diseases, and shows significant correlation with the grade of interstitial lung disease

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Conflict of interest: None

There are little numbers of reports regarding the relation of eosinophils with connective tissue diseases (CTD). However we have had an impression that peripheral blood eosinophil number (PB-EOS) is high in patients with SSc. We compared PB-EOS in various CTD. In addition, because eosiophils releases fibrogenic cytokines such as TGF-beta and IL-11, we studied the relationship between PB-EOS and the ILD grade. Patients who satisfy the followings were included: 1. glucocorticoid naïve, 2. determination of PB-EOS at the first visit, 3. chest CT near the first visit. The ILD grade was determined by CT images and evaluated into grade 0 to 3. This study included RA 126, SLE 20, diffuse SSc 11, limited SSc 57, PM/DM 10, MCTD 8, pSjS 19, and angiitis 12. The mean PB-EOS was as follows; diffuse SSC > limied SSc = angiitis > RA > PM/DM > pSjS > MCTD > SLE. When all the patients were included, there was a weak but significant correlation between PB-EOS and the ILD grade. In SSc alone, the correlation was moderate (r = 0.46), but when SSc was excluded, the correlation was not significant. In conclusion, it was suggested that eosinophils contribute to the pathogenesis of ILD in SSc to some extent, but the mechamisms of eosinophil activation remains to be elucidated.

W39-2

Comprehensive gene expression analysis of lymphocyte subpopulations from patients with systemic sclerosis who received autologous hematopoietic stem cell transplantation

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Conflict of interest: None

[Objectives] To evaluate gene expression profiles (GEP) of lymphocyte subpopulations from patients with systemic sclerosis (SSc) before and after hematopoietic stem cell transplantation (HSCT) and to reveal the mechanism of immune reconstitution. [Methods] Eight patients who received HSCT, 11 untreated patients and 5 healthy controls (HC) were enrolled. Peripheral blood mononuclear cells isolated from them were sorted into 8 subpopulations. GEP were analyzed by DNA microarray. [Results] Memory $CD4^+$ T cells (CD4T), effector memory $CD8^+$ T cells (CD8T) and memory $CD19^+$ B cells (CD19B) were investigated. Six genes were significantly up- or down-regulated in the CD4T from untreated SSc patients compared to HC; 47 were CD8T and 18 were CD19B. After HSCT, the expression levels of most regulated genes decreased to healthy level. The regulated genes in the CD8T were relevant to immune response and cell adhesion, and 2/6 genes from CD4T and 6/18 from CD19B were interferon signature genes. The genes which significantly changed before and after HSCT were associated with cell activation in CD8T and regulation of apoptosis in CD19B. [Conclusion] GEP of each subpopulation showed characteristic pattern. Improvement of abnormal gene expression was contributed to immune reconstitution after HSCT.

W39-3

Comparison of 1980 ACR and 2013 ACR/EULAR criteria for systemic sclerosis by analysis of the anti-centromere antibodies sero-positive patients

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Conflict of interest: None

[Objectives] Anti-centromere antibodies (ACA) are characteristic autoantibodies which are detected in patients with primary Sjögren's syndrome (pSS) and systemic sclerosis (SSc). However, differential diagnosis of ACA sero-positive pSS and SSc is difficult because of their similar clinical characteristics. 2013 ACR/EULAR classification criteria for SSc divided skin thickening of the fingers into sclerodactyly and puffy fingers and included ACA for diagnostic criteria. The present study we compared

1980 ACR classification criteria for SSc (ACR criteria) and ACR/EULAR criteria by analysis of ACA sero-positive patients. [Methods] Thirty-six ACA sero-positive pSS and secondary SS patients were studied. The classification and diagnosis were evaluated by ACR criteria and ACR/EULAR criteria. [Results] Ten of 36 patients (27.8%) fulfilled ACR criteria and 17 of 36 patients (47.2%) fulfilled ACR/EULAR criteria. Four of 7 (57.1%) pSS patients who fullfil ACR/EULAR criteria and did not fulfill ACR criteria had sclerodactyly, and 2/7 (28.6%) of them had esophageal dilatation. [Conclusion] ACR/EULAR criteria were more sensitive than ACR criteria for the diagnosis of SSc in the ACA sero-positive patients.

W39-4

Scleroderma renal crisis: a report of three cases of anti-RNA polymerase III antibody positive patient

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Conflict of interest: None

Case 1: a 46-year-old woman who diagnosed systemic scleroderma (SRC) was admitted to our hospital for loss of consciousness and convulsion. Her serum creatinine is 1.6 mg/dl and serum platelet decreased to 4.6000/μl. ACE inhibitor started but renal dysfunction was progressing to CRF on HD. She was died since her first admission. Case 2: a 70-year-old woman was admitted for bilateral leg edema. She diagnosed rheumatoid arthritis at 37 years old and treated by corticosteroid only. Her serum creatinine elevated 0.6 mg/dl to 1.1 mg/dl, and her platelet decreasing and hemolytic anemia. After starting ACE inhibitor, her renal function was recovered. Case 3: a 69-year-old man was admitted for severe headache and vertigo. His serum creatinine was 2.9 mg/dl and platelet was 60000/μl. Blood pressure was 240/136 mmHg. He had concomitant interstitial pneumonia. Starting ACE inhibitor, BP was well controlled, and his renal function was recovered rapidly. These three cases of SRC were both anti-Scl70 antibody and anti-centromere antibody negative, but anti-RNA polymerase III antibody (RNPP) positive. All cases were revealed onion-skin lesion in renal biopsy. A case with severe skin lesion was poor prognosis. Our observation indicate that RNPP is a riskfactor of occurring SRC.

W39-5

The utility of diffusing capacity for carbon monoxide / alveolar volume ($DLco/V_A$) and cardiac magnetic resonance imaging for diagnosis of pulmonary hypertension associated with systemic sclerosis

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Conflict of interest: None

[Objectives] Pulmonary hypertension (PH) is one of the complications with poor prognosis of systemic sclerosis (SSc). The aim of this study was to clarify the predictive factors of SSc-PH. [Methods] We retrospectively evaluated 25 consecutive SSc patients received right heart catheterization (RHC) in our hospital. We analyzed the results of RHC, spirometry, ultrasonic cardiogram and cardiac magnetic resonance imaging (CMRI). [Results] The mean age at RHC was 56 ± 12 years. Mean pulmonary arterial pressure (mPAP) was 28 ± 11 mmHg. Fifteen patients were diagnosed as having PH (13 classified as pulmonary arterial hypertension). In PH group, estimated pulmonary arterial systolic pressure was significantly high and $DLco/V_A$ was significantly low compared with non-PH group ($p = 0.003$, $p = 0.004$, respectively). Multiple logistic regression analysis revealed $DLco/V_A$ was an independent predictive factor of PH ($p = 0.014$). Among 14 patients who received CMRI, PH group had significantly lower right ventricular ejection fraction (RVEF) compared with non-PH group ($p = 0.006$). RVEF showed a clear inverse correlation with PVR ($R^2 = 0.433$, $p = 0.008$). [Conclusion] $DLco/V_A$ and RVEF on CMRI are useful for diagnosis of SSc-PH. Decrease of RVEF is also helpful for the assessment of severity.

W39-6

Can we predict the exist of pulmonary artery hypertension associated with connective tissue diseases (APAH) using Nailfold capillaroscopy (NFC) ?

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Conflict of interest: None

[Objectives] NFC is useful tool in patients with systemic sclerosis (SSc) and the reduced nailfold capillary density was reported to be associated with APAH. We aimed to examine whether 'capillary loss' (CL) or 'ramified capillary' (RC) at NFC is predictive factor for APAH in connective tissue disease (CTD) patients. **[Methods]** 19 patients (6 of diffuse, 11 of limited SSc, one of mixed CTD and one of dermatomyositis), performed NFC from May to October 2013, were included. We analyzed the relation between NFC findings and APAH, diagnosed with echocardiogram or/and right heart catheterization, retrospectively. We performed NFC with digital microscope (Dino-Lite Pro®), and we evaluated the findings with the standard proposed by M. Cutolo (Ann Rheum Dis 2012.71). **[Results]** In 4 APAH patients, more CL and/or RC findings were found than in other 15 non-APAH patients (CL; 2.8 fingers: 1.8 fingers, RC; 2.5 fingers: 1.8fingers). We could not demonstrate that the more extent of CL associated with a significantly increase risk of APAH, contrary to the past reports. Neither their length of disease history nor disease name have relations with NFC findings. **[Conclusion]** Our data did not show that NFC was an important predictor of APAH. We need to evaluate more cases and longer follow-up.

W40-1

Clinical features of dermatomyositis complicated by skin ulcers

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Conflict of interest: None

[Objectives] To investigate clinical features of dermatomyositis (DM) complicated by skin ulcers. [Methods] DM patients who admitted to our hospital from January 2001 to August 2013 were reviewed retrospectively from the clinical records. [Results] Among 86 DM patients, 21 (24%) had skin ulcers. Men: Women, 1:2; age, 50 ± 14 y.o. (mean ± SD). The number of patients with each symptoms and laboratory findings were as follows: fever (≧38°C), 10 (48%); weakness, 17 (81%); Raynaud's phenomenon, 4 (19%); arthralgia/arthritis, 15 (71%); Gottron's signs, 21 (100%); Heliotrope rash, 12 (57%); mechanic's hands, 6 (29%), palmar erythema/papule/rash, 16 (76%); periungual erythema, 15 (71%), facial erythema, 11 (52%); alopecia, 8 (38%); hoarseness, 6 (29%); and oral/tongue/pharyngeal pain, 8 (38%). Normal CK levels, 10 (48%); CK levels < 300 IU/l, 16 (76%); abnormal AST/ALT levels (≧60 IU/l), 13/8 (62%/38%); positive ANA (≧80×), 5 (24%); positive anti-Jo-1 antibody, 0 (0%); interstitial pneumonia (IP), 20 (95%); death due to acute or subacute IP, 3 (14%); and concomitant malignant tumors, 0 (0%). [Conclusion] High frequency of IP, arthralgia/arthritis, liver function abnormalities, and normal or mild elevation of CK levels were drawn as features of DM with skin ulcers.

W40-2

Connective tissue disease flavored interstitial pneumonia in idiopathic interstitial pneumonia; prevalence and clinical features

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Conflict of interest: None

[Objectives] The concept of "connective tissue flavored interstitial pneumonia" (CTD-flavored ILD) has been proposed recently. However, prevalence of this condition in idiopathic interstitial pneumonia (IIP) remains unknown and clinical features of these patients are to be elucidated. [Methods] ANA and myositis specific/ related antibodies including anti-aminoacyl-tRNA synthetases (ARS) Abs, anti-Mi2 Ab, ant-iSRP Ab, anti-Ro52 Ab, anti-PN/Scl Ab and anti-Ku Ab were measured in serum from 43 IIP patients without skin manifestations, muscle/joint symptoms or CK elevation. CTD-flavored ILD was diagnosed by positivity for myositis specific/related antibodies, ANA (>320), or ANA with cytoplasmic or nucleolar pattern (>80). [Results] CTD-flavored ILD was found in 44% of IIP; 21% of IIP were positive for myositis specific antibodies (anti-ARS Ab; 12%, anti-SRP Ab; 2%, and anti-M2 Ab; 7%). Anti-ARS Ab in IIP were non-Jo1 Ab (EJ, PL-7 and PL-12). Ro 52 was detected in 16% of ILD. In IIP patients with anti-ARS, MRI abnormal findings was detected in 4 out of 4 cases and some of who revealed myositis in muscle biopsy. [Conclusion] Patients of IIP with anti-ARS Ab have subclinical myositis, suggesting that IIP with ARS Ab belongs to the same disease of myositis with anti-ARS Ab.

W40-3

Clinical findings related to myositis-specific antibodies in patients with dermatomyositis complicated by interstitial pneumonia

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Conflict of interest: None

[Objects] We investigated clinical characteristics related to myositis-specific antibodies in patients with DM-IP. [Methods] This study was participated in by 31 patients with DM-IP admitted to Our Hospital from October 2011 to April 2013. This study excluded 11 patients of recurrence, and 2 with other connective tissue diseases. Anti-MDA5 antibody and anti-ARS antibodies (anti-OJ, EJ, PL-7, PL-12 and Jo-1 antibodies) were detected by ELISA. We divided the patients to two groups: positive for anti-MDA5 antibody (MDA5+) and anti-ARS antibodies (ARS+), and compared clinical characteristics between the two groups. [Results] Of the 18 patients, 6 were MDA5+, 7 were ARS+, 1 was positive for both, and 4were negative for both. Six of MDA5+ and 4 of ARS+ had acute or subacute IP (P=0.192). Six of MDA5+ and 3 of ARS+ were clinical amyopathic DM (P=0.069). The incidence of heliotrope eyelids (MDA5+ 6 and ARS+ 1) and $AaDO_2$ (MDA5+ 77.4±33.5 mmHg and ARS+ 33.7±23.2 mmHg) were higher in MDA5+ than those in ARS+ (P=0.047 and P=0.025, respectively). Three of MDA5+ and 1 of ARS+ were dead 24 weeks after the beginning of therapy, but not significant (P=0.266). [Conclusions] Heliotrope eyelids ware more frequent and lung involvement was severer in DM-IP with MDA5+ than ARS+.

W40-4

Clinical features in interstitial pneumonia with dermatomyositis

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Conflict of interest: None

[Objectives] We evaluated the clinical features in interstitial pneumonia (IP) with dermatomyositis (DM). [Methods] 23 patients with DM-IP were enrolled into this study. The patients were divided into 2 groups: actute/subacute progressive interstitial pneumonia with DM (DM-A/SIP) and chronic interstitial pneumonia (DM-CIP). We assessed clinical features and prognosis. Anti-MDA5 antibody was measured by using enzyme-linked immunosorbent assay. [Results] Mean age was 55.3±11.6 yo (9 male, 14 female). Of 23 patients, 14 patients were DM-A/SIP and 9 patients DM-CIP. The number of patients with anti-MDA5 antibody in DM-A/SIP and DM-CIP were 8 and 2, respectively. 18 patients were treated with cyclosporin, 7 patients tacrolimus, 2 patients MMF. IVCY was used in 18 patients. 24 week after the therapy, 6 patients died. 4 patients in DM-A/SIP with anti-MDA5 antibody died of aggravation of IP and the others died of infection. The serum level of ferritin and $AaDO_2$ were significantly higher in DM-A/SIP compared with DM-CIP, and the serum level of albumin (Alb) was significantly lower and inversely correlated with $AaDO_2$. [Conclusion] There is serological difference between A/SIP and CIP, and Alb may reflect respiratory condition. Patients with anti-MDA5 antibody in DM-A/SIP have a poor outcome.

W40-5

The maintenance therapy and recurrence of dermatomyositis and polymyositis

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Conflict of interest: None

【objective】To investigate the maintenance therapy and recurrence in patients with polymyositis (PM) and dermatomyositis (DM)【method】The medical records of 84 patients with PM and DM after more than one year from the disease onset were retrospectively reviewed.【result】51 patients of dermatomyositis and 33 patients of polymyositis were identified. 49 patients relapsed into active myositis. Glucocorticoid therapy initiated with prednisolone at a dose of 54.0mg/day in recurrence group and 51.9mg/day in non-recurrence group. 25 patients were treated with additional therapy. Tacrolimus (TAC) and Methotrexate were used most frequently in 9 patients each. 71 ptaitents were received maintenance treatment. The average dosage of PSL was 6.9mg/day. 34 patients were treated with corticosteroid alone, 32 patients with corticosteroid and immunosuppressant, and 6 patients remained in remission and were off corticosteroid. TAC was most commonly used in 23 patients. In Recurrence group, the dosage of PSL was7.0mg/day at the time of recurrence. The time to recurrence from the disease onset was 3.9years.【conclusion】TAC was most frequently used in both induction and maintenance therapy. The corticosteroid dose of the recurrence group did not differ from that of non-recurrence group

W40-6

Influence of Anticancer Therapy on Dermatomyositis with Malignancy Comparison of Surgical Intervention and Chemotherapy/radiation

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Conflict of interest: None

[Objectives] Malignant tumor is known as a complication of dermatomyositis (DM). We investigated whether only anticancer therapy can improve DM with malignancy or not. [Methods] We retrospectively reviewed 16 patients diagnosed as DM with malignancy, and divided them into 2 groups (8 patients of surgical intervention group and 8 patients of chemotherapy or radiation group) and picked up 8 patients except those who received prednisolone (over 0.5mg/kg/day). We measured serum creatine kinase (CK) after 2 and 4 weeks from the beginning of anticancer therapy. The primary objectives were the decreasing proportion of serum CK from the beginning of anticancer therapy. [Results] The decreasing proportion of serum CK were 75%/76% (2 weeks/4 weeks) in surgical intervention group (5 patients), and 54%/54% in chemotherapy/radiation group (3 patients). Anticancer therapy in both groups improved serum CK, but surgical intervention seemed to have improved faster than chemotherapy/radiation. [Conclusion] Only Anticancer therapy (both surgical intervention and chemotherapy/radiation) can clinically improve the DM with malignancy. Surgical intervention may improve faster than chemoradiation. Therefore it is important to diagnose malignant tumor in

patients with DM as soon as possible to treat by surgical intervention.

W41-1

Efficacy of adalimumab plus high dose Methotrexate combination therapy on RA patients in FRAB registry

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Conflict of interest: Yes

[Objectives] Since MTX dose limit has been elevated to 16 mg in Japan, efficacy of combination therapy of biologics with higher dose MTX is possibly improved. In this study, efficacy of adalimumab (ADA) plus high dose MTX (≥ 10 mg/week) combination therapy was investigated. This report is the interim analysis of efficacy during 24 weeks of therapy for first 45 out of 100 patients. [Methods] RRA patients who showed SDAI > 11 and initiated ADA after Oct 2012 were enrolled. Patients were divided into two groups based on MTX dosage with 10 mg/week and up (Group A) or less (Group B). SDAI remission rate at 24 weeks was set as a primary endpoint. [Results] A mean disease duration was 6.3 years and 6.4 years, a mean SDAI score was 25.3 and 22.1, a mean MTX dose was 12.7 mg/week and 7.1 mg/week in the group A and the group B, respectively. The group A showed higher clinical responses, such as remission rate of (SDAI, CDAI, DAS-CRP and Boolean), EULAR response and HAQ-DI. SDAI score was decreased at 24 weeks from 25.3 to 2.7 in the group A and from 22.1 to 10.1 in the group B. SDAI remission rate was 66.7% and 25.0% at 24 weeks in the group A and the group B, respectively. [Conclusion] Our results suggested that efficacy of ADA might be enhanced with increased dose of MTX.

W41-2

Study on risk factor of serious infection in RA patients treated with Biologics

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Conflict of interest: None

[Objectives] To clarify risk factor of serious infection (SI) in RA patients treated with biologics (Bio). [Methods] All of RA patients treated with Bio at our department (A·RA) and those suffered from SI while Bio therapy (I·RA) were investigated. [Results] Incidence of SI; 9.3% (A·RA 279: I·RA 26). 2) Proportion of stage III+IV; A·RA 74.6%: I·RA 88.5%. 3) Age at start of Bio; A·RA 58.8±9.7y: I·RA 64.7±8.1y (p=0.023). 4) Disease duration at start of Bio; A·RA 9.7±9.6 y: I·RA 16.0±11.7y (p=0.0016). 5) Average of period between start of Bio and occurrence of infection was 11.3 mo., 11 cases (47.4%) occurred within 6 mo. and 24 (92.6%) within 2 y. 6) Incidence of SI in patients treated with TNF blockers was 8.4% (25 out of 296) and that with nonTNF blockers was 3.1% (2 out of 65). 7) Bio switching was performed in 26.2% of A·RA and 22.7% of I·RA. 8) Twenty out of 166 patients (12.0%) who Bio was administrated earlier than Oct 2009 suffered from SI and 6 out of 116 patients (5.2%) later than Oct 2009. [Conclusion] [Advanced stage, elder, longer disease duration and TNF blockers among Bio were risk factor of SI in Bio therapy. Most of SI occurred within 2 yrs of Bio therapy. It was suggested selectivity of Bio and switching of Bio diminish SI risk.

W41-3

Childbirth and pregnancy in rheumatoid arthritis

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Conflict of interest: None

Objectives: Pregnancy is one of a big problem in young female patients with rheumatoid arthritis (RA). The clinical course pregnancy were studied by my private clinic. **Methods:** 27 cases were enrolled whose average age was 34 years and duration was 6.3 years. First childbirth were 13 cases, second 11cases and third or over 3 cases. The medication dugs were studied about prepregnancy, middle pregnancy and after pregnancy period. **Results:** Three cases were during pregnancy, one case was abortion at seven months, 1 case was spontaneous abortion at 5 months. The drugs in prepregnancy period were 12 cases, prednisolone, 8 cases, Salazosulfapiridine, 5 cases, gold sodium thiomalate, 2 cases, Bucillamine and 8 cases, Biologics (7 Etarnercept and 1 Tocilizumab). Just breast-feeding were 3 cases and breast-feeding end were 16 cases. Average interval of Breast-feeding were 13 months. In pregnancy period, low volume of steroid or Eetarnersept (Biologics) (7 cases) were used. **Conclusion:** In most of pregnancy cases, the rheumatoid activity was controlled relatively a good level by use of steroid or biologics. After child-birth period, even if the activity aggravated, re-control was possible in almost of cases.

W41-4

Examination of the result of a multicenter study of golimumab 100 mg by The Fukuoka RA Biologics Registry

Eisuke Shono
The Fukuoka RA Biologics Registry

Conflict of interest: Yes

[Objective] The result of a multicenter study of GLM 100 mg in RA patients was examined. [Methods] Of the RA patients in whom GLM 100mg was introduced during the period from Sep. There were 36 patients in the GLM-alone group and 19 in the GLM + MTX group, and the mean dose of MTX was 9.5 mg/week. As for the past treatment, there were 15 naïve patients and 40 switched patients (as a 2nd, 24 patients; 3rd, 10; 4th, 3; and 5th; 3). Regarding the prior bio usage, there were 23 anti-TNF-treated patients and 17 non-anti-TNF -treated patients. [Results] DAS-CPR after 24 weeks were improved from 3.81 to 2.61, and 28 of the 55 patients (50.9%) achieved clinical remission. Comparison of the naïve and the switch groups revealed that a significant clinical improvement was obtained at week 4 in the naïve. Regarding with use of MTX, after 24 weeks, the DAS28-CRP were improved from 3.71 to 2.37 and from 3.87 to 2.73 with MTX group and the group without use of MTX, respectively, indicating that there was no much difference between the 2 groups. The retention over 24 weeks was 80%. The reasons for discontinuation were insufficient efficacy (2 patients), adverse reactions (6), and the will of the patients (3). [Discussion] GLM 100mg may be effective not only in bio-naïve but also switching.

W41-5

Study of the cost-benefit balance of golimumab in 100mg dose: Results from the Japanese multicenter registry system (TBCR)

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Conflict of interest: None

[Objectives] Golimumab (GLM) has been available for rheumatoid arthritis (RA) patients since 2011. Increased dose option is available only in Japan; 100mg every four weeks, addition to the standard dose of 50mg. Some physicians believe that we should use 100mg dose from the initiation for the high disease activity (HDA) or bio-switch patients. We studied the clinical efficacy of 100mg GLM using the 'real world' data. [Methods] Included RA patients were treated with GLM and observed for at least 24 weeks (n=87), from the Japanese multicenter registry (TBCR).

We compared DAS28-ESR score between HDA RA patients using 50mg and 100mg, separately within bio-naïve and switch group. [Results] DAS28 changes from 0 to 24 weeks (50mg/100mg) were (5.89 to 4.11/ 6.22 to 3.60) in the naïve group and (5.72 to 4.32/ 6.37 to 4.85) in the switch group. There was no significant difference between the groups. Eleven patients took dose increasing. Increased GLM demonstrated better effectiveness only in the patients with apparent response to the standard dose. [Conclusion] We can use 100mg dose especially for the patients with clinical response to 50mg GLM and still insufficient efficacy. It is necessary to consider whether to use very expensive treatment option based on the cost-benefit balance.

W41-6

Long-term prognosis after discontinuation of infliximab (IFX) in RA patients with low disease activity

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Conflict of interest: None

[Objectives] We performed a retrospective analysis to evaluate long-term prognosis after cessation of IFX and to investigate background factors which would predict the possibility of the discontinuation of IFX. [Methods] 53 RA patients who had been treated with IFX and discontinued IFX after maintenance of low disease activity (LDA; DAS28-CRP < 2.6 or DAS28-ESR < 3.2) from Sep, 2003 to Jun 2010 were evaluated. We compared the background features of 20 patients who had been in LDA for 3 years even after cessation of IFX (LDA group) and the other 33 patients who could not maintain LDA for 3 years (Relapse group) [Results] Patients background data in each group (LDA / Relapse) at the cessation of IFX were as follows; mean age: 52.8/51.2 years old, female rate: 60/85 (%), mean duration of RA: 68.6/51.2 months, mean tender joint count: 0/0.2, maen swollen joint count: 0.2/0.6, mean doctor's VAS: 1.9/3.3, mean patient's VAS: 6.0/8.7, mean DAS28-CRP: 1.33/1.55, mean MTX dose: 7.9/8.3 mg/w, %PSL use: 20/21.2 (%), all were not statistically significant. [Conclusion] Long –term LDA can be maintained even after discontinuation of IFX in some patients. Although not significant, male sex and low doctor's VAS score at IFX cessation might be predictive factors for successful long-term LDA maintenance.

W42-1

Evaluation of the serum levels of Anti-Mullerian Hormone (AMH) in patients with RA after the TNF inhibitor administration

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Conflict of interest: None

[Background] Fertility is reduced in uncontrolled RA patients, and the reason is not well known. Although serum levels of AMH have been recently used for the ovarian reserve function, there are few reports in RA. [Subjects and Method] Ten RA female patients newly treated with the TNF inhibitor (IFX: 8, ETN: 2) were enrolled. Serum AMH levels (measured by ELISA assay) and DAS28 were examined before and after 14, 30 and 54 weeks of the treatment. As AMH is reported to be age-dependent, AMH Z scores for age were calculated by the recently report. [Result] 1) At 54 weeks, DAS28 were significantly decreased (p=0.002). Meanwhile, AMH levels were not signnificant difference in both actual values and Z scores (p=0.66, 0.94). 2) Before the treatment, there was no correlations between AMH levels and DAS28. That correlations had become apparent with the course of the treatment (in 54 wks, actual values; p=0.23, Z scores; p=0.08). 3) To clarify the relationship between all the component of DAS28 and AMH, negative correlation was showed between AMH Z scores and patient VAS in 54 wks (r=-0.64, p=0.047). [Conclusion] Our study suggested that the TNF inhibitor had no influence on the ovarian reserve function and that decreased AMH levels may be related to the cause of reduced fertility of RA patients.

W42-2

Examination of the successful cases of stopping administration of infliximab (IFX) because of good response with rheumatoid arthritis in daily clinical practice

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Conflict of interest: None

[Objectives] Examination of the successful cases of stopping administration of infliximab (IFX) because of the good response. [Methods] Targets were the 418 patients with RA starting administration of IFX in our hospital. We defined that the patients judged as good response by the physycian and stopped IFX and then DAS28<3.2 are the cases of stopping at the time, and the patients of them keeping DAS28<3.2 in a year after stopping are the group of successful cases, and those who of them resume biological agent in one year or their DAS28≧3.2 in one year after stopping were the group of failure groups. We examined the background factor between these groups. [Results] The cases of stopping because of good response were 26 patients and they were 6.2% of all. Successful group included 13 cases, failure group included 13 cases. As the group of successful cases vs the other group (n=405), the background factors didn't show significant differences except J-HAQ (0.7 vs 1.3). As the group of successful vs failure, there was significant differenses about IFX full bottle increase rate (61.5 vs 7.7%) and IFX dose (3.6±0.6 vs 3.1±0.4 mg/kg). [Conclusion] Full bottle increase rates and IFX doses were significantly higher in the group of successful cases of stopping administration of IFX.

W42-3

Clinical efficacy of golimumab by doses of concomitant methotrexate for patients with rheumatoid arthritis-multicenter analysis of FIT-RA registry-

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Conflict of interest: None

[Objectives] To assess the clinical efficacy of golimumab by doses of concomitant methotrexate (MTX) for patients with rheumatoid arthritis (RA). [Methods] We enrolled 48 patients with RA who were administered golimumab (50mg every 4 weeks) and observed for 1 year in FIT-RA (Fukui, Ishikawa, Toyama-rheumatoid arthritis) registry. Forty patients (83.8%) received concomitant MTX (mean dosage, 8.0 mg/week). We compared differences of clinical results with the doses of concomitant MTX. [Results] The retention rates at 1 year of patients with 0-4mg, 6-8mg and 10-16mg weekly doses of concomitant MTX were 66.7%, 77.3% and 71.4%, respectively. The mean DAS28-ESR scores at baseline for 0-4mg, 6-8mg and 10-16mg groups of concomitant MTX were 4.70, 4.66 and 4.58, respectively. These scores were significantly improved to 3.85, 3.23 and 3.37 at 12 months. [Conclusion] Our results showed that clinical efficacy of golimumab for patients with RA tended to be less in low dose MTX group, but was almost equal in the moderate and high dose MTX group.

W42-4

Discontinuation of biologics in patients with rheumatoid arthritis after achieving low disease activity state in daily practice

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Conflict of interest: None

[Objectives] To investigate discontinuation of biologics after achieving low disease activity in patients with RA in daily practice. [Methods] Forty-three RA patients who had received biologics between 2003 and 2012 (IFX 26, ETN 9, ADA 4, TCZ 2, ABT 2), and whose DAS28 score

was under 3.2 at discontinuation of biologics were extracted. Those patients were divided into “Bio-free” or “Bio-reuse”, based on biologics use at one year after of discontinuation. Those patients were also divided into “Bio-free success” or “Bio-free failure”, based on disease activity at one year after of discontinuation. Baseline features were compared in each two groups. [Results] The numbers of patients in the “Bio-free” and “Bio-reuse” groups were 34 (79.1%, IFX 20, ETN 8, ADA 3, ABT 2, TCZ 1) and 9 (20.9%), respectively. There were no significant differences in mean age, disease duration, DAS28, J-HAQ, MTX or steroid doses at initiation and discontinuation of biologics between those two groups. There were also no significant differences in these clinical features between the “Bio-free success” and “Bio-free failure” groups. [Conclusion] This study demonstrated that the rate of discontinuation of biologics after achieving low disease activity in patients with RA was relatively high in daily practice.

W42-5

Improvements in patient reported outcomes in Japanese RA patients were sustained with long-term treatment with Certolizumab pegol regardless of concomitant methotrexate

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Conflict of interest: None

Objectives To assess whether continued treatment with certolizumab pegol (CZP) maintains improvement of patient reported outcomes (PROs) in Japanese RA patients with and without concomitant methotrexate. Methods Patients were treated with CZP in double-blind trials with and without MTX, and open label extensions were conducted on both. In this analysis, PROs at weeks 28 and 80 were compared in DB completers who entered the OLE (63 with MTX, 81 without MTX). The dosing regimens during the 80 week period were: 400mg at week 0, 2, 4 followed by 200mg/2wk and subsequently 200mg/2wk or 400mg/4wks after week 28. Results With concomitant MTX, PROs at weeks 28 and 80 were pain VAS: 20.8vs18.9; Pt Global VAS: 21.5vs18.2; HAQ-DI: 0.46vs0.40; SF36-physical: 39.8vs41.3; and SF36-mental: 51.9vs52.2. Similarly, PROs at weeks 28 and 80 without MTX were pain VAS: 22.5vs21.2; Pt Global VAS: 22.7vs22.3; HAQ-DI: 0.50vs0.46; SF36-physical: 38.5vs39.8; and SF36-mental: 52.3vs50.1. The values at weeks 28 and 80 were similar in the each study. Conclusion The long-term CZP treatment sustained improvements in health-related QOL irrespective of concomitant MTX.

W42-6

Efficacy of golimumab (GLM) in rheumatoid arthritis – including evaluation of remission rate at 2 weeks after GLM introduction

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Conflict of interest: None

The clinical efficacy, including early efficacy at 2 weeks, sustain rate and change of CRP, DAS28-CRP of 28 cases which were introduced GLM during January 2012 to March 2013 at our hospital was evaluated. Twenty four of 28 were biologics naïve, and 4 cases were switched from other biologics. Sustain rate: Sustain rete at 24 weeks was 82.1% (23/28), 5 cases was discontinued due to changed hospital (2), adverse effect (2), patient request (1), and no discontinue case by lacked efficacy. Efficacy: CPR was decreased rapidly from 1.79mg/dl at baseline to 0.38mg/dl at 2 weeks. DAS28-CRP was also decreased rapidly, the remission (<2.3) rate at 2 weeks was 33.3%. And this rate was increased gradually, 63.6% at 24 weeks. The reason of high remission rate was guessed many biologics naïve in this evaluation. Comparing patients’ background between remission and non-remission at 24 weeks, CRP, DAS28-CRP and MMP-3 in remission cases were lower than non-remission, dose of MTX and concomitant rate of PSL were high. Summary: Regardless disease history, pre-medication, laboratory test and so on, GLM can appear effect immediate after administration, few discontinue therapy and sustain LDA or remission. Using enough amount of DMARDs combination may bring out the maximum effect of GLM.

W43-1

The change of serum cytokine levels in case of primary failure, secondary failure and recurrence among patients with RA treated with Adalimumab

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Conflict of interest: None

[Objectives] To explore the predisposing factor of the failure to biologics and pathogenesis of primary failure (PF) or secondary failure (SF). [Methods] 11 RA patients were studied. Good response (GR) to Adalimumab (ADA) was obtained in 5 patients. PF and SF was observed in 3 patients. Decrease more than 1.0 of DAS28 (CRP) and under 2.8 of absolute DAS28 (CRP) within 56 days after ADA treatment was defined as GR. Patients who did not meet this criterion were considered to be PF. Patients who experienced more than 1.0 increase of DAS (CRP) or over 3.2 of absolute DAS (CRP) was defined as SF. Serum cytokines were determined before and 14, 28, 56, and/or 84 days after administration of ADA. [Results] No difference was observed in cytokine profiles between GR and PF. However, more than 28 days after ADA administration, significant expansion of IFN-γ, IL-17A, IL-2, IL-5 and TNF-α was observed in PF. In PF, significant increase of IL-5, IL-1β, and TNF-α was observed compared with their baseline. In case of recurrences, increase of IFN-γ, IL-17A, IL-1β, IL-2, IL-4, IL-13 and TNF-α was noted. [Conclusion] Cytokine profiles at 28 days after administration of ADA may predict PF. Expansion of TNF-α, IL-1β, IL-17A, and some Th2 cytokines may explain the pathogenesis of PF or recurrences.

W43-2

The drug survival rate of adalimumab (ADA) in 469 patients with rheumatoid arthritis (RA) registrated in Tsurumai Biologics Communication (TBC) 2008-2013

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Conflict of interest: None

[Objectives] This study is to analyze the drug survival rate of adalimumab (ADA) in 469 patients with rheumatoid arthritis (RA) for 4 years. [Methods] In May 2013, 469 RA patients treated with adalimumab registrated in Tsurumai Biologics Communication (TBC). We investigated the drug survival rate by Kaplan-Meier method, and the reasons for discontinuation, such as inefficacy, safety reasons, and other factors. [Results] The drug survival rate of all patients was 66.4% at 1year, 60.0% at 2year, 57.4% at 3year, 55.8%. The rate of discontinuation for inefficacy at 4 years was 23.3%, for safety (adverse event) was 14.7%, for any other reasons was 5.5%. The drug survival rate of biological agent naïve patients in combination with MTX was 61.5% at 4year, biological agent switched patients in combination with MTX was 49.9%, biological agent naïve patients without MTX was 48.1%, biological agent switched patients without MTX was 45.1%. [Conclusion] Overall survival and efficacy will increase if a sufficient amount of MTX is combined with ADA.

W43-3

Predicting future response to golimumab in rheumatoid arthritis patients

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Conflict of interest: None

[Objectives] To analyze the prognostic significance of data collected at starting golimumab (GLM) to predict remission in rheumatoid arthritis (RA) patients at week 16. [Methods] Data from 32 GLM-treated patients at baseline were used as variables to predict clinical remission (DAS28-ESR <2.6) at week 16. Mean disease activity at baseline was 4.77 and 20.8 for DAS28-ESR and SDAI, respectively. Fourteen patients (43.8%) were naïve to biologic agents. Twenty-one patients (65.6%) were treated with 100mg of GLM. [Results] At 16 weeks, patients were categorized into 2 groups (Group 1: Nine (28.1%) patients achieved clinical remission, Group 2: 23 patients without remission). GLM-treated patients with naïve to biologics agents indicated significantly greater proportion in Group 1 (77.8%, p=0.0240) compared with Group 2 (30.4%). The proportion of those with large joints (shoulders, elbows, hips, knees and ankles) involvement was significantly lower in Group 1 (22.2%, p=0.0240) than in Group 2 (69.6%). There were, however, no differences between two Groups in the proportion of GLM-treated patients with 100mg and concomitant administration of MTX. [Conclusion] Naïve to biologics agents and large joints involvement have been associated with response at week 16 to GLM therapy in RA patients.

W43-4

The effect of biologics on innate immune system in synovial tissues in rheumatoid arthritis patients

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Conflict of interest: None

[Objectives] Rheumatoid arthritis (RA)'s onset and progression depend on many different factors, not only adaptive immunity but also innate immunity. The aim of this study was to investigate the immuneinflammatory cells, including Toll-like receptor (TLR)- equipped cells, in synovial tissue samples from RA patients on biologics (BIO) compared to patients, who are only on conventional disease-modifying antirheumatic drug (DMARD). [Methods] We analyzed immune-inflammatory cells in RA synovitis in patients of BIO group {n=20 (etanercept 14, infliximab 6)} or DMARD group (n=20). [Results] The grading scores of synovitis was both 1.7 in each group and correlated best with the T and B cells in the both groups (p<0.05). Interestingly, both T and B cell counts were lower in the BIO than in the DMARD group (p<0.05). In contrast, the C-reactive protein (CRP) and disease activity score DAS28-CRP did not show clear-cut correlations with the inflammatory grade of the synovitis. Similar numbers of cells immunoreactive for TLR-1 to TLR-9 were found in synovitis in both groups. [Conclusion] Patients clinically responding to biologics might still have the potential of moderate/severe local joint inflammation, composed in particular of and possibly driven by the autoinflammatory TLR+ cells.

W43-5

Efficacy and safety of infliximab therapy in rheumatoid arthritis patients from our analysis at 10 years

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Conflict of interest: None

BACKGROUND: Clinical, structural and functional remission become targets for infliximab (IFX) therapy from Japanese study such as RECONFIRM and RISING in patients with established rheumatoid arthritis (RA). After achieving remission, discontinuation of IFX may become an important issue from Japanese study such as RRR in patients with established RA. OBJECTIVE: To aim of this study is to analysis patients' background and disease activity of IFX therapy regarding efficacy and safety and to determine the most suitable management of that. METHOD: 619 patients with RA who had received infliximab treatment enrolled this study, and divided into 3 groups by events with the impacts. RESULTS: There were significant difference between BL-disease duration, BL-MTX dose and disease activity (The BL-disease duration was the earliest in the 3rd group. BL-MTX dose was the rate of remission rate of year 1 was highest in that group). There was no difference at adverse reaction at the survival rates. Remission rates (about 30%) were high in the 3rd group. CONCLUSION: The best use of infliximab therapy is less than 2 years of disease duration and more than 12mg/week of MTX before the therapy from this analysis.

W43-6

Multi-biomarker disease activity score for assessing disease activity in rheumatoid arthritis patients treated with TNF inhibitors

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Conflict of interest: None

【Objective】To evaluate multi-biomarker disease activity (MBDA) score as a tool for assessing disease activity in rheumatoid arthritis (RA) patients treated with TNF inhibitors.【Methods】We recruited 12 RA patients treated with infliximab (IFX), and 18 patients treated with etanercept (ETN). Blood was collected at baseline and after 2, 6, 14 and 22 weeks of IFX treatment; and also collected at baseline and after 1, 3 and 6 months of ETN treatment. We assessed clinical results and calculated DAS-28CRP. Serum 12 protein biomarkers (MMP-1, MMP-3, IL-6, TNFR-I, VCAM-I, EGF, VEGF-I, YKL-40, leptin, resistin, CRP, and SAA) were measured using ELISA and the concentrations were used to a prespecified algorithm to calculate MBDA scores.【Results】In IFX-treated patients group, the MBDA score highly correlated with DAS28-CRP at baseline and throughout the treatment course. On the other hand, in ETN-treated patients group, the MBDA score did not correlate with DAS28-CRP at baseline; however, throughout the treatment course, the MBDA score highly correlated with DAS28-CRP.【Conclusion】The MBDA score may be an objective index of RA disease activity treated with TNF inhibitors.

W44-1

The predictive factors of clinical and functional remission in rheumatoid arthritis (RA) patients treated with abatacept for 52 weeks

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Conflict of interest: None

Objective: To examine the predictive factors of beneficial effects of abatacept at 52 weeks in daily practice. Methods: Clinical findings and laboratory data of 48 RA patients with abatacept were collected in each 4 weeks. ITT analysis was performed. Missing data were imputed using the LOCF or interpolation according to neighboring values. DAS28 (ESR), DAS28 (CRP), SDAI and CDAI at 52weeks were evaluated using their remission criteria. Boolean remission was also evaluated. mHAQ was assessed as a functional remission. Results: Median age was 63.5 (34-76) and sex ratio was 1:11. The usage rate of corticosteroid was 18.8% and of MTX was 83.3%. Median disease duration was 4.3 years and 31.3% were within 2 years. Biologics naïve cases were 79.2%. Remission rates of DAS28 (ESR), DAS28 (CRP), SDAI, CDAI, Boolean were 91.7, 64.6,

89.6, 87.5, 81.3% respectively. The remission rate of mHAQ was 87.5%. According to Fisher's exact test, DAS28 (ESR) remission was related to MMP-3 and mHAQ, DAS28 (CRP) to RF and mHAQ, SDAI to RF and mHAQ, CDAI to mHAQ respectively. Boolean was related to RF. mHAQ remission was relevant to disease duration, the number of used biologics. Conclusion: Clinical remission including CRP might be related to the changes in RF in our study. Functional remission reflects other factors.

W44-2

Efficacy and safety of subcutaneous administration of tabalumab, an anti-B cell activating factor monoclonal antibody, in Japanese and non-Japanese patients with rheumatoid arthritis: Results from a phase 3 multicenter, randomized, double-blind study

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Conflict of interest: Yes

[Objectives] Evaluate the efficacy and safety of tabalumab (TAB) in RA patients (pts). [Methods] 1004 pts (114 Japanese) were enrolled and randomized to TAB 120 mg every 4 wks [120/Q4W], 90 mg every 2 wks [90/Q2W]) or placebo (PL). [Results] For overall efficacy population (N=849) at wk 24, no significant differences were observed for ACR20 (range: 32%-34%), DAS28-CRP, and HAQ-DI. For Japanese efficacy population (N=83) at wk 24, in the PL, 120/Q4W and 90/Q2W groups, ACR20 response rates were 19%, 55%, and 45%, changes in DAS28-CRP were 0.66, -0.05, and 0.08, and changes in HAQ-DI were 0.10, -0.11 and 0.08. For overall safety population (N=1000), incidences of TEAEs (range: 58%-64%) and SAEs (range: 2%-4%) were similar across groups. Incidences of infection were 22%, 23% and 26%, and incidences of serious infection were 0.4%, 1.1%, and 0.3% for each group. 3 deaths were reported in TAB groups. For Japanese safety population (N=114), incidences of TEAEs (range: 67%-80%) were similar across all groups. No death, SAE, or serious infection was reported. [Conclusion] In the overall population, TAB did not show significant efficacy. For the Japanese population, a numerically higher number of responders achieved ACR20 in the TAB groups. No new, unexpected safety findings were observed.

W44-3

Effects of biologic agents on inhibition of large joint-destruction in patients with rheumatoid arthritis and the risk factors of progress in joint-destruction

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Conflict of interest: None

[Objectives] The goal for treatment of rheumatoid arthritis is to inhibit and arrest joint-destruction. Many clinical trials tell us that biologic agents inhibit small joint-destruction, however, there have been a few reports demonstrating inhibitory effects on large joint-destruction. [Methods] Sixty-three patients receiving the latest biologic agent for a year or more are included in this study. The mean age at initiating the latest biologic agent was 60.5 year-old, and a total of 222 joints including shoulder, elbow, hip, knee, and ankle joints were evaluated whether there was progress in joint-destruction comparing the radiographs before and after treatment. [Results] DAS28/ESR was significantly improved from 4.18 to 2.58 after treatment ($p<0.01$). Progress in joint-destruction was found in 14 patients (22%) and 18 joints (8.1%), and there was significantly higher rate of progress in joint-destruction in Larsen grade III/IV than I/II joints ($p<0.01$). Multiple regression analyses showed that age at initiating biologic agents was a risk factor for progress in joint-destruction (odds ratio = 1.137). [Conclusion] These results showed that progress in joint destruction occurs in approximately 10% of large joints even if disease activities are well controlled using biologic agents.

W44-4

Drug Retention Rates of Biologic Monotherapies For Patients With Rheumatoid Arthritis In Clinical Practice

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Conflict of interest: None

[Objectives] Drug retention rate reflects the effectiveness and tolerability of the drug. There is few data comparing the retention rates between biological monotherapies for RA patients in clinical practice. The purpose of this study is to compare the drug retention rates of 3 biological monotherapies with different target molecules. [Methods] We collected the data from the patients who started monotherapies with ETN, TCZ, ABT as first-biologics since 2008 and registered in multi-center registry, TBCR. Drug retention rates were calculated by the Kaplan-Meier analysis. We investigated drug retention rates for discontinuation due to insufficient effectiveness (IE) and adverse events (AE). [Results] We analyzed 279 patients (141 in ETN, 63 in TCZ, 75 in ABT). The mean follow up time was 25.7 months. The age was 58.2±15.0, 57.7±13.8, 68.7±11.2 years, respectively. The disease duration was 12.8±11.6, 10.6±10.5, 10.9±10.5 years, respectively. Cumulative incidence rate for discontinuation due to IE was lower in TCZ ($p=0.019$). Cumulative incidence rate for discontinuation due to AE was lower in ABT ($p=0.007$). [Conclusion] We demonstrated that TCZ monotherapy had a lower discontinuation rate due to IE and that ABT monotherapy had a lower discontinuation rate due to AE.

W44-5

Efficacy and safety of biologic agents in elderly-onset Rheumatoid arthritis

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Conflict of interest: None

Objectives: To compare the efficacy and safety of 1st biologic agents for MTX-resistant and -intolerant patients with elderly-onset rheumatoid arthritis (EORA: onset > 65 yo) with over 65-yo patients with younger-onset RA (YORA: < 65yo). **Methods:** 20 patients with EORA (16 women, average age 77.0 yo, RF/ACPA+ 65%/70%) and 7 patients with YORA (7 women, 72 yo, RF/ACPA+ 86%/86%) had received 1st biologic agents since April 2011, including IFX (1/0 for EORA/YORA), ETN (3/2), ADA (4/1), GLM (2/1), CZP (1/0), TCZ (3/1), and ABT (6/1), respectively. Pneumococcal vaccine had been given all, INH were receiving in 10 patients (8 EORA/2 YORA) and HBV-DNA were regularly monitored in 3 EORA patients. **Results:** 10 EORA and 4 YORA patients had reached remission and low-disease activity (IFX 1, ETN 1, ADA 1, GLM 2, CZP 0, TCZ 2, and ABT 3 for EORA; IFX 0, ETN 1, ADA 1, GLM 0, CZP 0, TCZ 1, ABT 1 for YORA). An EORA patient with IFX experienced bacterial arthritis. **Conclusion:** Biologic agents are similarly effective and safe in refractory patients with EORA and YORA.

W44-6

Efficacy and safety of tofacitinib in patients with rheumatoid arthritis at Sagamihara National Hospital

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Conflict of interest: None

[Objectives] To analyze the efficacy and safety of tofacitinib (TOF) in patients with rheumatoid arthritis (RA) at our hospital. [Patients] Study-1: Twenty patients who participated in the phase 3 clinical trial and were given 10mg/day of TOF. Study-2: Thirteen patients including 9 patients who were continuously given TOF during and after the trial; 4 patients who newly started TOF after marketing. [Results] Study-1: Fourteen patients (70%) used MTX combined with TOF. Mean CDAI significantly decreased from 25.1 (at baseline) to 7.2 (after 12 months). Herpes Zoster (HZ) was found 8 times in 7 patients (35%). Compared to HZ (-) patients, HZ (+) patients tended to show higher CD4/CD8 ratio. Continuation rate of TOF was 90% at 24 months. Seven patients (35%) could not continue TOF (mean 32 months) because of laboratory test abnormality (n=2), malignancy (n=2), HZ (n=2), and withdrawal by patient's desire (n=1). Study-2: Of 13 patients who completed the trial, 5 continued 10mg/day of TOF. Dose of 4 patients was reduced to 5mg/day but their disease activity was still low. Four patients who discontinued TOF after marketing were also stable. [Conclusion] Incidence of HZ was high in TOF user. Dose reduction or discontinuation of TOF after a certain period of time may be able in some patients.

W45-1

Evaluation of factors associated with relapse in patients with microscopic poly angiitis: 5-year experience at a single center

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Conflict of interest: None

[Objectives] Early identification and treatment of microscopic polyangiitis (MPA) is important to prevent mortality; even with treatment, MPA has a tendency to relapse. We retrospectively studied the risk factors associated with relapse during remission maintenance therapy for MPA. [Methods] Fifteen patients diagnosed with MPA according to the European Medicines Agency classification algorithm during 5 years from January 2009 to August 2013, and who achieved remission after the first remission-induction therapy, were examined. [Results] The patient group comprised 2 men and 13 women and the mean age was 75.5 years. The rate of relapse was 20 % (3/15), and the mean interval between remission and relapse was 16.3 months. During maintenance therapy after remission, the risk of relapse went up when the reduction rate of the prednisolone dose was above 0.6 mg/kg. Erythrocyte sedimentation rate (ESR) at the start of induction therapy (odds ratio 0.464, $p = 0.01$) was identified as a risk factor for MPA. The titers of myeloperoxidase-anti-neutrophil cytoplasmic autoantibody (MPO-ANCA) did not increase when the MPA relapsed. [Conclusion] On multivariate analysis, relapse of MPA may be associated with high ESR before induction therapy as well as reduction of prednisolone.

W45-2

Characteristics of Japanese ANCA-associated Vasculitis Patients Classified as Granulomatosis with Polyangiitis by the European Medicines Agency Algorithm

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Conflict of interest: None

[Objectives] ANCA-associated vasculitis (AAV) is a disease with significant differences among different ethnic groups. Reports on characteristics of Japanese GPA patients are limited, and this study was undertaken to determine characteristics of Japanese AAV patients classified as granulomatosis with polyangiitis (GPA) by the European Medicines Agency (EMA) algorithm. [Methods] This was a retrospective chart study of GPA patients who had attended our departments between 2007 and 2012. [Results] Twenty-four GPA patients had attended our departments during the study period. Fourteen (58.3%) were positive for C-ANCA, and eight (33.3%) were positive for P-ANCA. P-ANCA positive GPA patients and C-ANCA positive GPA patients differed in the organs involved at diagnosis with P-ANCA positive patients having nose and sinus involvement less frequently compared to C-ANCA positive patients. Interstitial lung infiltrates were more common among P-ANCA positive patients compared to C-ANCA positive patients. [Conclusion] Japanese AAV patients who are diagnosed as GPA by the EMA algorithm includes a significant number of P-ANCA positive patients, and characteristics of those patients may be different from the classical picture of GPA.

W45-3

Characteristics of MPO-ANCA positive Granulomatosis with polyangitis in Japan

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Conflict of interest: None

[Objectives] This study attempted to clarifyfind the characteristics of MPO-ANCA positive Granulomatosis with polyangitis (MPO-GPA) in Japan. [Methods] Retrospectively we recruited 38 GPA patients cases who were diagnosed as GPA at the rheumatology departments of 8 hospitals since 2003 until 2013, and 41 MPA cases from one hospital. To exclude diagnostic overlaps, all cases were classified by EMA classification. Their clinical courses were analyzed based on sex, age, ANCA, organ involvements and treatment outcomes. [Results] Among GPA, 15 cases (39%) were positive for PR3-ANCA, 17 (45%) cases were positive for MPO-ANCA, and 6 cases were ANCA negative. All MPA were MPO-ANCA positive. Female was dominant in MPO-GPA group. Compared to PR3-GPA, MPO-GPA had significantly more otitis media, lower serum creatinine levels and more neuronal involvements. Compared to MPA, MPO-GPA showed significantly fairer progosis, and experenced more relapses like GPA. [Conclusion] In our study, we have equal number of MPO-GPA to that of PR3-GPA. MPO-GPA is characterized older female patients with otitis media, neuronal involvements, and less renal injuries and. They showed fairer treatment outcome with more relapse.

W45-4

Clinical analysis in 22 patients with eosinophilic granulomatosis polyangiitis (Churg-Strauss syndrome) at our department of Dermatology

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Conflict of interest: None

[Objectives] We examined eosinophilic granulomatosis with polyangiitis (EGPA) patients with cutaneous manifestations as an initial sign. [Methods] We retrospectively investigated the records of 22 patients (11 male and 11 female) with EGPA admitted to our hospital from 1997 to 2012. [Results] Ten patients (46%) were positive for serum MPO-ANCA. All patients were negative for serum PR3-ANCA. There was a significantly positive correlation between serum CH50 and C4 levels in patients with EGPA. Serum BUN levels differed significantly between MPO-AN-

CA positive and negative patients. Serum CH50 levels were higher in MPO-ANCA positive patients compared to negative patients. Eosinophils accumulated around the nerve fibers, and nerve bundles were also found in the affected cutaneous lesions in 18 patients (82%). Eight patients (36%) demonstrated histopathological granuloma formation in their skin biopsies specimens. [Conclusion] We propose that positive findings for MPO-ANCA high activity might be a risk factor for developing renal insufficiency. Assuming there are correlations between the presence of ANCA and complements, earlier diagnosis based on initial cutaneous manifestations could lead to earlier efficacious treatment and prevent renal insufficiency during the clinical course of EGPA.

W45-5

Current status and problems of eosinophilic granulomatosis with polyangiitis (EGPA)

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Conflict of interest: None

[Objectives] To find out the problems of medical care for EGPA. [Methods] Thirteen EGPA patients diagnosed by ACR criteria since April 2007 till March 2012 in our center were investigated retrospectively. Activity was evaluated by BVAS. Remission was defined as BVAS 0, and relapse was determined that BVAS increased or additional treatment was required. [Results] The mean age was 55.8. All patients had bronchial asthma (average preceding period: 26.9 months). MPO-ANCA was positive in 5 patients (38.5%), average WBC was 22600/μl, eosinophil count was 13035/μl, serum IgE level was 1607 IU/ml. Average BVAS was 24.1. Peripheral nerve involvement: 92.3%, GI tract: 61.5%, skin: 53.8%, lung: 46.2% and heart: 38.5%. Six cases were treated with steroid pulse therapy and in the other 7 cases the average of initial PSL dose was 52.8mg/day as induction treatment. IVCY was prescribed for the induction therapy in 3 cases. Remission rate (RR) at 3 months was 92.3% (n=12), RR at 12 months 76.9% (n=10). Between the relapse group and remission group after one year, there was no significant difference in patients' backgrounds. [Conclusion] Response rate to steroid therapy was high in EGPA. However, relapse was seen in some cases, so we need to explore new agents or regimens as maintenance therapy in the future.

W45-6

Clinical characteristics of anti-neutrophil cytoplasmic antibody-positive patients

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Conflict of interest: Yes

[Objectives] To compare the clinical characteristics of anti-neutrophil cytoplasmic antibody (ANCA) -positive patients. [Methods] We retrospectively analyzed the clinical characteristics of patients with positive ANCA test between 2005 and 2013 at our department. [Results] ANCA-positive 155 patients were analyzed. 96 patients were Myeloperoxidase (MPO) -ANCA-positive, 50 patients were Proteinase 3 (PR3) -ANCA-positive, and both antibodies were positive in 9 patients. Diagnosis in the MPO-ANCA-positive 69 ANCA-associated vasculitis (AAV) patients was mostly microscopic polyangitis (84%). Diagnosis in the PR3-ANCA-positive 13 AAV patients was mostly granulomatosis with polyangiitis (77%). PR3-ANCA-positive AAV patients were significantly younger than MPO-ANCA-positive AAV patients, and significantly affected eyes, ears and nasal cavities. Involvement into lung and kidney was not significant between MPO-ANCA-positive and PR-3-ANCA-positive AAV patients. Combined treatment with immunosuppressants and relapses were significantly more frequent in PR3-ANCA-positive than MPO-ANCA-positive AAV patients. [Conclusion] In this study, we classified patients by the presence of a defined ANCA, and observed remarkable differences in diagnosis and clinical characteristics between the groups.

W46-1

Oxidative modification in myeloperoxidase in patients with antineutrophil cytoplasmic antibody (ANCA)-associated vasculitides

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Conflict of interest: None

[Objectives] To elucidate mechanisms for the generation of myeloperoxidase (MPO)-anti-neutrophil associated antibodies (ANCA), we investigated post-translational modifications (PTM) of MPO from neutrophils of MPO-ANCA-positive patients. [Methods] Peripheral blood polymorphonuclear cells (PMN) were obtained from MPO-ANCA-positive patients and healthy donors. MPO in PMN was detected by 2 dimensional-western blotting (2D-WB) with or without oxidation by H2O2. Dityrosine formation, one of the oxidative modifications, was detected by 2D-WB. [Results] MPO was detected as multiple spots in the 2D-WB results, which indicated complicated PTM of the protein. Intensity of the heavy chain spots with high p*I* (>9.4) and high molecular weights (MW, >53kDa) was significantly greater in the patient group ($p<0.05$). H2O2 treatment of MPO increased p*I* and MW of the heavy chains in incubation time- and H2O2 concentration-dependent manners. Dityrosine formation was detected in the PMN proteins from MPO-ANCA-positive patients but not in the proteins from healthy donors. [Conclusion] MPO would be oxidized by reactive oxygen species in MPO-ANCA-positive patients. The oxidative modification may play a key role in the production of MPO-ANCA.

W46-2

NETs-ANCA vicious cycle in MPO-ANCA-associated vasculitis

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Conflict of interest: None

[Objectives] MPO-ANCA-associated vasculitis (MPO-AAV) is closely related to neutrophil extracellular traps (NETs). The aim of this study is to elucidate the enhanced formation and disordered regulation of NETs in MPO-AAV. [Methods] Patients enrolled in this study included 38 MPO-AAV and 23 SLE patients. NETs induction rate was evaluated by reaction of patient-IgG with healthy neutrophils primed by TNF-α. ANCA affinity was determined by the competitive inhibitory ELISA method. DNase I and NETs degradation abilities were evaluated by ELISA and the incubation of patient serum with formed NETs, respectively. [Results] MPO-AAV patient-IgG induced NETs. The induction rate was 16.6±9.7% and significantly higher compared to those in SLE patients and healthy controls. Moreover, the NETs induction rate was correlated with BVAS and ANCA affinity. While, DNase I, the important regulator of NETs in vivo, was generally low in MPO-AAV patients and many patients showed impaired degradation of NETs. Furthermore, the presence of anti-NETs antibodies, which could interfere with the degradation of NETs, was demonstrated in some MPO-AAV sera. [Conclusion] These findings suggested that NETs-ANCA vicious cycle could be involved in the pathogenesis of MPO-AAV.

W46-3

Identification of new disease activity markers in ANCA-associated vasculitis using quantitative proteome analysis

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Conflict of interest: None

[Objectives] We screened the new marker proteins which reflected disease activity of ANCA-associated vasculitis (AAV) by large-scale quantitative analysis of the serum proteome using the mass spectrometry (MS). [Methods] Serum samples (pretreatment and six months after treatment) of AAV patients registered with the Ministry of Labor and Welfare of Japan were examined by tandem MS analysis. The proteins in the serum were compared before and after treatment by the quantitative selected reaction monitoring (SRM) method. [Results] Approximately 400 proteins were identified by the proteome analysis of the 7 kinds of serum samples (MPA, 4 patients; GPA, 2; and EGPA, 1). Of these, 89 proteins which might be related to vasculitis were chosen, and candidate markers were further analyzed by the quantitative SRM method. Consequently, in addition to the inflammatory proteins including ORM, S100A8, and MMP9, candidate markers associated with vascular endothelial cell injury, renal damage and neutrophilic activation were also detected. [Conclusion] By quantitative proteome analysis using the high sensitive MS, we identified candidate new disease activity markers with expression profiles of the proteins at a concentration of ng/ml level in the serum of AAV before and after treatment.

W46-4

A role of NETs in ANCA associated vasculitis

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Conflict of interest: None

[Objectives] NETosis, a unique form of cell death of neutrophils, is characterized by the active release of chromatin fibers called NETs, that trap and kill invading microbes extracellularly. Although NETosis plays a crucial role in host defense, excessive NETs formation becomes self-defeating by promoting tissue injury and organ damage. It has been known that NETs are implicated also in the pathogenesis of autoimmune vasculitis such as SLE and AAV. We observed NETs formation by neutrophils in order to investigate the role of NETs in AAV. [Methods] Peripheral blood neutrophils from healthy donors were isolated and primed with phorbol myristate acetate (PMA), which is known as a strong inducer of NETs, and incubated. Neutrophils were stained with Hoechst 33342, Sytox Green and anti-MPO Ab and the percentage of NETs producing cells were calculated. [Results] Activated Neutrophils produced two types of NETs. One was fiber type and the other was non-fiber type. The ratio of two types of NETosis varied according to the donor's condition. [Conclusion] We distinguished two types of NETosis in the production of NETs by stimulated PMA neutrophils. It may be important to investigate which type of NETosis is more involved in pathogenesis of AAV.

W46-5

MRI findings of both thighs and clinical study on microscopic polyangitis

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Conflict of interest: None

[Objectives] To estimate the MRI findings of both thighs with MPA (microscopic polyangitis) patients. [Methods] 8 patients who were diagnosed with MPA or MPA suspected, and 7 patinets were under diagnosise of MPA but these 7patients were strongly suspected with MPA due to MPO-ANCA or pathologic findings. In all 15 patients were suffering from myalgia and MRI tests of both thighs were done in 15 patients. In 4 cases muscle biopsy was done. [Results] MRI findings of both thighs of 13cases in 15 cases suggest fasciitis and myositis. Some of them reveal strong findings of muscular inflammation and fasciitis, others of them show mild to moderate findings of myosiitis and fascitis In 2 cases of them, MRI test was done before and after treatment. In both cases, mild to moderate changes of MRI findings were observed after treatment. In 4 cases who were examined muscle biopsy, vasculitis of fascia were obtained in one case. [Conclusion] MRI findings suggested inflammation of both thighs in patients with microscopic polyangitis (MPA) and MPA suspected cases. We couldn't obtain pathological findings on muscle damage in these studies but even in only one case, we obtained the pathological evidence of vasculitis in fascia.

W46-6

Evaluation of skin perfusion pressure in Patients with eosinophilic granulomatosis with polyangitis or Sjögren's syndrome complicated with multiple mononeuropathy

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Conflict of interest: Yes

[Objectives] Multiple mononeuropathy arise from small vessel vasculitis by reduction of blood flow to peripheral nerve systems and tissues. The relatively new technique of laser Doppler imaging is noninvasive and measures skin perfusion pressure (SPP) shows superficial cutaneous microvascular blood flow. We investigated the values of the SPP in vasculitis patients. [Materials and methods] Both one patient with eoshinophilic granulomatous with polyangitis and Sjogren's syndrome complicated with multiple mononeuropathy were enrolled in this study. The SPP was measured using a Sensilase ™ PAD3000 (Kaneka, Osaka, Japan) before and after treatment. [Results] Low SPP values were observed at the site of neuropathy, even without apparent skin eruptions. This indicated underlying microvascular abnormalities. The SPP values were elevated after therapy. [Conclusion] The correlation between the low SPP value and the functional microvascular abnormalities has been indefinite yet. With further investigation, measurement of SPP in patients with multiple mononeuropathy could be a potential tool to evaluate disease progression and its therapeutic effectiveness.

W47-1

Fractures around hip joints in patients with osteomalacia

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Conflict of interest: None

[Objectives] The objectives of this study were to clarify the characteristics of proximal femoral fractures in patients with osteomalacia. [Methods] 4 cases of osteomalacia were investgated. [Results] Fractures were not evident radiographically. Bone scintiraphy revealed high uptake around the hip joints in all cases. Fracture lines were identified by MRI. All patients were hypophosphatemic (0.7~2.4mg/dl). In one case, serum level of FGF-23 was elevated, possibly due to FGF23-producing tumor. Others were diagnosed as dug-induced osteomalacia by adefovir and antiepileptic drugs. All the fractures were successfully treated coservatively. [Conclusion] In patients complaining hip pain, insufficiency fracture due to osteomalacia should be considered as a possile diffential diagnosis. The causes of hypophosphatemic osteomalacia can be diverse. The proximal femoral insufficieny fractures in our cases were treated conservatively but there are reports of cases that required operation. Thus careful assessmet is needed.

W47-2

Retrospective cohort study of osteonecrosis of the jaw (ONJ) and bisphoshpnate-related osteonecrosis of the jaw (BRONJ) in patients with rheumatoid arthritis-extracted from NinJa database- (Second report)

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Conflict of interest: None

[Objectives] To investigate the frequencies of osteonecrosis of the jaw (ONJ) and Bisphosphonate (BP) -related osteonecrosis of the jaw (BRONJ), in rheumatoid arthritis (RA) patients. [Methods] 4262 RA patients (770 male 3492 female, median age 64.2y, mean RA duration14.7 y) of 5 hospitals registered in the RA cohort database (NinJa) of 2011 were candidates to evaluate the frequencies of ONJ and BRONJ in RA patients. BRONJ was included in ONJ. [Results] 13 cases of ONJ were identified (all female, median age 75.3 y, mean RA duration16.0y) and the frequencies of ONJ were 4.75/100000 person-years (p-y) after birth and, 20.8/100000 p-y from the onset of RA. 10 among 13 ONJ candidates were BRONJ candidates (all female, median age 77.8 y, mean RA duration 16.6y.) Recent prescriptions of BP were all candidates with Alendronate. Mean duration of BP medication was 41.9months. The frequencies of BRONJ were 51.2/100000 p-y from the onset of RA and 172/100000 p-y from the BP administration. The frequency of BRONJ in RA patients was 70-200 times greater than in patients treated with BP reported before. [Conclusion] Frequencies of BRONJ and ONJ in RA patients are much higher than those reported before. Careful attention and precautions of BRONJ/ONJ are required.

W47-3

Significance of serum sRANKL and OPG concentrations in patients with rheumatoid arthritis

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Conflict of interest: None

【Objective】 Rheumatoid Arthritis (RA) is known as a cause of secondary osteoporosis. The purpose of this study is to investigate serum levels of soluble receptor activator nuclear factor κB ligand (sRANKL) and osteoprotegerin (OPG) in patients with RA.【Methods】 Serum levels of sRANKL and OPG in 360 patients with RA were measured by respective ELISA. We collected clinical data to analyze relationship among serum sRANKL and OPG, and these data. 141 healthy subjects were included as control in this study.【Results】 Both of the serum levels of sRANKL and OPG were increased significantly when compared to those of healthy subjects. The serum sRANKL was negatively correlated with age and CRP. It was negatively correlated with age, however, positively with HAQ by the multivariate analysis. On the other hand, the serum OPG was positively correlated with CRP, DAS28-ESR and MMP-3 as well as age and disease duration. In multivariate analysis, it was positively correlated with age and MMP-3. There was no correlation between the serum levels of sRANKL and OPG.【Conclusion】 These results suggested that advanced disabilities might increase the risk of osteoporosis, whereas advanced destruction of cartilage might not influence on bone metabolism in RA patients.

W47-4

Clinical significance of serum Dickkopf1 and Sclerostin levels in glucocorticoid-induced osteoporosis; a prospective study

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Conflict of interest: None

[Objectives] Wnt signaling pathway plays an important role in bone formation of osteoblasts. The purpose of this study is to clarify the significance of Wnt pathway inhibitors, serum Dickkopf1 (Dkk1) and sclerostin, after glucocorticoid (GC) therapy. [Methods] Forty patients (female 26, postmenopausal 16) with systemic autoimmune diseases who received initial GC therapy with 30-60 mg prednisolone daily were prospectively included in this study. Regular doses of bisphosphonates were co-administered in all patients. We measured serum Dkk1 and sclerostin, and bone turnover markers at 0, 1, 2, 3 and 4 weeks after GC therapy. [Results] The serum Dkk1 level was significantly decreased from 2nd to 4th week after GC therapy. In contrast, serum sclerostin level was significantly increased from 1st to 2nd week. Serum bone formation markers, OC (osteocalcin) and P1NP, decreased from 1st to 4th week, whereas serum bone resorption markers, TRACP-5b and NTX, did not change. [Conclusion] It is suggested that GC therapy in early-phase suppressed bone formation *via* Wnt signaling pathway.

W47-5

Relationship between serum 25(OH)D2 levels and incident vertebral fractures of glucocorticoid-induced osteoporosis in patients with connective tissue disease

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Conflict of interest: None

[Objectives] We evaluated serum 25 (OH)D2 (D) as a risk factor for incident vertebral fractures in glucocorticoid-induced osteoporosis (GIOP). [Methods] Subjects with connective tissue disease except rheumatoid arthritis were 15 males and 96 females, showing 60±15 y.o. of mean age, and 8.0±5.9 mg of mean daily dose. None of subjects had a medication of natural vitamin D. In this 2-year longitudinal study, an incident vertebral fracture was diagnosed with semiquantitative criteria by Genant (JBMR, 1993). Bone mineral density (BMD) was assessed by the radial DXA. [Results] There was significant difference in the serum level of D between subjects with a incident fracture and subjects without fracture (16.9 vs 20.0, $p<0.027$). The decrease of serum D concentration was an independent risk factor for an incident vertebral fracture with statistical significance (OR 1.6/5pg, $P<0.03$), after adjustment for age, total glucocorticoid dosage, mean daily glucocorticoid dosage, BMD, previous fracture, and therapeutic agents. [Conclusion] These data suggests that the decrease of serum D level is an independent risk factor and the severity of incident fractures in subjects with GIOP.

W47-6

S1P-mediated osteoclast precursor monocyte migration is a critical point of control in antibone-resorptive action of active vitamin D

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Conflict of interest: None

The migration and positioning of osteoclast precursor monocytes are controlled by the blood-enriched lipid mediator sphingosine-1-phosphate

(S1P) and have recently been shown to be critical points of control in osteoclastogenesis and bone homeostasis. Here, we show that calcitriol, which is the hormonally active form of vitamin D, and its therapeutically used analog, eldecalcitol, inhibit bone resorption by modulating this mechanism. Vitamin D analogs have been used clinically for treating osteoporosis, although the mode of its pharmacologic action remains to be fully elucidated. In this study, we found that active vitamin D reduced the expression of S1PR2, a chemorepulsive receptor for blood S1P, on circulating osteoclast precursor monocytes both *in vitro* and *in vivo*. Calcitriol- or eldecalcitol-treated monocytoid RAW264.7 cells, which display osteoclast precursor-like properties, migrated readily to S1P. Concordantly, the mobility of circulating CX_3CR1^+ osteoclast precursor monocytes was significantly increased on systemic administration of active vitamin D. These results show a mechanism for active vitamin D in controlling the migratory behavior of circulating osteoclast precursors, and this action should be conducive to limiting osteoclastic bone resorption *in vivo*.

W48-1

Assessment of 2012 EULAR / ACR new classification criteria for Polymyalagia Rheumatica (PMR) in Japanese diagnosed with Birds' criteria in our center

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Conflict of interest: None

【Objective】EULAR / ACR new classification criteria for PMR is published in 2012. The aim of this study was to investigate clinical feature in Japanese by 2012 EULAR / ACR new classification criteria for PMR in our center.【Methods】We assessed 2012 EULAR / ACR new classification criteria for PMR in 78 patients diagnosed with Birds' criteria and we divided the patients into PMR groups matched with the new criteria and non-PMR group matched without it.【Results】PMR group was 32 cases, non-PMR group was 46 cases. It was no significant difference in the absence of rheumatoid factor or antibody to cyclic citrullinated peptide between PMR group and non-PMR group. Individual 4 items were compared between 32 PMR patients and 46 non-PMR patients. In our result, only 21 patients (27%) had Morning stiffness (MS). MS was the independent factor that divide the two group. This suggested that MS was the crucial item with the new classification.【Conclusion】Some reviews described that MS is fewer in Japanese patients than European and American patients with PMR. Further studies are required about the new criteria with optional ultrasound criteria in Japanese patients with and without MS.

W48-2

Comparison of the three classification criteria for polymyalgia rheumatica and usage of steroid to polymyalgia rheumatica

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Conflict of interest: None

[Objectives] Comparison between 3 criteria for polymyalgia rheumatica was conducted and use of corticosteroid was investigated. [Methods] A total of 52 patients were identified from the clinical data base of our hospital with a provisional disease name polymyalgia rheumatica between January 2007 and July 2013. Through the peer review of the clinical records, 29 patients were selected as PMR by the criteria proposed by Bird and colleagues. [Results] Nine cases were turned out to be rheumatoid arthritis or other rheumatic diseases and other 14 cases were not met the criteria by Bird. The average age of the 29 PMR patients was 73.4 years old and the mean initial dose of prednisolone was 16.0mg. Ten cases out of 29 patients (34.5%) met the provisional criteria of PMR by EULAR/ACR 2012, and 25 cases (86.2%) met the criteria proposed by PMR research group in Japan 1985. The most frequent reason to unmet the new criteria from EULAR/ACR was the description of morning stiffness and its duration. Long term follow up revealed only 7 cases out of 29 patients no longer took steroids and one case was rheumatoid arthritis and another case was multiple myeloma. [Conclusion] We speculate that sensitivity of new criteria from EULAR/ACR will be increased by precise description of the patients.

W48-3

Sensitivity of the New EULAR/ACR Classification Criteria for Polymyalgia Rheumatica in Comparison with the Former Ones

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Conflict of interest: None

Objectives: To evaluate the diagnostic ability of the new ACR/EULAR classification criteria for PMR in a consecutive series of new onset Japanese PMR patients. Methods: All patients with suspected PMR are followed according to a standardized protocol. Consecutive patients seen in our centers with recent onset PMR and followed for at least 6 months were included. Diagnostic performance of new ACR/EULAR classification criteria were evaluated and compared to the sensitivity of the former diagnostic/classification criteria. Results: 32 patients entered the study (mean age 71+10.6y, female 46.9%, mean ESR 72+24 mm/hr, CRP 7.27+4.33 mg/dl). 32 (100%) pts had bilateral shoulders complains. 27 (84%) pts had increased levels of ESR (more than 40mm/hr), 56.3% had hip pain, 75% had normal RF and anti-CCP, 62.5% did not have peripheral joint involvement. 20 (62.5%) pts could be defined to have PMR according to the new ACR/EULAR classification criteria. Applying the former diagnostic/classification criteria 68.8% satisfied Hunder's criteria, 62.5% Healy's criteria, 40.6% Jones's criteria, 84.4% Bird's criteria, 53.1% Nobunaga's criteria. Conclusion: In our series of recent onset PMR patients the new ACR/EULAR criteria seems to have as well or better sensitivity as compared to the previous criteria.

W48-4

Outcome and Anlysis of treatment for steroid-resistant case or refractory case with polymyalgia rheumatica in Kurashiki Medical Center

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Conflict of interest: None

Here we report 38 patients (17 men and 21 women) with polymyalgia rheumatica (PMR) in our center. The average age at diagnosis was 68.0 years and followed up for average of 45.6 months. 2 patients complicated with temporal arteritis and mean CRP were 7.7mg/dl. The average initial doses of prednisolone was 14.7 ± 6.1 mg/day, a prompt response was observed in 37 patients and 15 patients was discontinued corticosteroid. But 14 patients had relapses after reduction of corticosteroids. Steroid discontinuation cases were younger (64.5 vs. 70.2 y), had lower CRP (6.38 vs. 8.61 mg/dl) and were treated with lower initial doses of steroid (10.6 vs 17.3mg/day). For refractory cases, 3 cases were treated with MTX, 1 case was treated with CPA, SASP individually. 3 cases with steroid induced complications were treated with MTX. 38 adverse events (included such as infection, hypertension, diabetes, hyperlipidemia, vertebral fracture, malignancy (breast cancer, renal cell carcinoma)) were recorded in 21 patients after treatment of PMR. Although PMR is a nonfatal disease, the high frequency of adverse events was noted in patients with long term PSL use and there are few case complicated with cancer. More careful observation of the treatment for PMR is needed.

W48-5

Predictive Factor for Outcome of Corticosteroid Therapy in Patients with Polymyalgia Rheumatica

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Conflict of interest: None

[Objectives] To clarify predictive factor for outcome of corticosteroid (CS) therapy in patients with PMR, we performed a retrospective cohort study. [Methods] 81 patients with PMR who fulfilled Bird's criteria and received an initial CS therapy in our hospital from 2007 until 2012 were selected for this study. We defined that event was the increase of CS due to exacerbation of PMR, and that observation period was the time after initial CS therapy for survival analysis. [Results] Age at initial CS therapy was 47-88 years old. The range of PSL was 4 to 20 mg in all patients. CRP was 7.0±5.2 mg/dl. 18 events were observated. 6 patients were treated with the additional immunosuppressants. Of the 18 patients, 7 patients were finally diagnosed as other connective tissue diseases (3), and a malignant tumor (4). The event rates in 0.5, 1 and 2 years were 1.3%, 2.0%, and 12.7%, respectively. Cox proportional hazard models showed that the hazard ratio (HR) for the event of normalization of serum CRP in initial 6 weeks was 0.30 (95% CI 0.06-0.99, p=0.048). The HR of serum CRP and dosage of PSL were not significant. [Conclusion] The results demonstrated that the normalization of serum CRP within 6 weeks was predictive factor for outcome of CS Therapy in patients with PMR.

W48-6

Serum matrix metalloproteinase 3 levels predict the response for treatment of glucocorticoid in patients with polymialgia rheumatica

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Conflict of interest: None

[Objectives] Polymyalgia rheumatica (PMR) is an inflammatory rheumatic disease of the elderly, and is characterized by aching in the neck, shoulders, and pelvic girdle. Recently, elevated serum levels of matrix metalloproteinase 3 (MMP-3) has been reported. But, it is unknown whether high level of serum MMP-3 means the resistance against treatment for glucocorticoid. [Methods] We examine the relation between MMP-3 level in patients with PMR and dose of glucocorticoid after twelve month from the start of treatment. [Results] Fifty-three patients of PMR (average 70.4±9.89 years old) were enrolled. [Conclusion] MMP-3 level is associated with dose of glucocorticoid after twelve month.

W49-1

The Incidence of Malignancy in Patients Who Were Initially Suspected with Polymyalgia Rheumatica In Our Clinic

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Conflict of interest: None

[Objectives] Because malignancy in patients (pts) with polymyalgia rheumatica (PMR) is affected the prognosis of the pts, we tried to examine the incidence of malignancy in pts who initially suspected with PMR in our clinic for five years. [Methods] The 30 pts were suspected with PMR from 2007 to 2011. The diagnosis of PMR was made by EULAR / ACR criteria 2012. The malignancy was examined by the methods such as endoscopy, CT-scan, and consultations of specialists for otolaryngology, gynecology and urology in every year. Statistical analysis was made by $\chi 2$-test and multivariate regression logistic analysis. [Results] 24 pts (80%) were diagnosed with PMR. 6 pts (20%) were complicated with malignancy and all of them had PMR. Statistically, no factors associated with malignancy were found in the pts. The incidence of malignancy tended to increase in pts with PMR (+)/giant cell arteritis [GCA] (-) as compared with PMR (+)/GCA (+), although it was statistically not significant (31% vs. 13%; p=0.11). [Conclusion] 20% of all pts suspected with PMR was complicated with malignancy and all of them had PMR. Because no factors associated with malignancy in the pts, careful following up may be necessary to find malignancy in pts with PMR, especially without GCA.

W49-2

Prognosis of RS3PE syndrome

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Conflict of interest: None

[Objectives] To clarify the prognosis of RS3PE syndrome. [Methods] The total of 29 cases, who were diagnosed as having RS3PE syndrome, were subjected to be analyzed the prognosis retrospectively. [Results] Average age was 78.5±6.4 years old. All patients had a good response to prednisolone. But 14 patients had prednisolone one year after the onset. 9 patients had reccurence of RS3PE syndrome. Malignancies were complicated in 9 patients (31.0%) with RS3PE syndrome. 3 patients died due to malignancies. [Conclusion] We suggested that RS3PE patients had poorer prognosis than had expected because they needed consequent steroid therapies and were frequently complicated with malignancies.

W49-3

Now diagnostic method of renal amylodiosis in urine samples and migration of amyloid deposits in renal tissues in patients with reactive amyloidosis associated with rheumatoid arthritis

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Conflict of interest: None

[Objectives] To examine amyloid protein in urine samples in patients with reactive amyloidosis associated with RA and investigates migration of amyloid deposits in renal biopsy samples. [Methods] Nine patients with reactive amyloidosis, who had been referred to Niigata University Hospital, were examined. The urine samples of these patients were centrifuged and divided into supernatant and sediment. The sediments were solubilized, and blotted by anti-SAA antibody recognized common AA size (AA76). Additionally, migration of amyloid deposits in renal biopsy samples were investigated. [Results] In urine sediments, 4 of 9 samples were detected AA76. In urine supernatant, 1 of 9 samples were detected AA76. In renal biopsy specimens, amyloid deposits were detected in epithelial cells of proximal tubules and deposited more from the lumen of proximal tubules as approached basement membrane side. However, in distal tubules, non of the amyloid deposits were detected. Additionally, migration of amyloid deposits from proximal tubules to peritubular capillary were observed. [Conclusions] It was possible to detect amyloid protein in urine samples of amyloidosis patients. It was suggested that amyloid deposits were migrated from proximal tubules to peritubular capillarly in renal biopsy specimens.

W49-4

Comparison of therapeutic effect among conventional DMARDS, anti-TNF inhibitor and anti-IL-6 receptor therapies in Amyloid A (AA) amyloidosis complicating rheumatic diseases by using serial duodenal quantification of AA protein

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Conflict of interest: None

[Objectives] To compare the therapeutic effect among conventional DMARDS (non-Bio), anti-TNF inhibitor (TNF) and anti-IL-6 receptor (TCZ) therapies in AA amyloidosis complicating rheumatic diseases by using serial duodenal quantification of AA protein. **[Methods]** We compared 3 therapy groups (non-Bio: 7patients, TNF: 6 patients, TCZ: 8 patients). We evaluated serial duodenal AA protein deposits (ng/mg of tissue) by ELISA. **[Results]** 1. Quantitative values (median) in each groups at the first biopsy were 1996.7 (non-Bio), 2056.5 (TNF) and 1721.5 (TCZ), respectively (p=0.9546). 2. Number of AA decreased cases at the last observation were 1/7 (14.3%: non-Bio), 4/6 (66.7%: TNF) and 8/8 (100%: TCZ). 3. Transitions of AA deposits (median, from the first evaluation to the last evaluation) were from 100% to 194.3% (non-Bio: increase, p=0.0469), 84.6% (TNF: no change, p=0.6875) and 14.0% (TCZ: decrease, p=0.0078)), respectively. 4. SAA values (μg/ml, median) in each group during observation period were 58.1 (non-Bio), 20.3 (TNF) and 3.0 (TCZ), respectively. **[Conclusion]** TCZ was confirmed to be superior to non-Bio as well as TNF in the treatment of AA amyloidosis complicating rheumatic diseases in the view of the turnover of AA protein.

W49-5

Systemic positron-emission tomography images with BF-277-amyloid-specific tracer in two cases of systemic amyloidosis

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Conflict of interest: None

[Background] Currently Amyloidosis has been diagnosed by the biopsy. Yet, in early stages, its sensitivity is low in spite of invasive and it is difficult to determine the therapeutic effect. Recently, PET using a novel probe BF-227, combined with amyloid protein specifically, was succeeded to detect the amyloid in Alzheimer's, and cardiac amyloidosis. [Objective] To visualize and image the distribution of amyloid accumulation using BF-227-PET. [Method] BF-227 is administered intravenously for two patients and a control and underwent systemic PET scan. Case1 (71yo F) had RA with high activity, and repeated backbone fracture, diagnosed as AA amyloidosis by an intestinal tract and kidney biopsies. She treated with Tocilizumab, and the symptoms got better. Then BF-227-PET was performed. Case 2 (62yo M) had renal failure by the multiple myeloma, diagnosed as AL amyloid by the kidney biopsy. Then BF-227-PET was performed. [Result] Case 1: Although the accumulation of amyloid to intestinal tracts and kidneys was not clear, accumulation for the backbone was detected. Case 2: Accumulation of amyloidosis to bilateral kidneys was detected. [Conclusion] BF-227-PET was suggested a possibility of becoming important for the new diagnostic method of amyloidosis, and determine the therapeutic effects.

W49-6

Localized form of AL amyloidosis in patients with primary Sjögren's syndrome

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Conflict of interest: None

[Objectives] Sjögren's syndrome (SS) is associated with diverse extraglandular manifestations, but localized form of AL amyloidosis (LFAL) in patients with primary SS is less well known. In this study we sought to clarify clinical characteristics and radiological findings of this condition. [Methods] We reviewed clinical records, imaging studies, and pathologic specimens in patients with primary SS who were diagnosed with LFAL. [Results] Six patients with primary SS were diagnosed with LFAL. Their median age at diagnosis of LFAL was 57.5 years. The diagnosis of LFAL preceded primary SS in four patients. Amyloid deposition occurred in multiple organs including the skin, eyelid, breast, stomach, glottis, trachea, as well as the lung. One patient had bloody sputum, and five remaining patients were detected amyloidosis incidentally by cancer screening without any symptoms. Chest CT showed multiple nodules and cystic lesions in all patients. Five patients were observed without administration of any specific therapy, and one patient was treated with prednisolone because of the risk of tracheal stenosis. [Conclusion] We need to screen for SS in patients with LFAL, and think that nodular and cystic lung lesions seen in patients with primary SS represent the possibility of LFAL.

W50-1

Glucocorticoid therapy and the risk of infection in patients with newly-diagnosed autoimmune disease

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Conflict of interest: None

Patients with autoimmune disease who were initially treated with GCs were enrolled. The 604 patients had a total follow-up time of 1105.8 person-years (mean 1.9 years per patient). 136 patients had at least one infection with objective confirmation and 73 patients had serious infections. Twenty-two cardiovascular events, 55 cases of diabetes, 30 fractures, 23 steroid psychosis events and 4 avascular bone necrosis events occurred during the follow-up period. The incidence of serious infections was 114.8 (95% C1 95.7-136.6) /1000 person-years, respectively. After adjustment for covariates, elderly age (HR: 1.25/10-year increment, p=0.016) the presence of interstitial lungdisease (HR: 2.01, p=0.011) and high dose GC (>29.9 mg/day, HR: 1.71, p=0.047) use and low performance status (Karnofsky score, HR: 0.98/1-score increment, p=0.002) were found to be independent risk factors for serious infection. During the follow-up period, 73 patients died, of which 35 died of infection. Although the primary diseases are important confounding factors, elderly age, male gender, the presence of interstitial lung diseases, high-dose GC and low performance status were shown to be risk factors for serious infection and mortality

W50-2

Serious Infection following glucocorticoid therapy in elderly patients with connective tissue disease

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Conflict of interest: None

Objectives: To assess the risk of serious infections (SIs) in elderly patients with connective tissue disease (CTD) receiving prednisolone (PSL). Methods: Data from 86 elderly patients (mean age: 76 years) with newly diagnosed CTD (vasculitis 49%, rheumatoid arthritis 16%, and inflammatory myopathies 13%) who were given PSL ≧0.5mg/kg/day were analyzed. We reviewed medical records to assess the occurrence of SIs within a-6-month period after the start of PSL. Results: Initial mean dose of PSL was 40mg/day, and 43% of patients were given immunosupressants. 50% of patients developed SIs. The most common SIs were cytomegalovirus infection (33%), followed by bacterial pneumonia (23%) and fungal infection (19%). Univariate analysis showed initial dose of

PSL and immunosuppressant use were not associated with SIs. Multivariate analysis showed that older age, lower albumin, glucocoriticoid pulse therapy were related to SIs. On the other hand, there was a statistically significant association between daily dose of PSL at 2 weeks after the treatment and SIs after the period (hazard ratio 1.51, 95% confidence interval 1.08-2.11). Conclusion: Daily dose of PSL at 2 weeks after the treatment, but not initial dose of PSL and immunosuppressant use, was associated with a significantly increased risk of SIs.

W50-3

Clinical investigation of infection in connective tissue diseases (CTD); association with glucocorcicoid (GC) and glucose intolerance

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Conflict of interest: None

[Objectives] The objective of this study was to analysis clinical characteristics of infections in connective tissue diseases (CTDs), especially corelation with glucocorcicoid or glucose intolerance. [Methods] We retrospectively reviewed the medical records of all patients with CTDs at the Department of connective tissue disease, Tokyo Medical Center, between 2006 to 2010. [Results] A total of 2830 patients visited. Total of 1170 patients were followed for more than half a years during the 5-year study period. Mean age 63.9 years. They followed up for a mean of 830 days. There were 177 patients (13.4%) with infection, respiratory infection in 36.4%, urinary tract infection in 26.5%, skin infection in 17.4%. Serious infection (SIE) in 33%. Prednisone (PSL) used in 74% with infection and 54% without. Immunosuppressant used in 29% with infection and 18% without, Biologics used in 5% with infection and in 2% without ($p< 0.01$-0.05). Multiple classification analysis suggested that the risk factors of infection in CTDs were PSL, age, CKD, chronic lung disease. Age, HbA1c and total dose of PSL in 6 month were higher in SIE than in nonSIE. [Conclusion] In this study, patients with CTDs were at increased risk of developing infections, especially with DM, CKD, Chronic lung disease and elderly.

W50-4

Serum presepsin (soluble CD14-subtype) as a useful novel biomarker for bacterial infection in rheumatoid arthritis patients

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Conflict of interest: None

[Objectives] Infection is one of the serious complications seen in the management of RA patients. PSEP has been reported to be a novel effective marker for the diagnosis of sepsis. The objective of this study was to evaluate the use of presepsin in RA patients during a bacterial infectious event. [Methods] 25 RA patients with bacterial infections, 34 RA patients with high disease activity, 34 healthy controls were enrolled in this study. RA patients in whom the pathogens were identified were designated as the infection RA group (iRA) and high disease activity RA patients without infection were designated as the flare RA group (fRA). PSEP, CRP and procalcitonin (PCT) and neutrophil CD64 molecules (nCD64) were measured. Levels of respective measurements at both pre- and post-treatment and comparisons of levels within each group were analyzed. [Results] In iRA, levels of PSEP, CRP, PCT, and nCD64 were 1755±3661pg/ml, 10.1±6.26 mg/dl, 8.84±19.2ng/ml, and 8742±9221 molecules /cell, respectively, at pre-treatment. All parameters were significantly higher compared to post-treatment ($p<0.001$). In fRA, PSEP, PCT and nCD64 showed no significant difference between pre- and post-RA treatment. [Conclusion] PSEP is an effective diagnostic marker for bacterial infection in RA patients.

W50-5

Analysis of Nocardiosis patients with connective tissue disease

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Conflict of interest: None

<Objective> To clarify the clinical features of Nocardiosis in patients with connective tissue disease. <Methods> Seven cases with Nocardiosis, who were admitted to our hospital from Jan 2004 to Jun 2013, were enrolled. The diagnosis was the basis that the Nocardia was cultured one or more times in a laboratory culture. We analyzed age of onset, sex, connective tissue disease, complications, laboratory data, the treatments, site of infection, and outcome retrospectively. <Results> 1) Mean age of onset was 57.4 ± 21.5, and sex was 2 males and 5 females. The duration of culture identification was 21.7 ± 15.8 days. 2) The number of CTD of patients: SLE 3, MRA 2, MPA 1, and RA 1. All cases were administered corticosteroids, and the average dose was 21.8 ± 13.7 mg/day (predonisolone conversion). Diabetes mellitus were observed in 4 cases. 3) Site of infection: lung 4 cases, lung + skin: 2 cases, lung + skin + brain: 1 case. 4) 4 cases recovered, and 3 cases died. Serum IgG was significantly lower in the group of death (678.3 ± 67.3 mg/dl vs 1079.0 ± 556.6 mg/dl, $P=0.03$). High tendency of β-D-glucan was observed in the group of death (78.7 ± 69.2 pg/ml vs 8.0 ± 5.4 pg/ml, $P=0.07$). <Conclusion> All 7 cases were administrated corticosteroids. Low serum IgG may be poor prognosis.

W50-6

Periodontal treatment decreases rheumatoid arthritis activity and serum citrulline level

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Conflict of interest: None

【Objectives】 *Porphyromonas gingivalis* has been implicated as an etiological agent of rheumatoid arthritis (RA) due to the expression of peptidylarginine deiminase. We evaluated whether periodontal therapy may affect RA activity and serum anti-*P. gingivalis* antibody and citrulline levels.【Methods】 RA activities and serum levels of anti-*P. gingivalis* and anti-CCP antibodies, citrulline, and rheumatoid factor were examined at baseline and 8 weeks later in RA patients with plaque control and supragingival scaling (treatment group, n = 26) or no periodontal treatment (control group, n = 29).【Results】 Both groups did not differ statistically in all parameters at baseline. The treatment group showed a significantly greater decrease in DAS28-CRP, serum levels of anti-*P. gingivalis* hemin binding protein 35 (HBP35) antibodies and citrulline than the control group. A significant positive correlation was observed between serum levels of anti-*P. gingivalis* HBP35 and anti-CCP antibodies, and between serum levels of anti-*P. gingivalis* sonicated extracts antibodies and rheumatoid factor.【Conclusion】 Periodontal therapy decreases DAS28-CRP and serum levels of anti-*P. gingivalis* HBP35 antibodies and citrulline in RA patients, reflecting a role of *P. gingivalis* in the protein citrullination.

W51-1

Effectiveness of trimethoprim-sulfamethoxazole for prevention of *Pneumocystis jirovecii* pneumonia in patients receiving immunosuppressive therapy for rheumatic diseases

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Conflict of interest: Yes

[Objectives] To identify effectiveness of trimethoprim-sulfamethoxazole (TMP-SMX) for prophylaxis of *Pneumocystis jirovecii* pneumonia (PCP) in patients with rheumatic diseases given immunosuppressive therapy [Methods] We prospectively observed 418 in-patients with rheumatic diseases who started prednisolone (PSL) ≥0.5mg/kg/day. Patients who started TMP-SMX at baseline (N=277, prophylaxis group) and patients without TMP-SMX throughout observation period of 6 months (N=141, non-prophylaxis group) were compared. [Results] Patients in the prophylaxis group had higher rates of pulmonary comorbidities (43.3% vs. 26.2%, p<0.01) and interstitial pneumonia (30.7% vs. 17.7%, p=0.04), but had a lower incidence rate of PCP (1.4% vs. 6.4%, p=0.01) than those in the non-prophylaxis group. Cox hazard regression analysis indicated that prevention with TMP-SMX lowered risk for development of PCP (HR 0.19, 95%CI 0.06-0.65), after adjusting for covariates at baseline. Of 112 patients who discontinued TMP-SMX (40.4%), four patients developed PCP after the discontinuation. [Conclusion] TMP-SMX was effective for the prevention of PCP in patients with rheumatic diseases who started PSL ≥0.5mg/kg/day. Studies questing for better usages of TMP-SMX with improved drug retention rates are warranted.

W51-2

Clinical study of Pneumocystis pneumonia (PCP) during rheumatoid arthritis (RA) treatment - Biological treatment (Bio) and MTX treatment-

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Conflict of interest: None

[Objectives] We reveal the onset factor that developed PCP. [Methods] I was examined 25 patients that developed PCP during RA at our department. Bio-PCP group was 13 patients and non-Bio-PCP group was 12 patients. I was studied retrospectively for Bio-PCP group and 128 patients not developed PCP to be administered more than six months on adalimumab (Bio group). Also, I was studied retrospectively 10 patients of MTX treatment that developed PCP (MTX-PCP group) and 138 patients not developed PCP for MTX (MTX group). [Results] 12 of 13 patients developed PCP within 24 weeks Bio started. In addition, Bio-PCP group was higher rate in lung disease, diabetes, and steroid combination as compared to the Bio group. However, We were no significant difference between gender, et al. On the other hand, MTX-PCP group has developed in the 281 week average. MTX-PCP group were older, coexistence lung disease, and combined rate of steroid was higher as compared to the MTX group. But, We were no significant difference between weight, et al. [Conclusion] If elderly, coexistence of lung disease, long disease duration, steroid combination have the potential to increase the risk of developing PCP in MTX. Making a prophylaxis may be effective at risk even six months on Bio because of PCP that developed on Bio are almost within 24 weeks.

W51-3

Clinical study of patients with autoimmune disease complicated by cytomegalovirus antigenemia

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Conflict of interest: None

We evaluated the occurrence of cytomegalovirus (CMV) infection and the background characteristics with autoimmune diseases. A total of 112 patients with CMV antigenemia who admitted to our department from May 2013 to May 2008 were analyzed. 31 patients were recurrence of CMV antigenemia. The median interval of CMV antigenemia was 28 days in recurrence group and 33 days in non recurrence group. The mean CMV antigenemia-positive cells of recurrence group were higher than non recurrence group. The treatment period of ganciclovir in recurrence group was longer than non recurrence group. 20 of 31 patients (65%) in recurrence group and 32 of 81 patients (40%) in non recurrence group were received of immunosuppressive agents. (P=0.07) In contrast, recurrence group was received significantly higher dose of total steroids than non recurrence group. (64727.7mg vs18898.7mg) P=0.0004 Clinical manifestation was demonstrated 52 of 112 patients (46%). Those patients had thrombocytopenia, increased liver enzyme levels. Recurrence group had lower number of lymphocyte and IgG. **【Conclusion】** Recurrence of CMV infection with autoimmune disease was induced by high dose steroids. These data suggested that immunosuppression by high dose steroids participate in the occurrence of CMV infection.

W51-4

The risk factors contributing to reactivation of cytomegalovirus in ANCA associated vasculitis during immunosuppressive therapy

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Conflict of interest: None

[Objectives] To assess the risk factors of reactivation of cytomegalovirus (CMV) in ANCA-associated vasculitis (AAV) during immunosuppressive therapy. [Methods] AAV patients who were treated with PSL 0.6mg/kg/day or more for induction therapy from 2006 to 2013 were retrospectively included. Observation period was up to the day PSL dose reduced to 0.4mg/kg/day. The differences of background between CMVpp65 antigen positive and negative group were evaluated. [Results] Fifty three patients (36 MPA, 10 GPA, 7 EGPA) were included. Compared CMVpp65 antigen positive group (17 MPA, 1 GPA) to negative group, serum level of CRP in active state were significantly higher and peripheral lymphocyte count at 4 weeks of treatment were lower than in negative group (p<0.05). The number of patients who were treated with steroid pulse therapy and patients who were complicated with nephritis were significantly higher in positive group than in negative group (p<0.05). [Conclusion] High level of serum CRP, lymphopenia at 4 weeks of treatment, steroid pulse therapy, and complication with nephritis might be a predictor of CMV reactivation. In addition, CMV reactivation might be a sign of poor prognosis.

W51-5

Prospective study of Hepatitis B virus reactivation during immunosuppressive therapy in patients with rheumatic diseases in Tohoku area, Japan

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Conflict of interest: None

[Objectives] The Japanese guideline for management of hepatitis B

virus (HBV) reactivation was published for patients with malignant diseases in 2009. In this study, we conducted a multicenter prospective study in Tohoku area to evaluate the usefulness of the guideline for patients with rheumatic diseases. [Methods] According to the guideline, titer of HBs antigen, anti-HBc antibody, and anti-HBs antibody were measured before immunosuppressive therapy. During the therapy, Levels of AST, ALT, and HBV-DNA were monitored every month in patients with positive anti-HBc antibody and/or anti-HBs antibody. [Results] A total of 807 patients with rheumatic diseases were enrolled. A total of 189 patients (23.4%) were HBs antigen negative, anti-HBc antibody positive and/or anti-HBs antibody positive, and 116 patients were monitored for a year. HBV-DNA were negative before therapy in all patients. During immunosuppressive therapy, 4 of 116 patients (3.4%) had positive HBV-DNA and 3 of 4 patients took entecavir. No patients had hepatitis by HBV reactivation. [Conclusion] The guideline is applicable to rheumatic diseases. Further evaluation is needed to clarify that how often and how long HBV-DNA should be monitored, and when entecavir should be administered.

W51-6

Several patterns of hepatic injury in the course of immunosuppressive therapy to HCV or HBV positive patients of the rheumatic diseases

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Conflict of interest: None

【Objective】Generally viral hepatitis get worse by using immunosuppressive drug. There were several pattern of the way of worsening of the hepatic injury.【Method】Typical 4 cases were presented.【Result】*Case1*. A 67yo HBV carrier patient of SLE was treated by steroids to the hepatic failure. The hepatic damage recovered by antiviral therapy. *Case 2*. A 54 yo HBV carrier patient of RA was treated by MTX. The MTX was very effective, but hepatitis got worse by increment of dose of MTX. *Case 3*. A 67 yo HCV positive patient was treated by steroids for membranous nephropathy. He was died of hepatic failure. *Case 4*. A 72 yo HCV positive RA patient was treated by Eternercept (ETN) with success. But haptic injury deteriorated and ETN discontinued. RA flaired up and Tacrolimus (TAC) was started. haptic injury deteriorated again. So TAC was discontinued. However hapatic damage furthermore worsen. Hepatic biopsy was done to the diagnosis of autoimmune hepatitis. She was cured by steroid.【Conclusion】There were various types of hepatic injury in the course of immunosuppressive therapy to the HCV or HBV positive case. We must analyze the etiology to individualized situation case by case.

W52-1

QFT test in RA patients---influence of treatment

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Conflict of interest: Yes

[Objectives] At the treatment of rheumatoid arthritis using MTX and biologics, tubercular screening is necessary for in the use. Although QFT test is recommended with diagnostic imaging, there may be the influence of the drugs and autoimmunity. [Methods] In the 100 patients with rheumatoid arthritis under medical treatment with informed consent, the QFT tests were performed, and the positive ratio of QFT and the relation of the treatment. [Results] In 100 patients (23 men, 77 women, an average of 59.2 years old of age), 81 patients were taking biologics, 71 patients were taking MTX, seven patients were taking calcineurin blockers. In eight patients, QFT test was positive, in nine case judgment suspension, and in 80 patients negative, and judgment impossible were 3 examples. The positive ratio of QFT was high in the male, the chest X-ray abnormalities, and the patients of INH prevention use, and it was low in a steroid, MTX, and the example of biologics use. In the multivariate analysis, QFT test was statistically positive in the cases of INH use and a chest X-ray abnormalities, and was statistically negative in a steroid and biologics use. [Conclusion] In a steroid and a biologics use case the QFT test may present false negative in patients with rheumatoid arthritis.

W52-2

The avaliability of QuantiFERON^{R} (QFT) and T-SPOT^{R} for tuberculosis screening in the patients of rheumatoid arthritis (RA) in our hospital

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Conflict of interest: None

[Objectives] Tuberculosis screening is necessary before using methotrexate (MTX) in RA patients. We performed both QFT and T-SPOT for screening tuberculosis in the patients and studied the backgrounds of those with positive of QFT and/or T-SPOT. [Methods] 124 patients with RA were performed both QFT and T-SPOT, and studied the backgrounds of those with either QFT or T-SPOT were positive. [Results] Of 124 persons, 7 (5.6%) were positive (4 in both, 1 in QFT, 2 in T-SPOT). 8 (6.5%) were judged by indeterminate results in QFT, and 2 (1.6%) were in T-SPOT, T-SPOT is significantly lower than QFT ($p<0.005$). Of the positive patients, 4 were performed tuberculin reactions previously, and 2 with positive results were given the isoniazid (INH) preventive therapy. And 4 were using biologic products, and 6 were using MTX. [Conclusion] This finding indicates that QFT and/or T-SPOT is useful for screening tuberculosis, and T-SPOT is less frequent in indeterminate results significantly.

W52-3

Serological assay by use of glycopeptidolipid (GPL) core antigen for *Mycobacterium avium*-complex pulmonary disease (MAC-PD) and risk factors for MAC-PD in patients with rheumatoid arthritis

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Conflict of interest: None

[Objectives] To investigate an usefulness of serum IgA antibodies (Abs) to *Mycobacterium avium*-cpmplex (MAC)-specific glycopeptidolipid (GPL) core antigen as a diagnostic procedure for MAC-pulmonary disease (PD) and identify risk factors for developing MAC-PD in patients with rheumatoid arhtritis (RA). [Methods] Anti-GPL Abs was measued in 398 RA patients. Extent of lung disease by CT image was scored. Diagnosis of MAC-PD was made according to the guidlines of the Jananese Society for Tuberculosis. Backgroud factors were compared between with and without MAC-PD. [Results] Serum anti-GPL Abs were detected in 22 patients, and 11 out of the 22 patients were diagnosed with MAC-PD. Five were diagnosed with MAC-PD in 376 anti-GPL Abs negative- patients. Specificity and sensitivity of the assay were 97% and 69%, respectively. A positive correlation between the extent of lung disease and the Abs level was noted. Older, less lymphocyte counts, presence of chronic pulmonary comorbidity, decreased BMI and use of oral prednisolone were significantly associated with development of MAC-PD. [Conclusion] This cross-sectional study indicates the anti-GPL Abs is useful for daignostic procedure for MAC-PD in RA patients. We identified risk factors of MAC-PD in RA patients as described above.

W52-4

Risk of nontuberculous mycobacterial pulmonary disease assessed with measuring anti-MAC (*Mycobacterium avium complex*) antibody in patients with rheumatoid arthritis

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Conflict of interest: None

[Objectives] Biologics therapies in RA patients with pulumonary NTM should not be administered. The incidence of positive sputum culture of MAC was low, and it is difficult to discriminate the bronchiectasis from RA or NTM infections. The usefulness of serum IgA antibody to glycopeptidolipid (GPL) core antigen, which is serological test for the specific antigen of MAC, has been reported. [Methods] We selected 40 RA patients (mean age 67 years, disease duration 10 years) with CT findings suspected MAC-PD, such as multiple nodules and bronchiectasis. The patients included 39 nodular /bronchiectatic type and 1 fibrocavitary type. Twenty-five patients received MTX and 20 received biologics. We investigated the serum levels of anti-MAC antibody, and assessed safety of therapy. [Results] Positive MAC antibody titer (³ 0.7 IU/ml: cutoff value) was found in 7 patients. Nnegative (<0.5 IU/ml) result was shown in 27 patients. According to diagnostic criteria (2008), MAC-PD was diagnosed in 8 patients, and 4 (50%) of them were positive antibody titer. Three of 7 recognized positive MAC titer were administerd biologics, and 1 was exacerbated pulmonary MAC. [Conclusion] Referred from the result of the anti-MAC antibody, the decision of theraputeic strategy of RA with MAC-PD may be ultilized.

W52-5

Clinical study of non-tuberculous mycobacterial infection (NTM) complicated with rheumatic diseases

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Conflict of interest: None

[Objectives] To evaluate the complication of NTM in patients with rheumatic diseases retrospectively. [Methods] We analyzed the clinical data of 30 patients with rheumatic diseases (RA 25, polymyositis 4, SLE 2 and systemic sclerosis 1) complicated with NTM, we had experienced for the last 20 years. [Results] Among 30 patients, 6 male and 24 female, the mean age was 66.9 years old, the mean duration of rheumatic diseases before the onset of NTM was 19.8 years. 23 cases were treated with corticosteroids, less than 10mg/day in all. The immunosuppressant was used in 14 cases; MTX in 10 cases, LFM in 2 and TAC and MZR in one each. *M.intracellulare* was 14, *M.avium* was 9 and *M.kansasii* was 5 cases. The infected lesions were localized in the lung in 25 cases, but 3 cases had pleurisy and one was affected knee joint, one case was pleurisy without pulmonary lesion. 21 cases were treated with antibiotics and two case were required surgery. 2 cases had aortic aneurysm which was supposed the relevance of NTM infection. [Conclusion] NTM is an important complication in the patients with rheumatic diseases included RA, especially with long duration and in the elderly. It was said that extra-pulmonary lesions were rare unlike tuberculosis in NTM, but there are some cases with pleurisy or arthritis.

W52-6

A case of Hemophagocytic Syndrome caused by *Mycobacterium avium complex* in a patient with Relapsing Polychondritis

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Conflict of interest: None

A 54 year-old male diagnosed with relapsing polychondritis (RP) three years ago presented to our hospital complaining of a high-grade fever lasting for more than two months and systemic lymphadenopathy. The patient had been treated with prednisolone and cyclosporine in his clinical courses. The laboratory data showed pancytopenia, liver impairment, hyperferritinemia, and the high levels of inflammatory markers. Bone marrow examination revealed hemophagocytosis sporadically. Treatment with methylprednisolone pulse was initiated, assuming hemophagocytic syndrome (HPS), but the fever continued. We performed a biopsy of supraclavicular lymph node and the result was lymphadenitis with detected numerous acid fact bacilli in the necrotic lesion by the Ziehl-Neelsen stain. The PCR of *Mycobacterium intracellulare* was positive in all the sights of lymph node, blood, and bone marrow. The patient was diagnosed HPS caused by disseminated *Mycobacterium avium complex* (MAC) infection. Following treatment with clarithromycin, ethanbutol, and rifampicin, the clinical symptoms and the laboratory data were gradually improved. In a case of presenting HPS in patient with immunosuppressive treatment, MAC infection is rare but should be included into the differential diagnosis.

W53-1

The causes of death in deceased patients with RA registreated in NinJa 2012 cohort

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Conflict of interest: None

[Objectives] The purpose of the present study is to evaluate the age at death and the cause of death in patients with rheumatoid arthritis (RA) in 2012 [Methods] 100 Japanese deceased patients with RA, who were registered in the large cohort database (NinJa: National Database of Rheumatic Diseases by iR-net in Japan). We investigated the age at death, the causes of death of all patients. [Results] The mean age at death was 73.5years old. The major cause of death in deceased patients was infection in 30 patients involving in pneumonia in 18 patients. Next was respiratory dysfunction involving intestinal pneumonia in 21 patients, malignancy in 18 patients, cardiovascular disease in 9 patients. [Conclusion] The major causes of death were still infection involving in bacterial or viral or pneumonia, opportunistic infection. But the trend of this year is the increase cause of death is intestinal pneumonia.

W53-2

Male-female differences about the causes of death in deceased Japanese patients with RA using NinJa cohort

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Conflict of interest: None

[Objectives] The purpose of the present study is to evaluate male-female differences of the causes of death in deceased Japanese patients with RA using NinJa cohort [Methods] 617 Japanese deceased patients with RA, who were registered in the large cohort databasefrom 2002 to 2012. We investigated the age at death, the causes of death of all patients in order to review male-female differences [Results] The male and female mean age at RA onset was 58.8 years old and 53.9 years old, respectively. The male and female mean age at death was 72.9 and 72.7, respectively.

The major cause of death in deceased male patients was malignancy (25%), bacterial or viral pneumonia (21%), respiratory dysfunction involving intestinal pneumonia (15%), cardiovascular disease (13%), infection except pneumonia (9.2%). The major cause of death in deceased female patients was infection except pneumonia (17.5%), malignancy (17.3%), bacterial or viral pneumonia (15%), respiratory dysfunction involving intestinal pneumonia (14%), cardiovascular disease (13%), cerebrovascular accident (7.3%). [Conclusion] The male age at RA onset is 5 years older than female because of increasing in elderly onset RA. But the male and female age at death is same. Female RA had poor prognosis.

W53-3

Change in physical function and prognostic factors in early rheumatoid arthritis patients in the national database of rheumatic diseases in Japan−mHAQ after 5 years more improved in 2007 than in 2004−

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Conflict of interest: Yes

[Objectives] To ascertain the effect of recent change in treatment of rheumatoid arthritis (RA) on the transition of physical function. [Methods] In the large observational database of NinJa (National database of rheumatic diseases by iR-net in Japan), 354 RA patients having disease duration ≦2 years and mHAQ>0 at baseline (2004 or 2007), and having records of mHAQ after 5 years were analyzed. The differences in the 5 years' change in mHAQ and factors were evaluated between baselines. Correlates with ΔmHAQ were evaluated by Spearman's rank correlation coefficients, and factors that raised mHAQ in 1 point after 5 years were ascertained by multiple logistic regression. [Results] ΔmHAQ was significantly lower in 2007 (P=0.04). At baseline, the dose of MTX and the rate of the early use of biologics (within 2 years from onset) were higher in 2007. Stage≧II, mHAQ, and early use of biologics significantly correlated with ΔmHAQ (r_s=0.14, −0.52, −0.11 respectively). In the multivariate analysis, early use of biologics significantly inhibited deterioration of ΔmHAQ (adjusted OR=0.34), and Stage≧II was seemed to raise ΔmHAQ (adjusted OR=1.88). [Conclusion] Among early RA patients, 5 years' change in mHAQ was more improved in recent year, and early use of biologics was a factor of the improvement.

W53-4

Changes in disease activity and physical function in patients with rheumatoid arthritis in 10 years of follow-up and factors affect on long term outcomes; analysis of IORRA cohort

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Conflict of interest: None

[Objectives] To investigate changes in disease activity and physical function in patients with rheumatoid arthritis (RA) in 10 years of follow-up in two groups of patient with different disease duration. [Methods] Patients with disease duration less than 2 years (Group A) and between 10 to 12 years (Group B) at the survey of IORRA in April or October 2002 were extracted. Changes in disease activity and physical function were assessed and risk factors for lost-to follow-up were analyzed by Cox regression model. [Results] Group A; 336 patients, female 77.7%, 55.3 years old. Group B; 575 patients, female 81.3%, 58.4 years old. DAS28 gradually decreased from 3.8±1.3 to 2.8±1.0 in Group A and from 3.9±1.3 to 3.0±1.1 in Group B. J-HAQ gradually improved from 0.63±0.64 to 0.40±0.54 in Group A, whereas J-HAQ remained unchanged in Group B (from 0.80±0.75 to 0.81±0.82). The risk factors associated to lost-to follow-up were older age (HR 1.02, p<0.001 in group A, HR 1.03, p<0.001 in Group B), and baseline J-HAQ=0 in Group A (HR 1.52, p<0.05) and J-HAQ>1.25 in Group B (HR 1.55, p<0.01) compared to 0<J-HAQ≦0.5. [Conclusion] Physical function of patients with longer disease duration was hard to recover. Effects of physical dysfunction is need to be considered in evaluating long term outcomes in RA.

W53-5

The QOL-score survey using EQ-5D-5L questionnaire among RA patient within The Japan Rheumatism Friendship Association

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Conflict of interest: Yes

【Objective】To measure RA patients' QOL score, using EQ-5D-5L questionnaires and assessing relationships between QOL score and disease activity / monetary expenses.【Method】Questionnaires were sent to members of JRFA. QOL scores (1.0: full health, 0.0: death) were measured via EQ-5D-5L and 3L questionnaires. Provisional tariff was used for converting 5L answers to QOL scores. Relationship between QOL scores and disease activity (mHAQ) and monetary expenses (medical, caregiving and others) were also analysed.【Results】684 fulfilled the questionnaire. QOL scores measured by 5L and 3L were 0.621±0.172, 0.644±0.180 (Mean±SD), respectively, and strongly correlated (r=0.839). Numbers of those who are scored "1.0 (full health) were 34 (4.9%) in 5L and 84 (12.4%) in 3L, which implied that 5L could mitigate "ceiling effect". mHAQ score was strongly correlated with 5L score (r=0.812). mHAQ score classified by 5L score (<0.5, 0.5-0.6, 0.6-0.7, 0.7-0.8 and 0.8<) were 1.83, 0.93, 0.39, 0.12 and 0.10, respectively. Monetary expenses got higher as QOL score decreased (p<0.05). According to multivariate regression, in which age, sex and mHAQ were adopted as coefficient, only mHAQ was statistically significant (β=-0.19).【Conclusion】EQ-5D-5L is useful for assessing QOL scores for RA patients.

W53-6

Evaluation of the Japanese patients with rheumatoid arthritis (RA) of rapid radiographic progression (RRP) treated with synthetic disease modifying anti-rheumatic drugs (DMARDs) in daily practice: A large-scale prospective longitudinal cohort study

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Conflict of interest: None

[Objectives] We are conducting a large-scale prospective study to investigate extent of radiographic progression in DMARDs-treated RA patients. [Methods] Nine hundred forty-two RA patients treated by synthetic DMARDs at entry were registered between May 09 and March 12. Regarding to the RA patients having DAS28-ESR at entry >3.2 or radiographic bone erosion treated by synthetic DMARDs for 1 year, three hundred ninety-two patients had evaluable data at present. DAS28 was assessed every 3 months. Radiographs of the hands and feet were taken every 6 months. RRP was defined as yearly progression of mTSS >3.0. [Results] RRP was found in 42 out of 392 patients. Fourteen variables including gender, age, disease duration, DAS28-ESR/CRP at baseline, time-integrated DAS28-ESR/CRP during 1 year, ESR and CRP at baseline, presence of autoantibodies, the introduction of MTX, the use of prednisolone, HAQ and mTSS at baseline were evaluated to explore the development of RRP at 1 year. Logistic regression analysis has found that female gender, high time-integrated DAS28-ESR/CRP and high ESR/CRP at baseline are independent variables to predict the development of RRP. [Conclusion] The accumulated disease activity appeared to be most involved in RRP. Therefore, tight disease control is needed in daily clini-

cal practice.

W54-1

Genetic architecture of Rheumatoid Arthritis Contribute to Novel Biological Insights and Drug Discovery

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Conflict of interest: None

[Objectives] We demonstrate a strategy to integrate genetic risk variants of rheumatoid arthritis (RA) with diverse genomic and biological datasets to provide insight into drug discovery. **[Methods]** We performed a trans-ethnic genome-wide association study in >100,000 subjects. We integrated RA risk loci with: functional annotation of SNPs; cell-specific eQTL analysis; pleiotropy analysis; Mendelian disease or cancer genes; epigenetic histone peaks and pathways. We evaluated connections of RA risk genes to target genes for approved RA drugs. **[Results]** We discovered 42 novel RA risk loci, bringing the total to 101 ($P < 5x10^{-8}$). These loci revealed: ethnically shared genetic architecture; many risk alleles altering gene expression; two-thirds of loci had pleiotropy on other human complex traits; overlap with genes of human primary immunodeficiency and hematological cancer somatic mutations; specific cell types (T_{reg} cells) and novel molecular pathways that contribute to RA pathogenesis. RA risk genes were significantly enriched in overlap with target genes of approved RA therapies, suggesting that overlapped drugs approved for other indications may be repurposed for RA. **[Conclusion]** Our study provides empirical evidence that the genetics of RA can contribute to drug discovery.

W54-2

The limited effects of smoking and shared epitope on the production of ACPA and RF in a Japanese adult population: The Nagahama Study

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Conflict of interest: None

[Objectives] To evaluate positivity of anti-citrullinated peptide antibody (ACPA) and rheumatoid factor (RF) in a general Japanese population and to detect correlates including genetic components for these autoantibody positivity. [Methods] ACPA and RF were quantified in 9,804 volunteers aged from 30 to 75. Logistic regression analyses were performed to evaluate the effects of candidates of correlates on the autoantibody positivity. Genome-wide association (GWA) study for the autoantibody positivity was performed using 394,239 SNPs for 3,170 subjects among the participants. HLA-DRB1 alleles were imputed based on the GWA data. [Results] 1.7% and 6.4% of subjects were positive for ACPA and RF, respectively, and the two showed a significant correlation ($p=2.0x10^{-23}$). Old age was associated with positivity of ACPA ($p=0.00062$). Sex, smoking, shared epitope (SE), and other candidates of correlates did not have significant effects on the positivity of ACPA or RF. Interaction between SE and smoking for the autoantibody positivity was not apparent. [Conclusion] ACPA and RF were suggested to share mechanisms even in healthy populations. Old age was associated with increasing ACPA positivity. Positivity of ACPA and RF was not associated with SE and smoking, either alone or in combination.

W54-3

Clinical application of the soluble lectin-like oxidized LDL receptor-1 (sLOX-1) in rheumatoid arthritis ~From bench to bedside~

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Conflict of interest: None

[Objectives] Previously, we have reported that levels of sLOX-1 (soluble Lectin-like oxidized LDL receptor 1) in the plasma of RA patients were significantly higher than those in healthy controls. Then, we investigated whether sLOX-1 levels are associated with RA disease activity or remission using a cohort study. [Methods] The study examined 278 RA patients in the cohort. Levels of sLOX-1 in plasma were measured by ELISA. To evaluate the correlation with sLOX-1, autoantibody status, DAS-ESR, SDAI, and Boolean-based remission were measured in all patients. [Results] The sLOX-1 levels in RF-positive or ACPA-positive RA were significantly higher than that in RF-negative or ACPA-negative RA. The sLOX-1 level in the patients with remission significantly lower than those with moderate disease activity. In the subgroup of patients who were not achieving Boolean-based remission, sLOX-1 level in RF-positive or ACPA-positive RA were significantly higher than that in RF-negative or ACPA-negative RA. [Conclusion] These results suggest that the sLOX-1 level in the patients who are not achieving remission, especially ACPA-positive RA, increase to reflect disease activity. Therefore, sLOX-1 levels may be useful to evaluate the therapeutic effects of the anti-cytokine therapies.

W54-4

A Comparison of clinical characteristic of sero-positive rheumatod arthritis (RA) patients with sero-negative RA patients by NinJa2012 data base in Japan

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Conflict of interest: None

[Objectives] To identify the clinical characteristics of sero-positive rheumatoid arthritis (RA) and sero-positive RA patients in NinJa 2012 registry in Japan. [Methods] Of 11940 patients registered in NinJa 2012, 3972 patients were classified into three groups by serological test, Group A: high-positive RF or high-positive ACPA, Group B: low-positive RF or low-positive ACPA, Group C: negative RF and negative ACPA. [Results] The age of onset of RA were 51.3 years old in Group A, 51.5 in Group B, and 57.0 in Group C, and the disease duration were 10.6 years, 9.6, and 6.6, respectively. The percentage of Steinbrocker stage classification group I and II was 59.3% in Group A, 66.2% in Group B, and 80.0% in Group C. Glucocorticoid was given to 41.6% of patients in Group A, 35.5% in Group B, and 35.1% in Group C, MTX was 66.2%, 59.6% and 57.2%, and Biologics was 26.5%, 19.2%, and 16.2%, respectively. The rate of achievement of DAS28 remission was 36.4% in Group A, 49.2% in Group B, and 51.8% in Group C. The percentage of the experience of

hospitalization during the year was 14.2% in Group A, 10.1% in Group B, and 9.0% in Group C. [Conclusion] In the group of high-positive RF or ACPA the disease activity may be higher than in sero-negative group in spite of more intensive treatment.

W54-5

***Porphyromonas gingivalis* infection exacerbated RA in mice model**

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Conflict of interest: None

[Objectives] *Porphyromonas gingivalis* (*Pg*) is a major periodontopathogenic bacteria. Citrullinated protein (CP) is one of the cause of Rheumatoid arthritis (RA). Recently, *Pg* infection has been reported to affect the onset of RA. Especially, CP generated by *Pg* might be related with RA. Therefore, we determined the effects of *Pg* infection in the enhancement of RA. [Methods] Human gingival fibroblast (HGF) lysates were incubated with *Pg* W83. Then, Western blotting was performed by using anti-citrulline antibody to detect CP. To determine the involvement of *Pg* infection in RA, model mice (SKG mice, CLEA Japan) were established by intraperitoneal injection of laminarin. Then, mice were divided into 4 groups [A) PBS injection, B) LA injection, C) *Pg*+LA injection, D) *Pg* injection]. Arthritis score was evaluated in those mice. Anti- CCP Ab and matrix metalloproteinase 3 (MMP-3) in serum were measured by ELISA. Osteoclast differentiation of mice bone marrow cells (BMCs) was examined. [Results] *Pg* W83 generated CP in HGF lysate. In group C, arthritis score was 3-fold increased compared to group B. Anti-CCP Ab and MMP-3 were highest in serum from group C. BMCs of group C showed highest osteoclastgenesis compared with the other groups. [Conclusion] *Pg* infection has potential for RA exacerbation.

W54-6

Intake of monounsaturated fatty acids might suppress the disease activity in patients with rheumatoid arthritis - TOMORROW Study-

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Conflict of interest: None

[Objectives] The relationship between nutrient intake and the disease activity of rheumatoid arthritis (RA) is often discussed. Monounsaturated fatty acids (MUFA) have been reported to have anti-inflammatory effect. Therefore, we studied the relationship of MUFA intake and RA patient disease activity in cohort (TOMORROW) study. [Methods] A total of 208 patients with RA and 205 age and gender matched healthy volunteers were included. The nutrient intake status was assessed with a brief-type self-administered diet history questionnaire (BDHQ). We assessed the relationships of MUFA intake, MUFA/saturated fatty acids (SFA) ratio, and disease activity. [Results] RA group showed significantly lower intake of MUFA than Control group ($P<0.01$). RA group with higher disease activity showed significant lower MUFA/SFA ($P<0.05$). There was a significant correlation between DAS28 and MUFA/SFA after age adjustment ($R=-0.228$, $P<0.01$). Logistic regression analysis showed high MUFA intake in RA group was extracted as a factor for being not higher disease activity (Odds: 0.51, 95%CI=0.25-1.02, $P=0.057$). The sequential change in DAS28 significantly correlated with MUFA/SFA ratio after age adjustment ($R=0.180$, $P=0.01$). [Conclusion] MUFA intake might have a suppressive effect on disease activity in RA patients.

W55-1

Association between Fcγ receptors and clinical parameters in rheumatoid arthritis

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Conflict of interest: None

[Objectives] We have previously reported that Fc gamma receptor (FcγR) IIIb (CD16b) polymorphisms are associated with infusion reaction in rheumatoid arthritis (RA) patients. However, the roles of FcγRs on monocytes in RA patients have not been fully elucidated. Aim of this study is to elucidate roles of FcγRs expressed on monocytes and determine their clinical significance in RA patients. [Methods] Heparinized venous blood was obtained from 48 RA patients and 12 HC. Surface expression of CD16, CD16b, CD32 and CD64 on CD14+ cells were measured by flow cytometry. Proportion of positive cells and mean fluorescence intensity (MFI) for each FcγR were calculated. They were analyzed in association with clinical parameters. [Results] Both proportions of CD16+ and CD16b+ cells on CD14+ monocytes were significantly increased in RA patients (18.7±8.0% and 8.5±6.5%) compared with HC (13.3±4.9% and 4.4±3.0%) ($p=0.025$ and $p=0.027$). CD64 MFI on CD14+ monocytes from RA patients (39.0±9.4) was significantly higher than that of HC (30.8±7.1) ($p=0.011$). Moreover, the expression level of CD64 was positively correlated with ACPA ($r=0.30$). [Conclusion] We found the expression of FcγRs were upregulated on CD14+ monocytes in RA patients. FcγRs may relate to inflammation and autoantibody production in RA.

W55-2

Comprehensive Immunoclinical Analysis of Rheumatoid Arthritis

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Conflict of interest: None

[Objectives] Immunological overview of rheumatoid arthritis (RA) and its relation to clinical heterogeneity have not yet been answered. Therefore, we performed a comprehensive analysis of clinical information, immune cells classification, and HLA-DRB1 genotyping. [Methods] Fifty RA patients and twenty-five healthy volunteers were included. We performed FACS subset classification and HLA-DR quantitation of CD4+ T cells, B cells, NK cells, Monocytes, and dendritic cells. We also analyzed clinical information and shared epitope (SE) positivity based on HLA-DRB1 genotyping. [Results] Positive correlations were observed between DAS28 and CD45RA-CXCR5-CCR6-CXCR3- cells ratio, RF and CD27high CD38high plasmablast ratio, and plasmablast and CD45RA-CXCR5+CCR6+CXCR3-(Tfh-Th17) cells ratios. New-onset untreated RA (NORA) patients showed increased plasmablast and Tfh-Th17 cells ratios. HLA-DRB1 expression on CD4+ T cells and NK cells was also increased in NORA patients. SE positive patients showed increased HLA-DR expression on B cells and monocytes. [Conclusion] These results suggest an association of CD45RA-CXCR5-CCR6-CXCR3- cells with disease activity, an association of plasmablast and Tfh-Th17 cells with autoantibody production, and reversible immunological changes in NORA.

W55-3

T-bet and RORγt co-expressed Th-17 cells positively correlates with the disease activity of rheumatoid arthritis

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Conflict of interest: None

[Objectives] To clarify the predominant subset in peripheral CD4+ T cells in the pathogenesis of rheumatoid arthritis (RA). [Methods] 1) CD4+ T cells were isolated from peripheral blood mononuclear cells by magnetic activated cell sorting in healthy subjects (HS) and patients with RA. 2) The cells were stimulated with anti-CD3 monoclonal antibody and anti-CD28 monoclonal antibody in vitro, and cytokine production and transcription factor expression were analyzed by flowcytometry. 3) We compared between HS and RA patients, and examined the relation of DAS28 which is a disease activity index of RA. [Results] 1) Expression of RORγt and production of interleukin-17 (IL-17) in peripheral CD4+ T cells were significantly higher in RA patients than HS ($P<0.01$, $P<0.05$). 2) Expression of T-bet was observed in RORγt+ CD4+ T cells, and the frequency of IL-17 producing cells were positively correlated with T-bet expression level in RA patients ($P<0.05$). 3) Frequency of IL-17 producing cells in CD4+ T cells were positively correlated with disease activity of RA, shown by DAS28 ($P<0.01$). [Conclusion] Our observations proposed the possibility that T-bet and RORγt co-expressed Th-17 cells might play an essential role in the pathogenesis in RA.

W55-4

Soluble Semaphorin 4D in Rheumatoid Arthritis

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Conflict of interest: None

Semaphorin 4D (Sema4D), which is a protein of the semaphorin family of guidance molecule, activates immune cells and inhibits osteoblast mediated bone formation. To elucidate the pathogenic role of Sema4D in rheumatoid arthritis (RA), we investigated the soluble Sema4D levels in sera and synovial fluid by ELISA. Surface Sema4D expression on cells from peripheral blood and synovial fluid was analyzed by FACS. Soluble Sema4D was increased in RA sera compared with sera from healthy individuals. In synovial fluid, the levels of soluble Sema4D were increased in RA compared with osteoarthritis. The levels of serum soluble Sema4D was correlated with disease activities of RA such as DAS28, CRP, rheumatoid factor, and urinary deoxypyridinoline. In addition, serum levels of soluble Sema4D were decreased after biologics treatments in RA patients. Interestingly, the cell surface expression levels of sema4D were not increased in PBMC and rather decreased in CD3+ cells in synovial fluid of RA patients. Collectively, these results not only indicate that the pathological roles of sema4D in RA, but also suggest that cell surface Sema4D might be a source of increased soluble Sema4D in RA synovium.

W55-5

Appropriate Hormone Replacement Therapy (HRT) Prevents the Occurrence of RA from Undifferentiated Arthritis in Peri-/Post-menopausal Women

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Conflict of interest: None

[Objectives] The pathophysiological mechanism of polyarthritis exhibiting consistently negative CRP levels has not been well understood. However, hormonal insufficiency has been considered an underlying mechanism for such undifferentiated polyarthritis. In this study, we have examined the clinical efficacy of hormone replacement therapy (HRT) for in preventing RA in peri-/post-menopausal females. [Methods] Among related 624 women, 226 patients were enrolled in this study, after excluding CTD, established RA, OA and so on. They were divided into 4 groups based on the presence or absence of RF and the use of HRT for 3 years. [Results] Subsequently, 3 of 30 patients treated with HRT and who were CRP (-) and RF (+) (Group I) at the time of entry, developed RA. On the other hand, 15 of 34 receiving no treatment and who were CRP (-) and RF (+), (Group II) developed RA. Moreover, 0 of 60 cases of HRT (+) and RF (-) patients developed RA. On the other hand, 2 of 102 cases of HRT (-) and RF (-) developed RA. The efficacy of HRT was evaluated by comparing the outcomes between Group I and II, using the Log-rank test. The chi-square value was 8.9 with P=0.00288. [Conclusion] These findings suggest that HRT is effective in preventing RA in peri-/post-menopausal women.

W55-6

A cross-sectional analysis of forefoot deformities in rheumatoid arthritis ~ KURAMA cohort~

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Conflict of interest: None

[Objectives] Forefoot is one of the most-frequently deformed joints in rheumatoid arthritis (RA). However, it is not well understood that the frequency, degree and effects on ADL of the forefoot deformities. We investigated the frequency and impact using the KURAMA cohort which was a large-scale cohort. [Methods] In the RA patients who enrolled in KURAMA cohort, we investigated 740 pairs of feet in 370 patients (average age; 62.9 years old, female ratio; 87.6%). We conducted a statistical evaluation about the association between radiographic index (hallux valgus angle, M1M2 angle, Larsen grade, dislocation of the MTP joint) and demographic data such as age, sex, duration of the disease, disease activity and the functuional index. [Results] In hallux valgus deformity, broad foot, Larsen grade and the dislocation, a significant correlation with duration of the disease ($p=0.003$) was found, but there were no correlations with age, sex, medication contents and the disease activity at the time of investigation. [Conclusion] It is considerably high in the frequency of the forefoot deformities in RA and correlates with duration of the disease.

W56-1

Analysis on Predictors for Clinical efficacies of Golimumab in Patients with Rheumatoid Arthritis: Ad-hoc analysis from GO-FORTH study (with MTX)

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Conflict of interest: Yes

[Objective] To assess the predictability using clinical data of baseline and 12 weeks after Golimumab (GLM) treatment on Japanese clinical trials (GO-FORTH) with rheumatoid arthritis (RA), to achieve clinical remission after 1 year. **[Methods]** The correlations between clinical remission (DAS28ESR<2.6) at 52 weeks and clinical data of baseline or 12 weeks after treatment were screened by logistic regression analysis (univariate analysis) using Akaike Information Criteria. Then, we estimated the value of predictive variable achieving clinical remission with 50% probability at 52 weeks. In order to evaluate the effect of GLM on clinical remission, we used dataset with only subjects who were assigned to active groups in all analyzes. **[Results]** As a predictor of baseline or 12 weeks, DAS28ESR that was correlated with clinical remission at 52 weeks was selected. DAS28ESR values of 50% achieved remission estimate in 50mg and 100mg group to achieve remission at 52 weeks were 5.11 (4.53-5.69/95%CI) and 4.63 (4.00-5.26/95%CI) at baseline, 3.18 (2.74-3.62/95%CI) and 3.14 (2.79-3.49/95%CI) at 12 weeks respectively.

[Conclusion] These results suggest that it is possible to predict clinical remission after 1 year by clinical data of baseline or 12 weeks after GLM treatment for RA patients despite of MTX.

W56-2

Study of the efficacy of golimumab and tocilizmab in rheumatoid arthritis with anti-Ro/SS-A antibody

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Conflict of interest: None

[Background] We reported that the presence of anti-Ro/SS-A antibody (anti-Ro) in rheumatoid arthritis (RA) patients might be related to the inefficacy and the discontinuation of infliximab compared to other TNF inhibitors. [Objectives] To study the difference in clinical response between anti-Ro-positive and -negative patients treated with golimumab (GLM) and tocilizmab (TCZ). [Methods] Thirty-six patients with GLM and 38 patients with TCZ were studied the efficacy. Clinical response according to DAS 28 EULAR response criteria at 24 and 48 weeks was compared between anti-Ro-positive and -negative patients. [Results] Anti-Ro was detected in 7 (19.4%) with GLM and in 10 (26.3%) with TCZ. The EULAR response of over moderate was no difference between anti-Ro-positive and -negative patients with both treatment at 24 and 48 weeks (24 weeks: 85. 7% vs. 70.4%; respectively, p=1.000, 100% vs. 89.3%, respectively, p=0.552, 48 weeks: 71.4% vs. 70.4%; respectively, p=1.000, 100% vs. 92.9%; respectively, p=1.000). Continuation rate in anti-Ro-positive patients was 74.4% and 90.0%, respectively. [Conclusion] There was no difference of the efficacy between anti-Ro-positive and -negative patients with both treatment. It was suggested that GLM was effective in patients with anti-Ro.

W56-3

Restart for sustaining remission of rheumatoid arthritis in use of etanercept -RESUME study-

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Conflict of interest: Yes

Objective In clinical practice, some of the patients with rheumatoid arthritis (RA) are obliged to stop receiving biologics due to the high cost. Flare of disease activity (DA) after discontinuation of etanercept (ETN) is of concern. We aimed to reveal efficacy of restart of ETN after discontinuation in lowDA (LDA). **Method** For 2 years from 2011 BIO-naïve RA patients in moderate or high DA (DAS28≧3.2) were enrolled (UMIN8164). After the administration of ETN (50mg/week), the dosage of ETN will be discontinued when LDA (DAS28<3.2) was achieved. If patients recur from LDA, same dose of ETN will be administered again by the observation of every 2 months. This strategy will be maintained for 2 years. **Result** Among 31 patients enrolled in this study ETN was not discontinued in 13 patients because of inadequate response of ETN and in 5 cases no flare of DA was observed. In remaining 13 cases (8 women) this strategy was maintained; average age 60 years, disease duration 5 years, mean dose of MTX 10mg/w, and mean follow-up period 20 months. All 13 cases of ETN re-administration in this strategy achieved Low DA in 3.7 months in average. **Conclusion** All patients in this strategy achieved Low DA in final follow up. Joint damage is to evaluate, however, LDA was at least achieved in low cost.

W56-4

The predictive factors for continuation of adalimumab for three years in patients with rheumatoid arthritis

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Conflict of interest: Yes

[Objectives] To find predictors to continue adalimumab (ADA) for 3 years in RA patients. [Methods] Data from multicenter study (TBCR) was used. 121 RA patients who start ADA from August 2008 to August 2009 were divided into two groups. One was the group in which ADA was continued over 3 years (3YG: 54 cases) and another was the group in which ADA was stopped before 3 years (SG: 67 cases). Baseline patients' characteristics and disease activity at 4w after ADA initiation were compared with each other. [Results] Drug retention rates were 63.2% at 12m, 56.1% at 24m and 47.8% at 36m. The reasons of stopping ADA were lack of efficacy in 56.7% and adverse events in 38.8%. Regarding to baseline characteristics, the rates of Class1 or 2, MTX use and bio-naïve were significantly high in 3YG compared with in SG. Regarding to baseline disease activity, VAS and ESR were lower in 3YG than in SG. All of examined parameters on disease activity at 4w were significantly lower in 3YG compared with SG. The predictive factors recommended from ROC analysis were CRP at 4w and DAS28 at 4w. [Conclusion] Although this study was based on low dose MTX usage, this study suggested that baseline patients' characteristics and early disease activity could be used as the predictors for long-term continuation of ADA.

W56-5

The 4-year effectiveness of long-term adalimumab treatment in rheumatoid arthritis in FRAB registry

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Conflict of interest: Yes

[Objectives] To examine effectiveness of the long-term adalimumab (ADA) treatment in patients with RA from 4-year data of FRAB registry, and to assess predictive factors for clinical remission achievement at 4 years. [Methods] One hundred and nineteen patients who passed a follow-up period of 4 years were enrolled. LOCF was used for clinical outcomes of disease activity, drug survival rate and clinical remission rate. Patient characteristics and clinical responses at 3 months were analyzed for predictive factors for the remission achievement after 4 years. [Results] A mean DAS28-CRP scoredecreased from 4.5 at baseline to 2.7 at 4 years. Clinical remission rate was 42.4% at 4 years. Concomitant MTX group showed a statistically significantly higher effectiveness, as measured by EULAR response and drug survival rate. The biologics naïve group a showed higher clinical remission rate. A multiple regression analysis showed that DAS28-CRP at 3 months was a predictive factor for clinical remission achievement at 4 years. ROC analysis indicated that the cut-off point of DAS28-CRP at 3 months was 2.6. [Conclusion] Efficacy of ADA was maintained for 4 years. Given DAS28-CRP score decrease to 2.6 at 3 months, these patients will achieve clinical remission at 4 years.

W56-6

Evaluation of discontinuing adalimumab therapy due to the efficacy and safety in RA patients

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Conflict of interest: None

[Objectives] We evaluated reasons for discontinuing adalimumab (ADA) therapy in RA patients in daily practice. [Methods] 476 RA patients were reviewed for ADA therapy using the TBCR study results. Kaplan–Meier curves were generated to estimate the continuation rate and probabilities for therapy discontinuation, and results for different baseline characteristics were compared using the log rank test and Cox regression. [Results] After 4 years, the continuation rate of ADA therapy was 52%. 111 patients who discontinued ADA because of ineffectiveness, 57 patients discontinued because of secondary loss of efficacy. Lack of efficacy were significantly frequent with no MTX use than with MTX use, with Switched than with Naïve. Targeting the ineffective example, baseline high DAS score was a significant risk factor (hazard ratio 1.4, $p < 0.01$). 69 patients discontinued ADA therapy because of safety issues. The rate of incidence of discontinuation due to safety issues (100 person-years) were blood disorders 0.54, infectious diseases 2.7, tuberculosis 0.40, PCP 0.13, organizing pneumonia 0.27, interstitial pneumonia 0.40, skin disorders 2.0, liver failure 0.40, malignant lymphoma 0.13, solid cancer 0.27. [Conclusion] ADA discontinuation due to secondary loss of efficacy occurred linearly.

W57-1

Tofacitinib facilitates expansion of myeloid-derived suppressor cells and ameliorates arthritis in SKG mice

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Conflict of interest: None

[Objectives] Myeloid-derived suppressor cells (MDSCs) are a heterogenous population of cells that have an ability to suppress T cell responses. The aim of this study was to evaluate the effects of tofacitinib on MDSCs in a mouse model of rheumatoid arthritis. [Methods] Arthritis was induced in SKG mice by zymosan A injection. For adoptive transfer experiments, isolated MDSCs from the bone marrow (BM) of arthritic SKG mice were administered to arthritic mice. Tofacitinib was administered subcutaneously via osmotic pump. For a depletion assay, anti-Gr1 mAb was injected to mice treated with tofacitinib. BM cells were incubated in GM-CSF, with or without tofacitinib and the percentage of MDSCs was evaluated. [Results] Total and polymorphonuclear (PMN) MDSCs in spleen were significantly increased in mice. Adoptive transfer of MDSCs reduced arthritis compared to control. Significantly higher number of total and PMN MDSCs in BM was observed in tofacitinib-treated group. Furthermore, administration of anti-Gr1 mAb exacerbated the arthritis of tofacitinib-treated mice. Tofacitinib facilitated the differentiation of MDSCs and inhibited the differentiation of DCs *in vitro*. [Conclusion] Tofacitinib facilitates expansion of MDSCs both *in vivo* and *in vitro*, and ameliorates arthritis in SKG mice.

W57-2

Systemic inflammation in the PD-1 deficiency T-bet transgenic mice through to decreased Foxp3 Treg cells

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Conflict of interest: None

[Objectives] To clarify the role of programmed cell death-1 (PD-1) in the differentiation of $CD4^+$ T cells. [Methods] PD-1 deficient T-bet transgenic mice (P/T) were generated by crossing T cell specific T-bet transgenic mice with PD-1 deficient mice. 1) The growth and body weight were examined in P/T mice. 2) The pathological evaluation of several organs was performed. 3) Cytokine production and transcription factor expression in $CD4^+$ T cells isolated from spleen were analyzed by FACS. 4) $CD4^+$ T cells were cultured in the condition in favor of $Foxp3^+$ regulatory T cells (Treg) differentiation and they were analyzed by FACS. 5) Splenocytes were transferred into Rag-2 KO mice. [Results] 1) P/T mice showed growth retardation and died within 10 weeks. 2) Histological examination revealed the infiltration of mononuclear cells in several organs. 3) FACS analysis showed high production of IFN-g and significant reduction of Foxp3 expression in $CD4^+$ T cells in P/T mice. 4) $CD4^+$ T cells did not differentiate to $Foxp3^+$ Tregs in P/T mice. 5) Mononuclear cells in various organs were observed in Rag-2 KO mice transferred with the splenocytes of P/T mice. [Conclusion] Systemic inflammation and short-life span in P/T mice might be induced by the augmented Th1 response and the reduced $Foxp3^+$ Treg cells.

W57-3

AT-rich interactive domain-containing protein 5a functions as a negative regulator of RORγt-induced Th17 cell differentiation

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Conflict of interest: None

[Objectives] Pro-inflammatory cytokine IL-6 is implicated in the pathogenesis of rheumatoid arthritis (RA), and the blockade of IL-6 signaling by an anti-IL-6 receptor antibody, Tocilizumab (TCZ), provides clinical benefits for RA patients. This study aimed to clarify the mechanisms underlying the efficacy of IL-6 blockade for RA. [Methods] We examined gene expression profiles of $CD4^+$ T cells by DNA microarray analysis before and after the treatment with TCZ in responder patients. We then examined the roles of a newly identified molecule whose expression was significantly reduced by TCZ therapy in helper T cell differentiation by using murine $CD4^+$ T cells. [Results] We identified AT-rich interactive domain-containing protein 5a (ARID5A) as a new molecule downregulated by TCZ therapy. IL-6 induced the expression of ARID5A in $CD4^+$ T cells during Th17 cell differentiation by a Stat3-dependent mechanism, whereas IL-6-induced ARID5A expression was not affected by the absence of RORγt, a lineage-specifying transcription factor of Th17 cells. Furthermore, ARID5A physically associated with RORγt and inhibited RORγt-induced Th17 cell differentiation. [Conclusion] ARID5A is a lineage-specific attenuator of Th17 cell differentiation and may be involved in the pathogenesis of RA.

W57-4

A non-synonymous SNP of PDLIM4, a negative regulator of STAT3 transcription factor, is associated with susceptibility of rheumatoid arthritis

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Conflict of interest: None

The differentiation of Interleukin 17-producing T helper (Th17) cells is tightly regulated, otherwise exaggerated Th17 responses causes autoimmune diseases, including rheumatoid arthritis. STAT3 is a key tran-

scription factor for Th17 cell development. It, however, remains unclear how Th17 cell response is negatively controlled. We have demonstrated that PDLIM4 (PDZ and LIM domain protein-4) bound to STAT3 and negatively regulated Th17 cell differentiation. PDLIM4 associated with and recruited to PTPBL, a protein tyrosine phosphatase, through LIM domain, and facilitated dephosphorylation of tyrosine residue of STAT3, thereby suppressing STAT3 signaling. We further found that a single nucleotide polymorphism (SNP) of PDLIM4 is associated with rheumatoid arthritis susceptibility (rs4877; odds ratio 1.13, P=0.0041). This SNP, found at 30% in Japanese population, causes the substitution of a glycine residue in the LIM domain into cysteine. Interestingly, PDLIM4 mutant containing this amino acid substitution in the LIM domain revealed reduced binding to PTPBL, and therefore partially impaired to dephosphorylate STAT3 and suppress STAT3 signaling. These data delineate an essential role of PDLIM4 to prevent the onset of human autoimmune diseases by negatively Th17 cell differentiation.

W57-5

Role of adhesion molecules on synovial fibroblasts for cytokine production from CD4$^+$T cells

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Conflict of interest: Yes

[Objectives] To study the role of adhesion molecules on synovial fibloblast (FLS) in regulating cytokine production from CD4$^+$T cells. [Methods] We cultured naïve CD4$^+$T cells from healthy donors with or without FLS or skin-fibrolast, stimulated them with anti-CD3/28 in the presence or absence of transwell plate or anti-ICAM-1 or VCAM-1 antibody. Cytokine production from CD4$^+$T cells was assessed by ELISA or intracellular staining. In some experiments, CD4$^+$T cell alone were stimulated by anti-CD3/28 and plate-bound recombinant ICAM-1 or VCAM-1. [Results] Both FLS and skin-fibroblasts enhanced cytokine production (IFN-γ, IL-17, IL-2, and TNF-α) from anti-CD3/28 stimulated CD4$^+$T cells which was inhibited by transwell plate or anti-ICAM-1/VCAM-1 antibody. Notably, IL-17 production was observed with FLS but not skin-fibroblast. FLS expressed both ICAM-1 and VCAM-1, while skin-fibroblast expressed ICAM-1 alone. Plate-bound recombinant ICAM-1 enhanced the production of IFN-γ from anti-CD3/28 stimulated CD4$^+$T cells, while plate-bound VCAM-1 enhanced the production of both IFN-γ and IL-17. [Conclusion] ICAM-1 expressed both on FLS and skin-fibroblast promoted IFN-γ but not IL-17 production, while VCAM-1 specifically expressed on FLS promoted both IFN-γ and IL-17 production from naïve CD4$^+$T cells.

W57-6

Histone acetylation is associated with IL-6 overproduction in rheumatoid arthritis synovial fibroblasts

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Conflict of interest: None

[Objectives] There are growing numbers of reports showing epigenetic abnormalities in rheumatoid arthritis (RA), however, evidences of histone modifications are limited. High levels of histone acetylation (H3ac) and histone 3 lysine 4 trimethylation (H3K4me3) in promoter regions are related to increasing gene transcription. RA synovial fibroblasts (SFs) excessively produce interleukin (IL)-6. We investigated the relationship between histone modifications of the IL-6 and IL-6 overproduction in RASFs. [Methods] SFs from RA and osteoarthritis (OA) patients were harvested. H3ac and H3K4me3 of the IL-6 were analyzed by chromatin immunoprecipitation assay. IL-6 mRNA and protein levels after stimulation with tumor necrosis factor (TNF)-α were measured. H3ac of the IL-6, IL-6 mRNA and protein levels after treatment with curcumin, a histone acetyltransferase-inhibitor, in RASFs were analyzed. [Results] H3ac and H3K4me3of the IL-6 in RASFs were significantly elevated. IL-6 mRNA and protein levels after stimulation with TNF-α in RASFs were significantly increased more than in OASFs. Furthermore, curcumin treatment significantly reduced H3ac of the IL-6, IL-6 mRNA and protein levels in RASFs. [Conclusion] High levels of H3ac of IL-6 in RASFs could be involved in the pathogenesis of RA.

W58-1

Btk inhibitor ibrutinib suppresses osteoclastic bone resorption in vivo

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Conflict of interest: None

[Objectives] Rheumatoid arthritis (RA) is considered an inflammatory autoimmune disorder that causes the destruction of joints, and enhanced bone destruction by osteoclasts is observed in RA. We previously showed that Tec tyrosine kinases Btk and Tec are essential for osteoclast differentiation and the treatment with a Tec kinase inhibitor results in the protection from bone loss in mice. In this study, we analyzed effects of a novel Btk inhibitor ibrutinib on osteoclasts in vitro and in vivo. [Methods] Effects of ibrutinib on osteoclast differentiation and function were evaluated by in vitro assays, and therapuetic efficacy in mice with bone loss induced by RANKL injection was analyzed by microCT and bone histomorphometric analyses. [Results] Ibrutinib treatment suppresses osteoclastic bone resorption by inhibiting both osteoclast differentiation and function. In addition, oral administration of ibrutinib ameliorated the bone loss induced in a RANKL-injected mice. [Conclusion] A previous study suggested that ibrutinib ameliorates the inflammation and subsequent bone destruction in RA mouse models. The administration of ibrutinib, which targets immune cells and osteoclasts, is suggested to be an interesting new strategy for the treatment of RA.

W58-2

Dynamic visualization of RANKL-mediated vascular permeability in living bones by intravital multiphoton microscopy

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Conflict of interest: None

Bone tissue is highly vascularized and a large number of fenestrations in the vessel walls increase vascular permeability in this region. These unique features of bone are assumed to affect the migration of cells. For example, various kinds of hematopoietic cells are differentiated in bone marrow cavity and migrate to the peripheral tissues through the blood circulation. Controlling vascular permeability must be very important for the recruitment and egress of these cells. However, it remains unclear how vascular permeability is regulated in bone marrow *in vivo*. To answer this question, we utilized an advanced imaging system for visualizing living bone tissues with intravital multiphoton microscopy that we have originally developed. By means of this technique, we found that the vascular permeability in bone marrow cavity was much higher than in other tissues and that it could be variable in pathological conditions. We also found that RANKL, which is known as a key molecule for osteoclastogenesis, could also regulate the vascular permeability in bone marrow. Furthermore, the vascular permeability in bone marrow was associated

with the bone density. These novel approaches using intravital multiphoton microscopy are very useful for studying cellular dynamics in bone marrow *in vivo*.

W58-3

IL-6 accelerated calcification by induction of ROR2 in human adipose tissue-derived mesenchymal stem cellsin a STAT3-dependent manner

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Conflict of interest: Yes

(Purpose) Subcutaneous ectopic calcification is occasionally observed in inflammatory diseases such as Juvenile dermatomyositis and scleroderma. We investigated the involvement of inflammatory cytokines and human adipose tissue-derived mesenchymal stem cells (ADSC). (Methods) ADSC was differentiated by osteoblast induction medium in the presence of inflammatory cytokines (IL-6/sIL-6R, TNFα, IL-1β). (Results) Inflammatory cytokines accelerated calcification and expression of RUNX2. Among the cytokines IL-6/sIL-6R had the greatest effect. The ROR2 mRNA, involved in the non-canonical WNT pathway, was increased, while β-catenin expression, an essential factor in the canonical WNT signaling pathway for osteoblast differentiation, did not change. Suppression of STAT3, but not STAT1, by siRNA exerted a strong inhibitory effect on RUNX2 and ROR2 expression, and inhibited accelerated calcification. Finally, calcified cutaneous tissue obtained from a JDM patient showed positive staining with IL-6 and RUNX2 specific antibodies. (Conclusions) IL-6/sIL-6R stimulation induced ROR2 expression in ADSC in a STAT3-dependent manner, augmented calcification. These results suggest that the mechanisms of ectopic calcification accelerated by IL-6 in ADSC may be involved in chronic inflammatory tissues.

W58-4

A novel alveolar macrophage activation mechanism toward development of treatment for interstitial lung disease in connective tissue disease

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Conflict of interest: None

[Objectives] Interstitial lung disease (ILD) is a critical prognostic factor in patients with connective tissue disease (CTD). There has not been well-established therapy for ILD. Upregulated TNF-α from alveolar macrophage (AM) and accumulation of neutrophils (Neu) exacerbate neutrophilic alveolitis, thus anti-TNF therapy was expected. However, it's unlikely to be effective for SSc-ILD. Recently we found a novel mechanism of Mac activation depended on Neu-contact. IRAK-M is a negative regulator of the IL-1/TLR signaling, which is a main pathway leading Mac to activate and to produce TNF-α. IRAK-M has cleavage motifs by CASP. Thus, the aim is to determine if IRAK-M loses its function after cleavage by caspase after Neu-contact. [Methods & Results] In the Neu/Mac co-culture experiment we found that Neu-contact but not LPS, induces IRAK-M cleavage followed by TNF-a production. We performed in vitro cleavage assay using recombinant proteins. Then we found IRAK-M is substrate for CASP6. We developed CASP6 knock down Macs and IRAK-M mutant resistant to CASP6 to confirm the Neu contact dependent IRAK-M cleavage by CASP6. [Conclusion] IRAK-M and CASP6 plays critical role in AM activation in Neu -contact dependent manner. These molecules might be promising as a new target for ILD in CTD.

W58-5

Decreased MAIT cell frequency associated with reduced cell proliferation and enhanced cell death in systemic lupus erythematosus

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Conflict of interest: None

[Objectives] Mucosal-associated invariant T (MAIT) cells are restricted by MR1 and express a semi-invariant TCRα chain: Vα7.2-Jα33 in humans and Vα19-Jα33 in mice. As MAIT cells are suggested to play both proinflammatory and regulatory roles in autoimmune models, we sought to investigate whether MAIT cells are involved in the pathogenesis of systemic lupus erythematous (SLE). [Methods] MAIT cells were identified as $CD3^{+}\gamma\Delta TCR^{-}V\alpha7.2TCR^{+}CD161^{high}$ cells by FACS, and the expressions of molecules including CD95, CD45RA, CCR7, and active caspase-3 were assessed. The usage of Vα7.2-Jα33 TCR of single-cell sorted cells was analyzed by PCR. Cell proliferation upon TCR or cytokine stimulation was examined. [Results] The frequency of MAIT cells was reduced in SLE patients. Single-cell PCR analysis indicated that the decrease of MAIT cells in SLE was not due to downmodulation of surface markers. Lupus MAIT cells showed reduced proliferation and increased cell death. MAIT cells did not expand after repeated stimuli in vitro. The proportion of naïve cells among lupus MAIT cells was not increased. [Conclusion] This study indicated that enhanced cell death, reduced proliferation, and limited thymic emigration of MAIT cells may be responsible for the decreased frequency of lupus MAIT cells.

W58-6

Plasticity of T follicular helper cells and its pathogenic role in systemic lupus erythematosus

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Conflict of interest: None

[Objectives] T follicular helper (Tfh) cells are a new subset of T cells that regulate B cell function. However, the mechanisms that direct their specification and role in the pathogenesis of autoimmune diseases remain unclear. [Methods] Naïve $CD4^{+}$ T cells obtained from healthy donors were cultured with TCR stimulation and various cytokines. Cell surface markers, transcription factors, cytokines production and phosphorylation of STATs were assessed by flow cytometry. The proportion of helper T cell subsets in PBMC from 33 SLE patients and healthy donors were evaluated. [Results] Among various cytokines, IFN-γ induced $CXCR5^{+}CXCR3^{+}$ and Bcl-6^{+}T-bet^{+} (Tfh/Th1-like) cells. IL-12 and IFN-γ worked synergistically to induce the cells which produce IL-21 and IFN-γ via phosphorylation of both STAT1 and STAT4. The proportion of activated Th1 and Tfh cells increased and $CXCR5^{+}CXCR3^{+}$ Tfh/Th1-like cells has detected in SLE. The number of activated Tfh cells showed positive correlation with titers of anti-Sm, but no correlation with disease activity was observed. [Conclusion] The results argue the phenotypic heterogeneity between Tfh and Th1 cells, which is introduced by IFN-γ-STAT1 and IL-12-STAT4 pathways. Activation of flexible Tfh cells may be involved in the autoantibody production in SLE.

W59-1

Clinical features and outcomes of microscopic polyangiitis: 5-year experienceat a single center

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Conflict of interest: None

[Objectives] To determine the clinical features and outcomes of microscopic polyangiitis (MPA). [Methods] This retrospective observational study included 24 patients who were diagnosed with MPA according to the European Medicines Agency classification between January 2009 and August 2013 at Itabashi Chuo Medical Center, and who achieved remission after the first remission-induction therapy. [Results] The median age of the patients was 75.5 y, and the sex- ratio (M/F) was 0.5. Of the 24 patients, 15 were included in the study and 9 were excluded. Clinical fea-

tures included rapidly progressive glomerulonephritis (54.0%), interstitial pneumonia (41.0%), and mononeuritis multiplex (20.8%). Renal biopsies from 2 cases revealed pauci-immune crescentic glomerulo-nephritis. Plasma exchange was performed in 2 cases owing to pulmonary hemorrhage. Induction therapy comprised cyclophosphamide IV and corticosteroids. After induction therapy, complete remission was achieved in 80% of the patients. Additionally, 37.5% had cytomegalovirus (CMV) infection, and all were cured by antiviral therapy. The mean duration of CMV infection at the start of induction therapy was 6.7 mo. [Conclusion] We should keep in mind the possible occurrence of CMV infection even at the early stage of prednisolone therapy.

W59-2

Antineutrophil cytoplasmic antibody-associated vasculitis associated with systemic sclerosis in Japan: a review of the literature

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Conflict of interest: None

[Objectives] Cases of Antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) during the course of systemic sclerosis (SSc) have recently been reported. Japanese cases of AAV associated with SSc were collected from the literature, and the characteristics of patients in Japan were analyzed. [Methods] A literature review was performed using MEDLINE and the database of the Japan Medical Abstracts Society. A total of 61 cases were reviewed, including 58 cases from 42 reports (6 in English and 36 in Japanese) and 3 cases from our hospital. [Results] In SSc-associated AAV, the average age at onset was 57.0 years. In SSc-associated AAV, the male:female ratio was 1:9. In SSc, the proportions of the diffuse and the limited types were equal; anti-Scl-70 antibody was positive in 35 cases, and anti-centromere antibody was positive in 6 cases. The mean duration between diagnosis of SSc and AAV was 10.3 years (range, 1–41 years). In AAV, alveolar hemorrhage developed in 24%, and rapid progressive glomerulonephritis developed in 81%. On the other hand, neurological manifestations were less frequent in SSc-associated AAV (24%). No cases were positive for anti-PR3 antibody. Twelve cases died, and the most frequent cause of death was infection (7 cases).

W59-3

Fourteen cases of ANCA positive otitis media

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Conflict of interest: None

[Objectives] Although sensorineural hearing loss is one of the symptoms of Granulomatous polyangiitis (GPA), it is rare that physicians consider GPA from sensorineural hearing loss. [Methods] Fourteen patients (five males, nine females) with ANCA positive otitis media who were admitted to Niigata University Medical and Dental Hospital from 2010 through 2013 were recruited. [Results] Six patients were diagnosed as having GPA. Two were suspected having GPA. In six patients, ANCA associated vasculitis (AAV) was suspected. Some biopsies were tried in eight cases and histopathological findings of vasculitis were detected in four cases. The initial symptoms in 13 patients (93 %) were ears' one, such as congested feeling, impaired hearing, otalgia, or otorrhea. MPO- and PR3-ANCA were positive in 11 (79 %) and 3 cases (21 %), respectively. Hypertrophic pachymeningitis was observed in four cases (29 %). Otitis media was involved in bilateral ears in ten cases (71 %) and in unilateral in four cases (29 %). The periods from the onset to the measureing ANCA were 0.6 to 15 months (6.6 +/- 4.2 months, median 7 months). [Conclusion] Since sensorineural hearing loss is one of the initial symptoms of AAV, measuring ANCA should be considered in refractory otitis media.

W59-4

Successful steroid mono-therapy for pulmonary hemorrhage in ANCA associated vasculitis

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Conflict of interest: None

[Objectives] ANCA-associated vasculitis (AAV) is categorized based on the level of severity to assist treatment decisions. Alveolar hemorrhage is considered a severe disease, and a combination of glucocorticoids and cyclophosphamide (CPA) is recommended to achieve remission. However, CPA may be unfavorable in some cases because of its toxicity, especially in elderly patients. [Methods] Of 69 AAV patients admitted to our hospital during 2006–2012, we retrospectively analyzed 4 patients with alveolar hemorrhage. [Results] Three patients had MPA and one had EGPA. The mean age was 74.3±10.7 years, and the male to female ratio was 1:1. In addition to alveolar hemorrhage, 3 patients had nephritis, 3 had mononeuritis multiplex, and 2 had interstitial pneumonia. Alveolar hemorrhage was diagnosed based on CT results and rapidly progressing anemia in 3 cases, and on BALF examination in 1 case. Three patients received steroid pulse therapy; 2 of them received subsequent treatment with prednisone alone, and 1 received intravenous immunoglobulin. The patient who did not receive steroid pulse therapy underwent plasma exchange. All patients with alveolar hemorrhage achieved remission without CPA. [Conclusion] Elderly patients with pulmonary-renal syndrome can be treated successfully without CPA.

W59-5

Outcome of Patients with ANCA associated vasculitis with diffuse alveolar hemorrhage

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Conflict of interest: None

[Objectives] The mortality of patients with pulmonary vasculitis remains high. [Methods] We retrospectively reviewed the clinical records of patients with ANCA associated vasculitis (AAV) admitted to our hospital between January 1st 2008 and September 30th 2013, inclusive. We analyzed the age, CRP, Hb, disease activity (BVAS), and treatment in respect to outcomes. [Results] Sixty-seven patients were diagnosed with AAV (GPA17, MPA40, EGPA10) and 18 patients (25%) had diffuse alveolar hemorrhage (DAH). The average age was 65.4 years old (MPA 53.4, GPA71.4), and the sex ratio was 2:3. Other severe comorbidities were progressive glomerulonephritis (mortality 3/4), and interstitial pneumonia. (mortality 2/2) Eight patients died and six underwent remission maintenance therapy. The average BVAS was 19.38±4.31 in the deceased group, and 18.2±5.63 ($p= 0.68$) in the survival group. There was a significant difference in the average age of the survival and death group (survival group 47.2±29.19, death group 79.1±6.10, $P = 0.01$). All patients in the survival group were undergoing CY therapy. Patients who underwent combined steroid pulse, CY, and plasma exchange were able to undergo remission maintenance therapy. [Conclusion] The mortality of younger patients with DAH who underwent CY therapy is low.

W59-6

Four patterns of relapse in patients with MPO-ANCA positive EGPA

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Conflict of interest: None

[Objectives] EGPA (Eosinophilic granulomatosis with polyangiitis) have MPO-ANCA (Myeloperoxidase anti-neutrophil cytoplasmic antibody) in the about 50%. However, the context of the clinical findings and the titer of MPO-ANCA at the time of relapse is still unclear. Therefore, we have examined the relapse of MPO-ANCA -positive EGPA. [Meth-

ods] Thirteen patients with MPO-ANCA -positive EGPA (7 male and 6 female), who were admitted to Kyorin University Hospital from1998 to 2012. We analyzed the clinical findings and date at the time of relapse. [Results] i) There were 7 patients of relapse (54%), 13 times (three cases two times, one case four times). ii) The first relapse from the onset was 40 months. Only one case had non medication. iii) The relapse type was divided into four groups. Type I: MPO-ANCA positve and increase of eosinophi, Type II: MPO-ANCA positive and normaleosinophil, Type III: MPO-ANCA negative and increase of eosinophi, Type IV: MPO-ANCA negative and normal eosinophil. iv) The relapse frequency: Type I: 38.5%, Type II: 46.1, Type III: 7.7%, Type IV: 7.7%. v) Though the pathogenesis in Type III and IV was unknown, severe vasculitis were seen. [Conclusion] Relapse was observed in about the half in MPO-ANCA-positive EGPA. We should treat for MPO-ANCA-positive EGPAin consideration of four patterns.

W60-1

Clinical characteristics of patients diagnosed with anti-neutrophil cytoplasmic antibody-associated glomerulonephritis accompanied by immune complex deposits

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Conflict of interest: None

[Objectives] Anti-neutrophil cytoplasmic antibody-associated glomerulonephritis (ANCA-GN) is pathologically characterized as a pauci-immune type of necrotizing crescentic glomerulonephritis. Several earlier studies reported ANCA-GN was frequently accompanied by glomerular immune complex (IC) deposits. To clarify the clinical significance of the IC deposits, we conducted a comparative study involving ANCA-GN patients. ***[Methods]*** We retrospectively investigated 27 patients with rapidly progressive kidney impairment who were positive for serum ANCA with biopsy-proven necrotizing crescentic glomerulonephritis. Pathological and clinical data were compared between patients with and without IC deposits. ***[Results]*** In total, 30% patients exhibited glomerular IC deposits. Baseline kidney function and serum activity of ANCA vasculitis did not differ between groups, while massive proteinuria was detected in the patients with IC deposits. The estimated glomerular filtration rate (eGFR) was decreased in the patients with IC deposits over the 24 months after diagnosis. ***[Conclusion]*** Glomerular IC deposits were frequently detected in the patients with ANCA-GN in our study. The level of proteinuria and decrease in eGFR were exacerbated by the IC deposits, suggesting they may aggravate kidney dysfunction.

W60-2

Clinical characteristics of renal disease in patients with ANCA associated vasculitis

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Conflict of interest: None

To clarify the clinical features of renal disease in patients with ANCA associated vasculitis (AAV), we analyzed clinical, laboratory and immunologic manifestation of 80 patients in our hospital. The diagnosis of AAV according to Watts's algorithm revealed MPA in 51 patients, EGPA in 15 and GPA in 14. The patient's mean age were 64.4 years old and mean disease durations were 2.4 months. Laboratory data revealed positive test for MPO-ANCA and PR3-ANCA in 66 and 9 patients, respectively. All patients received oral corticosteroids. Twenty-four patients were treated with pulsed methylprednisolone, 40 patients with immunosuppressive agents. Forty-five patients showed renal disease. Renal biopsy revealed crescent glomerulonephritis in 14 patients and interstitial nephritis in one patient. Patients with renal disease showed significantly higher age, BVAS score and MPO-ANCA than those without renal disease. During the follow up, 8 patients with renal disease were died. There were no significant difference of clinical and laboratory manifestations between death and survival group. But, patients with high five-factor score (FFS) showed poor prognosis than those with low FFS. Our data indicated that early treatment with immunosuppressive agents should be initiated in patients with high FFS.

W60-3

An autopsy case of Eosinophilic Granulomatosis with Polyangitis accompanied by rapidly progressive glomerulonephritis and putaminal hemorrhage

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Conflict of interest: None

[Case] 78 -year-old man [Clinical History] From 5 years ago, the patient underwent medical treatment for chronic atrial fibrillation and bronchial asthma. From 2.5 months ago, clinical symptoms including fever, cough, and skin rash, accompanied by eosinophilia and Chest XP abnormality, which were non-responded to antibiotics, appeared. Steroid pulse therapy attenuated these findings, but kidney dysfunction gradually became apparent. From 0.5 months ago, hemodialysis therapy was started. Since MPO-ANCA positivity was detected, he was administered to steroid pulse therapy again. Four days later, putamen hemorrhage occurred, and he was dead next day. [Autopsy findings] Granulomatous vasculitis was detected in interlobular and arcuate arteries in kidney, and striatum artery in brain, as well as mediumsized afteries in various organs, suggesting diagnosis of Eosinophilic Granulomatosis with Polyangitis (EGPA). The direct cause of death was suspected to be putamen hemorrhage due to EGPA. [Clinical importance] It is reported that most cases of EGPA were controllable via steroid therapy from early phase, and that kidney and brain were less affected. We here report a rare severe case of EGPA accompanied by RPGN and putamen hemorrhage, and discuss about details of disease situation.

W60-4

Clinicopathological prognostic factor for the anti-glomerular basement membrane antibody glomerulonephritis

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Conflict of interest: None

【Objectives】Anti-glomerular basement membrane (GBM) antibodies induce serious vasculitis to kidneys and/or lungs. Although the Japanese guidelines for the rapidly progressive glomerulonephritis (RPGN) were published in 2002, RPGN cases with anti-GBM antibodies remain poor prognosis.【Methods】We investigated clinicopathological characteristics of ten patients who diagnosed as RPGN with anti-GBM antibodies at Kanazawa University Hospital and affiliated hospitals after 2002. 【Results】Five cases were female and five were men. Age; 61±13 years old, follow-up duration; 987±1143 days, urinary protein; 3.2±1.9 g/day, serum Cr; 5.6±5.5 mg/dL, CRP; 10.6±7.6 mg/dL, the titer of anti-GBM antibodies 120.6±103.1 EU. Nine out of ten cases were under dialysis within one month, and two died during follow-up period by pneumonia or gastrointestinal hemorrhage. Predonisolone (Starting dose was 44.5±11.7 mg/day) and 5.7±2.8 times of plasma exchange were used in all cases. The titer of anti-GBM antibodies decreased to 15.2±25.2 EU by the end of these therapies. Two cases with low ratio of crescent formation recovered from dialysis.【Conclusion】Anti-GBM glomerulonephritis cases with low ratio of crescent formation would have the potential to recover from dialysis.

W60-5

Efficacy of the biologics in Takayasu arteritis: multicenter results

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Conflict of interest: None

[Objectives] There have been several reports showing the efficacy of the biological agents in patients with Takayasu arteritis (TA), but no case series have been published in Japan. [Methods] We present the effectiveness of the biological agents in 9 TA patients by the e multicenter survey. [Results] All patients were women. The median age of diagnosis was 19 (range 16-35), and the median follow-up period was 26.4 months (7-53 months). Infliximab (IFX) was used in 8 cases, adalimumab (ADA) in 4, golimumab (GLM) in 2, and tocilizumab (TCZ) in 4. IFX was administered for as the first biologic agent in all cases; all patients went into remission, although 4 cases experienced relapse afterwards. GLM was administered to 2 patients 1st agent and 4th agent, both of them achieved remission. Three of 4 cases treated with TCZ and one case treated with ADA achieved remission. TCZ showed steroid-sparing effect. Seven cases discontinued biologics and changed to other agents, because of relapse (5 cases) and lack of efficacy (2 cases). No cases discontinued due to adverse event. [Conclusion] Biologics can be useful in refractory patients with TA.

W60-6

Prognostic factors of the patients with Takayasu arteritis

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Conflict of interest: None

[Objectives] To clarity the outcome and poor prognostic factors of the patients with Takayasu arteritis (TAK). [Methods] A total of 25 TAK patients visited our department from September 1992 to April 2013, were included in this retrospective study. End point was defined as death or revascularization procedures. Overall and event free survival curves were constructed by the Kaplan-Meier method. [Results] The mean age was 30.8 years old at the time of initial treatment and 28.2 years old at the time of presenting symptoms. Median duration of the disease was 102 (range 11-504) months. Five-year overall survival rate was 100% and five-year event free survival rate was 84%. One patient died due to sepsis at the 330 months from the time of initial treatment. Six patients required revascularization procedures, followed for a median of 178 (2-363) months. The average dose of prednisolone at the event was 5.7mg/day and there were no patients received immunosuppressive agents. Aortic regurgitation and hypertension were poor prognostic factors ($p = 0.01$ and $p < 0.05$, log-rank test, respectively). [Conclusion] Aortic regurgitation and hypertension at the time of diagnosis are risk factors of the subsequent revascularization procedures.

W61-1

2-year outcome date of plasma exchange therapy for pulmonary-renal syndrome in patients with ANCA-associated vasculitis

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Conflict of interest: None

[Objectives] This study aimed to report a 2-year outcome date of plasma exchange for pulmonary-renal syndrome (PRS) in patients with ANCA-associated vasculitis (AAV). [Methods] 8 patients with AAV accompanied with both diffuse alveolar hemorrhage (DAH) and sever renal injury, were entered in this study. Plasma exchange (PEX) was undertaken for the induction therapy. We had examined mortality, activity of disease and renal function for 2 years. [Results] ANCA and CRP were rapidly decreased after PEX. PEX resolved DAH within 1 month in all patients. 3 of 5 dialysis-dependent patients could leave from dialysis. Renal function did not decrease after induction therapy (Cr: 3.43 ± 3.43mg/dl at 6 months, 3.49 ± 2.88mg/dl at 24 months). 3 patients died for severe infection, difficulty of dialysis and pancreas carcinoma, respectively. While, no patients did not died for activity of the diseases. [Conclusion] Prompt PEX along with immunosuppressive therapy can soon resolve PRS, leading to prevent more worsening of organ involvements and control activity of the diseases for a long time.

W61-2

The change of peripheral blood neutrophil count before and after IVIg therapy for EGPA

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Conflict of interest: None

[Objectives] Intravenous immunoglobulin therapy (IVIg) is known to be effective for eosinophilic granulomatosis with polyangitiis (EGPA) with refractory neuropathy or cardiopathy. But its mechanism is not yet clarified. [Methods] The changes of laboratory data including peripheral blood neutrophil count before and after IVIg in EGPA patients who visited our hospital between 2006 and 2013 were examined. The changes of peripheral blood eosinophil count, and serum IgG and IgE levels were also examined. The data before and after IVIg were defined those observed within 2 days before, and those within 3 days after, respectively. [Results] 5 EGPA patients with refractory peripheral neuropathy (3 males and 2 females, aged 67.2±4.4) had 17 IVIg courses, totally. In all of the17 courses, IgG level showed increase, and neutrophil count showed decrease from before and after IVIg ($p<0.01$). A negative correlation was observed between IgG level and neutrophile count ($r=-0.6$, $p<0.01$). Neither eosinophil count nor IgE level showed no statistically significant difference between before and after IVIg. [Conclusion] The peripheral blood neutrophil count decreased significantly from before to after IVIg, and showed negative correlation with serum IgG level, during the course.

W61-3

Clinical usefulness of mycophenolate mofetil in patients with ANCA associated vasculitis

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Conflict of interest: None

[Objectives] The concomitant use of cyclophosphamide (CY) for remission induction and azathioprine (AZA) for the maintenance are recommended as a standard therapy for ANCA associated vasculitis (AAV). However these concomitant drug are sometimes difficult to continue if treatment failure or adverse effect. [Methods] We evaluated the clinical usefulness in 14 patients with AAV treated with mycophenolate mofetil (MMF). [Results] Three patients with granulomatosis with polyangiitis and 9 patients with microscopic polyangiitis were included; their average age was 65 years. Although 3 of 4 patients with refractory disease achieved remission, only 1 patient could maintain remission. The mean dosage of glucocorticoid (GC) in 10 patient with relapsing disease under previous treatment were 5.5 mg/day and their concomitant drug before

MMF were mizoribine (N=6), AZA (N=3), CY (N=1). All cases achieved second remission and 80% (8 /10) maintain remission for 1 year. Only 1 patient experienced second relapse and only 1 patient discontinued because of adverse effect. The mean dosages of GC were increased up to 13.5 mg/day at relapse but could be decreased to 5.9 mg/day after 1 year. [Conclusion] MMF may be useful as the second line concomitant drug for remission maintenance.

W61-4

B cell abnormality and efficacy of rituximab therapy in ANCA associated vasculitis

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Conflict of interest: None

[Background] B cell depletion by rituximab is effective treatment for ANCA associated vasculitis (AAV). However, the selection criteria for RTX remains unclear. **[Methods]** Circulating B cell subsets were defined by flow cytometry in 8 AAV patients (3 GPA, 2 MPA, and 2 EGPA). Based on the analysis, the patients were considered suitable to receive immunosuppressive drugs or RTX. **[Results]** There were 4 male and 4 female patients analyzed, whose mean age was 62.9 years, and mean duration of disease was 22.9 months. All patients had organ involvements including upper and lower respiratory tract or nephropathy, and were treated with high dose steroids. The proportion of effector memory or class-switched memory B cells was increased in 4 patients, thereby treated with RTX (375mg/m2 once per week for four times) and all achieved in remission. Four patients without B cell abnormality received immunosuppressants (2 IVCY and 2 azathioprine): 3 patients achieved remission, but one died from alveolar hemorrhage. **[Conclusion]** The results suggested that RTX therapy is effective in AAV patients with abnormal B cell differentiation to effector memory B cells. The evaluation of B cell phenotype may serve to predict to the response to RTX therapy in AAV.

W61-5

Can We Treat Microscopic Polyangiitis with Corticosteroids alone?

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Conflict of interest: None

[Objectives] To investigate the remission rate and adverse events of induction therapy with or without cyclophosphamide for microscopic polyangiitis (MPA). **[Methods]** We evaluated 43 patients with MPA at Saitama Medical Center between January 2005 and August 2013. Twenty-four patients were treated with pulse cyclophosphamide (pCY) and prednisolone (PSL) (PSL-pCY group), 12 patients with only PSL (PSL group) and 7 patients with pulse steroid therapy and pCY (PST-pCY group). Disease activity was assessed by using BVAS, and the remission was defined as BVAS=0. **[Results]** The remission rate at 6/12 months was 95%/72% in PSL-pCY group, 82%/63% in PSL group and 83%/80% in PST-pCY group. Serious infection as adverse events was observed such as pneumocystis pneumonia (PCP) (n=1), cytomegalovirus (CMV) antigenemia (n=1) and herpes zoster (HZ) (n=3) in PSL-pCY group, CMV enteritis/pneumonia (n=1), PCP (n=1), bacterial pneumonia (n=1) and HZ (n=1) in PSL group and bacterial pneumonia (n=3), PCP (n=2), cellulitis (n=1) and CMV gastric ulcer (n=1) in PST-pCY group. **[Conclusion]** The remission rate of PSL group was lower than the other 2 groups with pCY and the highest remission rate at 12 months was obtained in PST-pCY group. However, adverse events were seen most frequently in PST-pCY group.

W61-6

Clinical characterization of glucocorticoid-resistant polymyalgia rheumatica

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Conflict of interest: Yes

[Objectives] Treatment with glucocorticoid (GC) is the preferred therapy for polymyalgia rheumatica (PMR), but some patients show poor responses to GC. This study was intended to compare clinical characteristics and therapeutic outcomes between GC responders and GC-resistant patients. [Methods] The subjects were all patients who had been diagnosed as having PMR at our hospital between October 2007 and October 2011. The GC responders were defined as patients who had achieved remission with 15 mg/day of GC and maintained remission for over a year. [Results] Fourteen out of 21 patients well responded to GC and achieved remission within 2-6 weeks. At the time of submission, these patients' disease activity was controlled with or without 2-5 mg/day of GC. Seven patients failed to achieve remission with GC. Their PMR activity scores, CRP levels, patient's pain assessment scores, and EUL scores at diagnosis were significantly higher compared with the GC responders. Methotrexate, salazosulfapyridine, and tocilizumab were effective for the GC-resistant patients. [Conclusion] In this cohort, 33% of PMR patients were GC-resistant and high disease activity at baseline was apparently associated with GC resistance. Guidelines for management of GC-resistant PMR are required.

W62-1

The effect of tocilizumab on preventing relapses of adult-onset Still's disease; a retrospective, single center study

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Conflict of interest: None

[Objectives] To investigate the effectiveness of tocilizumab (TCZ), an anti-interleukin-6 receptor monoclonal antibody, on preventing relapses of adult-onset Still's disease (AOSD). [Methods] Clinical data of 40 patients under regular follow up at our institute in June 2013, including 10 patients who used TCZ, were analyzed retrospectively. Relapse free rate was analyzed by Kaplan-Meier method. [Results] Median (interquartile range, IQR) age of disease onset was 39 (29-52) years old. Median (IQR) duration of disease in June 2013 was 86 (41-193) month. A total of 87 relapses were documented. Thirteen patients had not experienced any relapse. Ten patients with refractory or relapsing disease received 8 mg/kg TCZ every 2 to 4 week. After 6 months of TCZ treatment, median levels of C-reactive protein and ferritin were significantly decreased from 6.3 to 0.01 mg/dl and from 938 to 53 ng/ml, respectively. Eleven relapses were observed before using TCZ, and no relapse was observed after TCZ. Relapse free rate of the 10 patients after using TCZ was significantly better in the comparison with all the 40 patients at baseline (100% and 79% at 6 month, p=0.02). [Conclusion] TCZ might be effective not only on improving activity of AOSD but also on preventing relapses.

W62-2

Clinical significance of serum interleukin-18 level in the differential diagnosis of adult onset Still`s disease and malignant lymphoma complicated by hemophagocytic syndrome

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Conflict of interest: None

【Purpose】 Adult onset Still`s disease (AOSD) is an inflammatory

disease that is frequently associated with activation of macrophage and hemophagocytic syndrome (HPS). It has been suggested that various cytokines such as IL-18 and IL-6 are associated with the pathogenesis of AOSD. AOSD resembles HPS complicating malignant lymphoma (HPS/ML) in symptoms and laboratory data, and serum ferritin level is extremely elevated in both patients with AOSD and HPS/ML. So, It is difficult to differentiate these diseases. We evaluate the usefulness of serum IL-18 level to differentiate AOSD and HPS/ML.【Methods】9 patients with AOSD (1 with HPS) and 3 patients with ML (3 with HPS), admitted to our hospital between November 2011 and October 2013, were enrolled. AOSD were diagnosed according to Yamaguchi criteria. Serum concentration of CRP, LDH, ferritin, sIL-2R, IL-6 and IL-18 was determined in both AOSD and ML.【Results】Between AOSD and ML, serum concentrations of CRP, LDH, ferritin, sIL-2R and IL-6 were not significantly different. The serum IL-18 level in AOSD patients was significantly higher than that in ML patients (AOSD; 205344±48497pg/ml, ML; 3527±1942pg/ml p=0.0423).【Conclusion】The serum level of IL-18 is thought to be a useful marker for the differential diagnosis between AOSD and HPS/ML.

W62-3

Abacterial subcutaneous abscess of the anterior chest in a patient with SAPHO syndrome treated with tocilizumab: a comprehensive analysis of serum cytokine levels

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Conflict of interest: None

[Objectives] SAPHO syndrome is characterized by both cutaneous pustular lesions and osteoarticular manifestation. There are no case reports of SAPHO syndrome which was treated with tocilizumab (TCZ). We report here a case of SAPHO syndrome which developed abacterial subcutaneous abscess of the anterior chest after the first administration of TCZ. We also performed a comprehensive analysis of serum cytokine levels in the patient. [Case and Methods] The patient was a 78-year-old man with SAPHO syndrome. He has been suffered from recurrent painful swelling of the sternoclavicular joints and chronic renal failure due to type AA amyloidosis. TCZ was given at 8 mg/kg. However, after the 3 weeks after the first administration of TCZ, he presented with abacterial subcutaneous abscess of the anterior chest. Serum levels of 26 types of cytokines were measured by a bead-based multiplex assay. [Results] Serum levels of IL-6, G-CSF, MCP-1, IP-10 were found to be greatly higher in the patient compared with those of healthy controls (unit pg/ml; patient, controls; IL-6: 5472.5, <3.2; G-CSF: 889.4, 12.9±5.5; MCP-1: 3806.5, 606.0±56.2; IP-10: 130.8, 32.5±6.2). [Conclusion] Our patient further emphasizes the importance of recognizing the increases in serum IL-6 in patients receiving TCZ.

W62-4

Clinical Features and Treatment Results of Japanese Patients with SAPHO (synovitis-acne-pustulosis-hyperostosis-osteitis) Syndrome

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Conflict of interest: None

[Objectives and Methods] We investigated the clinical features and treatment results in 36 Japanese patients with SAPHO syndrome (M/F: 10/26) diagnosed and treated between 2003-2013. [Results] The avg. age at diagnosis was 53 y.o (16-74). The avg. FU period was 48 mo. Sternocostoclavicular hyperostosis was recognized in 32 cases (89%), spondylitis in 17 (47%). PPP and/or acne were seen in 31 cases (86%), Oral ulcer in 6 (17%). Most patients had intermittent attacks of pain and NSAIDs were needed in all cases. Oral PSL was used in 14 cases (39%). NSAIDs and/or PSL were effective for temporary pain-relief. SSZ was used in 16 cases and the pain-relief >50% was seen in 4 cases (25%). MTX was scarcely effective for pain-relief. In 2 refractory cases with severe spondylitis, adalimumab (ADA) was tried. Both cases showed immediate pain-relief and ADA was effective during at least 1 year. HLA typing in 30 cases showed the allele frequency of HLA-B27 was 0%. But the frequency of HLA-B61 was 27%, significantly higher than in healthy controls. [Conclusion] Mucosal lesions seem to be a rather frequent complication of SAPHO. The efficacy of DMARDs was limited. ADA was effective in refractory spondylitis. This study revealed HLA-B61 was significantly increased in Japanese patients with SAPHO.

W62-5

Clinical features of relapsing polycondritis in our hospital

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Conflict of interest: None

Relapsing polycondritis (RP) is a rare autoimmune disease characterized by the reccurrent inflammation of cartilage. we analized 10 cases with RP treated in our hospital. There were 3 males and 7 females, their average age of onset was 53 years old. The average time from onset to diagnosis was 21 months. Auticular condritis and arthritis were detected in all cases, scleritis in 5 cases, tracheal involvement in 4 cases, innar ear involvement in 2 cases. As for first therapy, corticosteroids were used to all cases except for one stable case, steroid pulse therapies were to 2 cases with optic neuritis or aseptic cephalomeningitis. Five cases were resistant to first therapy and additional therapies were given. Steroid pulse therapies were given to 3 cases, infliximab were to 2 cases, immunosuppressive drugs were to 4 cases (IVCY in 1, MTX in 2, CsA in 2). The antibodies against type II collagen were detected in 8 out of 9 cases, and the antibody titer correlated with the level of C-reactive protein. Behcet disease was complicated in 3 cases. All cases with Behcet disease were resistant to corticosteroid monotherapy and received additional therapy. The associated disease with RP correlated with outcomes. So we should pay attention to associated disease state with the treatment of RP.

W62-6

Clinical and dermatopathological findings in patients with relapsing polychondritis with cutaneous involvement

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Conflict of interest: None

[Objectives] Relapsing polychondritis (RP) is a rare inflammatory disorder of the cartilaginous structure, including ear, nose, and respiratory tract. Although about 35% of RP patients present skin manifestations, clinical feature of cutaneous involvement is poorly understood compared to other symptoms. We here present three cases of RP patients who involved various skin manifestations, and examine clinical and dermatopathological findings of RP. **Case1:** A 71-year-old man. He had been diagnosed with myelodysplastic syndromes (MDS). Erythema nodosum-like lesions of the limbs and pustules of the face were observed. Colchicine was effective. **Case2:** A 74-year-old man. He developed infiltrative erythemas of the face, neck and trunk. Minocycline was effective. **Case3:** A 78-year-old man. He had infiltrative erythemas of the neck, chest and limbs. Variety of skin manifestations were observed in patients with RP. Histopathological examination revealed that robust neutrophilic infiltration was observed in all cases, possibly relating the pathogenic roll of neutrophil in RP. Furthermore, MDS was co-present in one case and suspected in others. In the previous study, 91% of RP patients with MDS had skin manifestations. It should be noted to the underlying disease in RP with skin manifestations.

W63-1

Retrospective study for Japanese patients with reactive arthritis induced by intravesical BCG therapy for bladder cancer

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Conflict of interest: None

[Objectives] To evaluate clinical characteristics and prevalence of Japanese patients with reactive arthritis (ReA) induced by intravesical BCG therapy (iBCG) for bladder cancer. [Methods] The clinical symptoms, laboratory, and imaging findings of patients received iBCG (n=134) of bladder cancer (n=1054) in our hospital from March 1997 to October 2012 were retrospectively assessed. [Results] Of 134 patients received iBCG (age 71±10; M/F 95/39), 40 (30%), 41 (31%) and 59 (44%) presented fever, hematuria and painful urination, respectively. ReA and uveitis were revealed in 3/134 (2.2%), and conjunctivitis in 12/134 (8.9%). Moreover, 2 of 3 patients with ReA also had hepatic dysfuntion. All ReA were developed after 3-times of iBCG. Clinical, ultrasound and FDG-PET/CT findings of ReA showed asymmetric inflammatory changes in multiple joints. Laboratory exam showed high CRP and HLA-B27 (in 1 of 3 cases). All ReA patients were improved by prednisolone and isoniazid. [Conclusion] The incidence of ReA induced by iBCG in our study was almost equal or more than previous reports (0.5 to 1 %) from western countries. There were no common HLA typing as background in our study. We must investigate further cases of ReA induced by iBCG in order to elucidate its incidence, pathophysiology and mechanisms.

W63-2

Association between HLA-B27 and spinal involvement of PsA patients in Japanese

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Conflict of interest: None

The association between ankylosing spondylitis and HLA-B27has been well-established. However the association between psoriatic arthritis (PsA) and HLA-B27 has seldom been studied in Japanese. [Objectives] The aim of this study was to investigate the association between axial involvement and HLA-B27 in Japanese PsA patients. [Methods] The subjects of the study were fifty-six patients with PsA (35 males and 21 females) who underwent HLA-B haplotyping and spinal radiological examination. HLA-B haplotyping was performed by PCR-rSSO method. In this study, psoriatic spondylitis was defined as the presence of radiological sacroiliitis. [Results] In 56 PsA patients, two patients (3.6%) had HLA-B27. In 16 patients with spondylitis, one patient (6.3%) was HLA-B27 positive. In 40 patients without spondylitis, one patient (2.5%) was HLA-B27 positive. HLA-B27 positivity was higher than that in Japanese general population (0.3%), however, much lower than those in Caucasians or Han-Chinese. [Conclusion] It was suggested that HLA-B27 was associated with psoriatic spondylitis in Japanese, although the effect of HLA-B27 on the development of psoriatic spondylitis may be smaller than those in Caucasians and Han-Chinese.

W63-3

Efficacy of methotrexate and anti-TNF-α biological drugs treatment with active psoriatic arthritis patients

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Conflict of interest: None

[Objectives] The aim of this study was to assess the efficacy and safety of methotrexate and anti-TNF- α biological drugs treatment for active psoriatic arthritis patients. [Methods] We retrospectively investigated 44 cases who fulfilled CASPAR criteria. We assessed VAS score, PASI score, DAS28 (CRP), number of swollen joints (0-66), tender joints (0-68), mHAQ, CRP and MMP3 before treatment and week 24. [Results] 29 case were male and 15 cases were female with mean age of 50.3±13.2. 41 cases were plaque psoriasis and 3 cases were pustular psoriasis. Duration of psoriasis to onset of arthritis was 10.2±9.1 year. 20 cases had the affection of sacroiliac joints and spine, 14 cases had enthesitis. Before treatment, VAS was 54.5±23.8, PASI score was 15.5±10.3, DAS28 was 4.01±0.85, count of swollen joints was 5.56±4.81, count of tender joints was 4.08±3.79, mHAQ was 0.49±0.49, MMP3 was 146.5±161.5, CRP was 2.39±3.72. At week 24, VAS was 22.2±16.4, PASI was 3.97±4.96, DAS28 was 1.96±0.55, counts of swollen joints was 0.31±1.08, counts of tender joints was 0.48±0.92, mHAQ was 0.28±0.57, MMP3 was 83.5±91.5, CRP was 0.34±0.48. Reduction of disease activity was induced at week 24. [Conclusion] Our study demonstrated that methotrexate and anti-TNF- α biological drugs was effective for treatment of active PsA.

W63-4

Assessment of predictors for clinical relevance of anti TNF therapy in 26 Japanese ankylosing spondylitis patients

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Conflict of interest: None

[Objectives] To investigate the predictors related to clinical effect of TNF inhibitors in ankylosing spondylitis (AS) patients. [Methods] Enrolled were 26 AS patients who started Adalimumab (ADA) or Infliximab (IFX) from Mar 2006 to Jan 2013, followed for 24 weeks. Student's t-test was used to assess the improvement in BASDAI, BASFI, CRP, and ASAS20/40 from the baseline and data retrieved from weeks 2, 6, 12, and 24. [Results] Mean duration of illness was 12.1 years and mean age was 33.0 years in 26 patients treated with ADA (10 patients) and IFX (16 patients). HLA-B27 was positive in all 17 patients who were able to collect the record. Mean scores at baseline and week 24 were, BASDAI 1.95 and 0.47, BASFI 4.49 and 3.02, CRP 1.95 and 0.47, respectively and have shown significant improvement through 24 weeks. We then compared responder (15 patients) and non-responders (11 patients). The achievement of BASDI50 at week 12 was most likely to predict responders at week 24. The evaluation of clinical improvement at week 12 suggests a possibility to reevaluate the treatment goal and strategy at week 12. [Conclusion] Reevaluation of Anti TNF therapy in AS patients at 12 weeks may be beneficial for adjusting the treatment strategy.

W63-5

The survey of clinical condition and the treatment of CTD-PH in our facility

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Conflict of interest: None

Background: CTD-PH is important disease to control a prognosis. The choice of treatment for CTD-PH requires careful attention because the etiology of PH is various. Therefore we should understand clinical state of CTD-PH accurately. The CTD-PH is classified in one group in Dana point classification. However CTD-PH has the clinical feature in several groups. Therefore RHC is essential pathology when we choose

appropriate treatment. **Objectives:** We investigate the clinical feature and treatment for 17 cases that were suspected CTD-PH and performed RHC in our facility. **Methods:** We classified group 1 alone, group 2 alone, group 3 alone, group 1&2, group 2&3, group 1&3, group 1&2&3 and other by results of RHC, UCG, CT and PFT. We analyzed about the treatment and efficacy in each group. **Results:** Group 1, group 1&2, group 1&2&3 were 5, 5, 4, 3 cases respectively. At the point of underlying disease, MCTD was most frequent. As for treatment, ERA is used most frequently as the initial treatment. The combination therapy using two or three PVDs at the initial therapy was conducted in 3 cases. Immunosuppressive therapy in 70% non-SSc cases is strengthened. **Conclusions:** It is important to recognize the pathology of CTD-PH because the onset of it has various factors.

W63-6

Clinical feature of 78 pregnancy complicated with connective tissue disease in our institution

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Conflict of interest: None

[Objectives] We examine the relationship between preterm birth and abortion, LFD (light for dates), perinatal complication and change of disease activity or dose of corticosteroid in our facility. [Methods] We investigated 78 cases retrospectively; exacerbation of underlying disease, anti SS-A antibody, antiphospholipid antibody, preterm birth and abortion, neonatal birth weight, perinatal complication and dose of corticosteroid treatment. [Results] 9 cases among all cases were exacerbated underlying diseases, and 6 needed additional immunosuppressive treatment including corticosteroid pulse therapies. Positive anti SS-A antibody was found in 28 cases, but there was no complication related with its antibody. Positive antiphospholipid antibody revealed in 20 cases (5 cases was diagnosed of APS before). Among 20 cases, one had a preterm birth. Another one case had miscarriage repeatedly. There was no relationship between preterm birth (11 cases), LFD (7 cases) or perinatal complication (27 cases) and dose of corticosteroid. [Conclusion] In pregnancy complicated with CTD, preterm birth, LFD, perinatal complication is associated with the disease activity significantly. Therefore, we need to control the disease activity strictly during pregnancy and delivery.

W64-1

The clinical characteristics and the significance of anti-citrullinated-glucose-6-phospate isomerase (GPI) antibodies in patients with rheumatoid arthritis

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Conflict of interest: None

[Objectives] To clarify the clinical characteristics and the significance of anti-citrullinated GPI antibodies (Abs) in patients with RA. [Methods] 1) The levels of anti-CCG (cyclic citrullinated GPI peptide)-2, 4, 7 and CEP-1 Abs were measured before and after 6 month treatment with tocilizumab (n=45) or abatacept (n=28). The change in the Abs was compared with disease activity. 2) The expression of citrullinated protein in RA and OA synovium was examined by immunochemical staining using anti-modified citrulline Abs. 3) Anti-CCG-7 and CEP-1 Abs were purified from RA serum using peptide-affinity column. The deposition of anti-CCG-7 and CEP-1 Abs in RA and OA synovium was examined by immunofluorescence staining. [Results] 1) The mean levels of anti-CCG-4, 7 Abs decreased significantly after tocilizumab treatment. Correlation coefficient of Abs and the DAS-28 was high (0.615) in anti-CCG-7 Abs with abatacept treatment. 2) Citrullinated protein was specifically detected in the surface layer of RA synovium. 3) Affinity purified anti-CCG-7 and CEP-1 Abs were specifically deposited to RA synovium. [Conclusion] The change in anti-CCG Abs in RA patients might correlate with disease activity. Citrullinated proteins and anti-citrullinated GPI Abs were specifically deposited in rheumatoid synovium.

W64-2

Characterization of anti-moesin antibody in systemic lupus erythematosus

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Conflict of interest: None

【Objective】Moesin is a 78kDa intracellular protein, which plays an important role in the cytoskeleton formation or various signal pathways. The previous report showed that anti-moesin antibody (AMoA) was positive in about one-third in rheumatoid arthritis (RA), but not precisely investigated in systemic lupus erythematosus (SLE). We examined the frequency of AMoA in SLE and analyzed the clinical features compared with RA.【Methods】AMoA were detected by immunoblot analysis using full-length recombinant moesin protein for 236 patients with SLE, 125 with RA and 58 normal healthy controls. Then we examined autoantigenic epitopes recognized by AMoA-positive sera by ELISA with 23 overlapping moesin peptides.【Results】AMoA were positive in 9.7% of SLE and 7.2% of RA, whereas 1.7% of normal healthy control. AMoA titers were significantly higher in SLE than in RA for 14 moesin peptides ($P<0.05$), especially including the peptide inside the FERM subdomain C of moesin, which interacts with ICAM-2.【Conclusion】Although AMoA was found not only in sera from RA but also in SLE, the epitope reactivity by AMoA was significantly different.

W64-3

Anti-Melanoma Differentiation-Associated Gene 5 Autoantibody Titer is Associated with Efficacy of corticosteroid and Intermittent Intra-venous Cyclophosphamide and/or Cyclosporine A Combination Therapy for Rapidly Progressive Interstitial Lung Disease with Dermatomyositis

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Conflict of interest: None

[Objectives] To examine the relationship between anti-CADM-140/MDA5 antibody titer and efficacy of intermittent intra-venous cyclophosphamide and/or cyclosporine a combination therapy in patients with clinically amyopathic dermatomyositis (CADM) and rapidly progressive interstitial lung disease (RP-ILD). [Methods] 9 patients with CADM and RP-ILD positive for anti-CADM-140/MDA5 antibody were retrospectively evaluated for the associations between antibody titer and the change in high resolution computed tomography findings (alveolar and interstitial score proposed by Kazerooni et al) or outcome after treatment. [Results] The combination therapy was effective for seven of nine CADM and RP-ILD patients. The mean titer of antibody of these seven significantly decreased after treatment (135.4 units vs. 8.6 units, $P= 0.008$, cut-off level = ~15 unit). In parallel with the reduced antibody titer, respiratory symptoms improved and the mean alveolar score significantly decreased (3.4 vs. 2.4, $P= 0.009$), whereas no changes were seen in the mean interstitial score. [Conclusions] These results emphasize the clinical importance of using anti-CADM-140/MDA5 antibody to monitor disease activity of lung involvement and to evaluate the response to treatment in patients with DM and RP-ILD.

W64-4

Inhibitory serum autoantibodies to angiotensin converting enzyme 2 in patients with scleroderma or MCTD having pulmonary hypertension or digital necrosis

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Conflict of interest: None

[Backgrounds] We have reported serum autoantibodies to angiotensin converting enzyme 2 (ACE2) in patients with rheumatic diseases and pulmonary arterial hypertension (PAH) or digital necrosis. In this study, we estimated in vitro ACE2-inhibition by serum IgG from patients with MCTD or systemic sclerosis (SSc). [Methods] Serum IgG fraction was purified from 21 patients (pts) with MCTD or SSc including 8 vasculopathy pts (3 PAH, one SSc renal crisis, 4 digital necrosis), and 13 non-vasulopathy pts. ACE2 in vitro activity under co-incubation with 1 mcg IgG fraction was assayed using substrate Mca-APK-Dnp. Triplicate assay compared with control data was evaluated statistically by t-tests. [Results] Significant inhibition of ACE2 activity by IgG was shown in 5 (3 PAH, 2 digital necrosis) out of the 8 vasculopathy pts, which were 5-25% of the control activity in 4 pts. Anti-ACE2-ELISA titer was positive in 2/3 of PAH pts and 2/4 of digital necrosis pts. One SSc patient having the history of renal crisis seven years ago showed negative serum anti-ACE2-antibodies. None of the IgG fractions from 13 non-vasculopathy pts showed ACE2 inhibition. [Conclusion] Patients with constrictive vasuculopathy and SSc or MCTD have inhibitory serum autoantibodies to ACE2.

W64-5

Intestinal microbiota plays a critical role in the production of antinuclear antibodies in lymphopenia-induced autoimmunity

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Conflict of interest: None

[Objectives] Antinuclear autoantibodies (ANA) were observed in systemic autoimmune diseases but the mechanism of their production is unclear. Past studies showed lymphopenic transfer model mice, in which $CD4^+CD25^-$cells were transferred into athymic nude BALB/c mice, produced ANA and various organ-specific autoimmune diseases. We evaluate the production of autoantibodies in this model, in terms of lymphopenia-induced homeostatic proliferation (LIP), follicular helper T (T_{FH}) cells and the role of gut microbiota. [Methods] $CD4^+$T cells from wild-type BALB/c mice were adoptively transferred into BALB/c nude mice. Gut microbiota were depleted by orally administering broad-spectrum *antibiotics*. [Result] Transfer of $CD4^+CD25^-$cells resulted in the production of various patterns of ANA and organ-specific antibodies. Germinal center formation and IL-21-producing PD-1^+T_{FH} cells generated via LIP of transferred $CD4^+CD25^-$cells were observed. Depletion of gut microbiota resulted in the inhibition of LIP and LIP-induced T_{FH} differentiation, and the significant reduction of systemic and organ-specific antibodies. [Conclusion] The novel insight that intestinal microbiota plays a critical role in ANA production, would help to understand the immunopathogenesis of systemic autoimmune diseases.

W64-6

Specificity of autoantibodies in patients with rheumatologic inflammatory syndrome following mineral oil injections is similar to those in mice with adjuvant mineral oil-induced autoimmunity

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Conflict of interest: Yes

[Objectives] Intraperitoneal injection of pristane or adjuvant mineral oil in mice induces autoantibodies to U1RNP and Su/Argonaute2 (Ago2). Injection of mineral oil as a cosmetic procedure is common in Mexico and inflammatory syndrome in these subjects has been reported. In the present study, autoantibodies in patients who had mineral oil injection and inflammatory syndrome were examined. [Methods] Twenty-one cases of patients, who had mineral oil injections and developed rheumatologic symptoms were studied. Autoantibodies were tested by immunofluorescence antinuclear antibodies (ANA), immunoprecipitation (IP) and ELISA (Ro52, U1RNP-70kD). [Results] In ANA, 62% (13/21) were positive in nuclear (n=5), nucleolar (n=3), mitochondria-like (n=3), or GW bodies (n=2) pattern. One anti-U1RNP, 2 anti-Su and 3 anti-Ro60 by IP and 2 anti-Ro52 (ELISA) were found. Among these 6 cases (2 had more than one), a case with anti-Su+Ro52 had a diagnosis of SLE, however, other 5 cases had non-specific rheumatological symptoms only. [Conclusion] Patients with rheumatologic inflammatory syndrome after mineral oil injections have autoantibody specificity similar to those in mice with adjuvant mineral oil-induced autoimmunity (anti-U1RNP and Su/Ago2). In addition, they also developed anti-Ro60 and Ro52.

W65-1

Epidemiology of Adult Still's disease in Japan: A nationwide survey

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Conflict of interest: None

The objective of this study is to estimate the prevalence of adult Still's disease (ASD) in Japan, and to assess the clinical features and treatments of the patients. The Research Team for Autoimmune Diseases, the Research Program for Intractable Disease by the Ministry of Health, Labor and Welfare conducted primary and secondary surveys in 2010. The estimated number of ASD patients in Japan was 4,760 by the primary survey. The clinical data obtained from 169 ASD patients showed the mean age of patients was 46 years, and the male-female ratio was 1 to 2.6. The major clinical features were: spiking fever, typical rash and arthralgia. Hyperferritinaemia was shown in 89% of the patients. Ninety-six percent of the patients were treated with oral glucocorticoids. Forty percent and 26% of patients were treated with methotrexate (MTX) and cyclosporine, respectively. Incidence of relapse was lower in the patients who were treated with MTX (n=29) than those without (n=132) during induction therapy (21% vs 42%, OR 0.35, P=0.03). Biologic agents were used in 14% of ASD patients and 83% of them were treated with Tocilizumab (TCZ). TCZ showed efficacy in the maintenance therapy or for refractory cases. Treatment for decrease of remission rate in ASD patients were shown in this survay.

W65-2

Exploration of the physical function measures fitted for evaluating joint destruction in hands among patients with rheumatoid arthritis

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Conflict of interest: None

[Objectives] We aimed to identify useful physical function measures which reflect joint destruction in hands among patients with rheumatoid arthritis (RA). [Methods] Clinical data was collected from 44 RA patients. Scores of HAQ-DI, MHQ, and DASH were compared using Pearson's correlation analysis. Cutoff scores equivalent to HAQ=0.5, which is generally accepted as threshold for functional remission of RA, was calculated for MHQ and DASH through ROC analysis. Generalized linear analysis with Genant-modified sharp score (TSS) as an objective variable and HAQ-DI, MHQ, DASH, DAS28ESR, grip strength, and pinch strength as explanatory variables was conducted. [Results] Mean TSS was 42.3. The correlation coefficient was 0.96 for HAQ-DI vs MHQ, and 0.92 for HAQ-DI vs DASH, both of which showed significant relationships. The cutoff values equivalent to HAQ=0.5 was MHQ=48 and DASH=26. AUC, sensitivity, and specificity of them were 0.84, 88%, and 71% for MHQ and 0.98, 92%, and 100% for DASH. Analysis using generalized linear model showed that pinch strength was highly related to TSS. [Conclusion] DASH is a useful physical function measure reflecting joint destruction of hands among RA patients. Pinch strength has a potential to be an easy-to-use substitute for TSS.

W65-3

Study of associated factor of chronic kidney disease (CKD) onset in rheumatoid arthritis patients

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Conflict of interest: None

[Object] We investigated the possible factors associated with CKD progression in RA patients who are treated with steroid. [Method] We evaluated 43 non-diabetic RA patients treated with MTX or biologics in whom the doses of steroid were not changed for more than 6 months. Study period was three years between Sep 2010 and Sep 2013. Renal function was evaluated by eGFR and CKD was defined as stage G3a or more. First, we investigated the incidence of CKD and evaluated the possible factors influencing CKD progression. We also evaluated the factors associated with the rate of change for eGFR in the patients showing a decline of eGFR during the study period. [Result] The frequency of CKD at the end of the study was 23%, with 5 out of 10 showing newly onset CKD. Overall, the factor associated with CKD prevalence was the initial ESR. In these 5 cases, the initial and the final values of SDAI during the study were significantly higher than 5 cases that had shown CKD initially. Three years later, eGFR increased in 22, and decreased in 21 cases, respectively. In the latter group, the rate of change for eGFR showed a significant correlation with age, the initial ESR, and SDAI at the end of the study. [Conclusion] Age and the continued RA activity were associated the progression of CKD.

W65-4

The impact of disease activity, functional disability and joint damage on employment status and work impairment in rheumatoid arthritis

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Conflict of interest: Yes

[Objectives] This study is aimed to investigate how disease activity, functional disability and joint damage affect work impairment in rheumatoid arthritis (RA). [Methods] We chose the 370 of consecutive RA patients in our clinical cohort study and assessed clinical variables, disease activity, HAQ, mTSS, and work module of DASH score. [Results] The number of employees was 31.6%. DAS28 was 3.20+-1.18 in paid worker (PW), and 3.21+-1.15 in not-employee (NE). In the analysis of each parameter between PW and NE, it were significantly differences in age, disease duration, stage, class, HAQ-DI, ESR, and mTSS. There were associations between influence of working hours and HAQ-DI ($r=0.45$, $P<0.0001$), PtGA ($r=0.42$, $P<0.0001$), pain VAS ($r=0.42$, $P<0.0001$) and CDAI ($r=0.40$, $P<0.0001$). Moreover, there were associations between limitation of work and HAQ-DI ($r=0.51$, $P<0.0001$), PtGA ($r=0.41$, $P<0.0001$) and pain VAS ($r=0.46$, $P<0.0001$). [Conclusion] Disease activities of RA have not significantly difference between PW and NE. Age and disease duration, joint damage and functional disability related to employment status. In addition, functional disability, PtGA and pain VAS influenced working hours and contents.

W65-5

Longer disease duration predispose rheumatoid arthritis patients to serious adverse events during treatment with biologics; analyses from the REAL database

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Conflict of interest: Yes

[Objectives] To evaluate effect of disease duration on safety of biologics in patients with rheumatoid arthritis (RA). [Methods] We compared 301 RA patients with disease duration ≤2 years (E group, 638 patient-years [PY]) and 1092 patients with disease duration >2 years (L group, 2243 PY) in the REAL database. Types and incidence rates (IRs) of serious adverse events (SAEs) during 3 years were analyzed. [Results] The patients in the L group were significantly older, had more advanced Steinbrocker's stages and higher prevalence of pulmonary comorbidities (PC), and received significantly higher dosage of oral corticosteroids than those in the E group. The crude IR ratios (95% CI) comparing the L group with the E group for SAEs and serious infections (SIs) were 1.9 (1.4-2.6) and 2.2 (1.3-3.6), respectively. The Cox regression analysis showed that older age (by decade) (hazard ratio 1.3[1.2-1.5]), Stage III or IV (1.6[1.1-2.5]), and presence of PC (1.7[1.1-2.5]) were significant risk factors for SIs. [Conclusion] The higher IR of SIs in the patients with longer disease duration was associated with older age, advanced stage, and presence of PC. It is relevant to carefully consider the influence of these identified risk factors on the safety of biologics when we treat established RA patients.

W65-6

Analysis of risk factors for MTX-related lymphoproliferative disorder in patients with RA using IORRA cohort

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Conflict of interest: None

[Objective] To investigate risk factors for MTX-related lymphoproliferative disorder (MTX-LPD) in RA patients using a large observational cohort IORRA. [Methods] RA patients who self-reported lymphadenopathy in the IORRA survey in October 2012 were extracted, and the patients with lymphadenopathy during taking MTX confirmed by medical records were defined as MTX-LPD. For a control group, one case to ten controls matching with RA disease activity was used from RA patients

taking with MTX without lymphadenopathy (Nested case-control study). The hazard ratios (HRs) for MTX-LPD were calculated according to baseline clinical features and drug use as explanatory variables using multivariate analysis. [Results] Twenty-six patients with MTX-LPD were extracted (female: 73.1%, mean age: 62.2 years old, and mean disease duration: 13 years.). Multivariate analysis confirmed that male (HR: 3.20 [95%CI: 1.12-9.16]) was significant factor associated with MTX-LPD, however, age, RA disease duration, disability level, biologics use, steroid use, or MTX dose were not significant factors. [Conclusion] Male gender was significant risk factor for MTX-LPD in RA patients taking MTX, whereas neither concomitant MTX dose nor biologics use were risk factors.

W66-1

Orthopedic surgery for RA in NinJa report 2012

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Conflict of interest: None

[Objectives] Analyze/report RA-related orthopedic surgeries performed in ’12 using NinJa. [Methods] Presence or absence, type, frequency, etc. of surgeries examined in 11940 patients registered in ’12 (♀9632, ♂2308) & compared with ’03 to ’12. [Results] Of 11940 patients in ’12, 376 patients/452events (3.1%/3.8%) underwent RA surgeries. The number of RA surgery cases decreased from 8.5% in ‘03 to 3.8% in ‘12. In ’12, RA surgeries to total patient number ratios were (per type) 1.9% (artificial joint), 0.2% (synovectomy), 0.8% (arthroplasty), 0.4% (arthrodesis) & 0.2% (tendon repair). Medication: 62%, 24% and 0.4% of patients received total MTXs, total biologicals & total JAK inhibitors, respectively: an increase. In the main-Bio group, the rate of RA surgery peaked at 15% in ‘06 and decreased thereafter to 4.7% in ’12. In the main-MTX group, the rate of surgery also decreased from 9.5% in ‘03 to 3.5% in ‘12. Among patients receiving JAK, three surgeries had been performed. [Conclusion] Although the number of surgeries decreased with increasing use of drugs in the Bio and MTX groups, the rate of decrease was decreasing. We plan to continue to follow up on changes in surgery rates with the emergence of new drugs such as JAK. Follow up planned.

W66-2

Depression and anxiety in patients with rheumatoid arthritis: Analysis of NinJa 2012 database

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Conflict of interest: None

[Objectives] To analyze the disease rate and the factors of depression and anxiety in patients with rheumatoid arthritis (RA) with data from NinJa 2012 database. [Methods] We tested RA patients (Pts) registered in NinJa 2012 with the Hospital Anxiety and Depression Scale (HADS). A total of 4,458 Pts were analyzed. D group (DG) with more than 11 scores which suggest a probable case of depression and non-DG with less than 10 scores, and the variances of Pts’ clinical data were analyzed between two groups. [Results] DG included 415/4458 (9.3%), non-DG 4043/4458 (90.7%). Pts in DG were significantly higher age compared with non-DG Pts (64.6±12.6 vs 62.9±13.0 ys) and had longer disease duration (14.2±11.7 vs 12.4±10.9 years, $p<0.005$), higher disease activity (DAS28-CRP 3.1±1.2 vs 2.5±1.1, $p<0.001$), higher Pts’ global assessment (3.0±2.7 vs 2.5±2.2 cm, $p<0.001$), Pts’ pain assessment (3.8±2.7 vs 2.4±2.2 cm, $p<0.001$), and mHAQ (0.89±0.82 vs 0.41±0.60, $p<0.001$). Further, Pts in DG showed a higher progression stage of joint damage and class of functional impairment ($p<0.001$). [Conclusion] Pts with longer disease duration and higher progression of joint damage and functional impairment were considered to have higher rate of depression and the association between disease activity and pain and depression.

W66-3

The minimally important difference for EQ-5D in patients with rheumatoid arthritis: from a large observational study, IORRA

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Conflict of interest: None

[Objective] EuroQol 5-descriptive system (EQ-5D) is one of the most useful measures to evaluate quality of life (QOL). We analyzed IORRA cohort database to determine the minimally important difference (MID) for EQ-5D in patients with rheumatoid arthritis (RA) in daily clinical setting. [Methods] Data was analyzed for 4,847 patients with RA enrolled in IORRA of whom EQ-5D was available both in October, 2011 and in April, 2012. The MID was estimated by evaluating change in EQ-5D during six months and a 5-point Likert scale for their overall status in April, 2012. [Results] The MID for EQ-5D in patient who felt “somewhat improved” was 0.018. When stratified by baseline DAS28 with low, moderate and high disease activity, the MID were 0.017, 0.032 and 0.076, respectively. When stratified by baseline disease duration with < 2 years, 2-5 years, 5-10 years and 10years≧, the MID were 0.043, 0.022, 0.016, 0.014, respectively. When stratified by baseline J-HAQ with <0.5, 0.5-1.5, 1.5≧, the MID were 0.005, 0.027, 0.032, respectively. [Conclusions] The MID for EQ-5D in RA patients was 0.018 in daily clinical setting using IORRA cohort. The MID varies in concordance to patient background such as disease activity, disease duration and physical dysfunction.

W66-4

Changes in type of disease, treatment and course in SLE patients depending on time - from JUDE cohort study-

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Conflict of interest: None

[Objectives] We investigated changes depending on time, in types of diseases, course of treatment, and relapse among SLE patients, who have been followed up for more than 10 years since 1973. [Method] We have carried out JUDE cohort study on SLE patients. We have divided the patients into 3 groups: every 10 years from 1973. For relapse, we have used the SELENA-SLEDAI evaluation. [Result] The types of diseases at the time of onset include, fever, arthritis, rash, abnormal urinary findings, central nervous system abnormalities, which we found no difference in each group. However, increasing trend in cytopenia and serositis was observed. The treatments administered at the time of onset include, steroid pulse, IVCY, and when some oral immunosuppressive agent was used concurrently, increasing trend was observed. There was no difference in relapse ratio within 10 years. For disease types at the time of relapse, we found a decrease in abnormal urinary findings, and increases in central nervous system abnormalities and in cytopenia. [Conclusion] There were changes in disease types and treatment at the time of onset and relapse between those time groups. Although, frequency of use of immunosuppressive agents has increased, there was no change in relapse ratio within 10 years.

W66-5

The prevention of steroid-induced osteonecrosis of femoral head in systemic lupus erythematosus by warfarin and statins

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Conflict of interest: None

[Objectives] Osteonecrosis of femoral head (ONF) is a serious complication associated with corticosteroid therapy for SLE. We investigated whether the incidence of ONF can be reduced by the prophylactic use of warfarin and statin. [Methods] Warfarin and statins were administered for three months to patients with recently diagnosed SLE treated with 40mg or more prednisolone. Prophylaxis continued for three months, and the development of ONF was evaluated by MRI. [Results] Twenty-seven patients (Group Pr) accomplished prophylaxis, 34 patients (Group Pr1M) were given prophylaxis at least one month, and 12 patients (Group C) were not given prophylaxis. ONF development was observed at 19%, 24% and 42% in groups Pr, Pr1M, and C, respectively. And clinical ONF developed at 7%, 9%, and 25%, respectively. Seven patients discontinued warfarin because of cytopenia, liver dysfunction and hypermenorrhea. [Conclusion] Prophylactic use of warfarin and statins tended to reduce the incidence of ONF, although not statistically significant in patients with SLE.

W66-6

Axial Spondyloarthritis - imflammatory spinal pain, enthesitis and dactylitis - in Japanese

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Conflict of interest: None

[Objectives] We examined gravity of evaluation of imflammatoly spinal pain, polyenthesitis and ductilytis for diagnosis early spondyloarthritis (SpA) in Japanese patients. [Methods] In 300 outpatients developing musculoskeletal symptom of the rheumatology clinic in Osaka City University Hospital, symptoms of SpA described before and Anti-cyclic citrullinated peptide antibody (ACPA) were examined. [Results] Two patients developed imflammatoly spinal pain, polyenthesitis or ductilytis in 95 patients that showed positive of ACPA. On the other hand 88 patients developed these symptoms in 205 patients that showed negative of ACPA. [Conclusion] It is suggested that aggressive evaluation of imflammatoly spinal pain, polyenthesitis and ductilytis enables early diagnosis of axial SpA in ACPA negative patients.

W67-1

MRI classification type C and bilateral cases are prognostic factors for surgical intervention after steroid induced avascular necrosis of the femoral head

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Conflict of interest: None

[Objectives] We evaluated the prognostic value of the MRI classification in patients undergoing surgical intervention after avascular necrosis of the femoral head (AVN) associated with connective tissue disease in Japanese patients. [Methods] We applied the MRI classification (revised in 2001 by the Japanese Investigation Committee) in 150 AVN patients (222 hips). To define prognostic factors for future surgical intervention after AVN, Cochran-Armitage trend test and multivariate logistic regression analysis were performed. [Results] Regarding the MRI classification, 14 hips were type A, 54 hips were type B, 92 hips were type C1, and 62 hips were type C2. Among them, 0/14 hips, 6/54 hips, 32/92 hips and 42/62 hips had future surgical intervention, respectively for type A, B, C1 and C2 ($P<0.0001$ by trend test). The results of the multivariate logistic regression analysis indicate that types C1 and C2 of the MRI classification ($P=0.0010$) and bilateral cases ($P=0.0095$) were associated with future surgical intervention after AVN. [Conclusion] Type C (C1 and C2) on the MR imaging classification at the time of diagnosis of AVN and bilateral AVN cases are the risks for future surgical intervention after diagnosis of AVN.

W67-2

Spontaneous Osteonecrosis of the Knee in the early phase

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Conflict of interest: None

[Objectives] Spontaneous osteonecrosis of the knee (SPONK) is characterized by a painful lesion in the elder people, frequently leading to osteoarthritis and subsequent knee surgery. Our purpose is to evaluate the short-term prognosis of SPONK patient who visit to our hospital in the early phase (period from onset to our clinic visitation is within 3 months). **[Methods]** 17 patients (3M/14F, age 67.1±11.7 years) in the early phase SPONK were evaluated about their disease duration, Koshino-stage, lesion rate of the AP radiographic view of the condyle (lesion rate), treatment, and prognosis. **[Results]** 7 patients came within 2 weeks from the onset, 2 between 2w to 1m, 8 from 1m to 3m. Koshino-stage is I: 1, II: 14, III: 2, IV: 0. Conservative treatment with lateral wedge, weight bear restriction were applied to 10 patients (groop C). Arthroplastic surgeries were performed to 7 (groop S). Average lesion rate of groop C and S are 32.2 and 44.1 % individually. They are significantly different (t-test). **[Conclusion]** Lesion rate>40% is one of the cut off value to predict prognosis of the early phase SPONK.

W67-3

Component Impingement Measures in THA After Previous Intertrochanteric Valgus Osteotomy

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Conflict of interest: None

[Objectives] We utilize the S-ROM in THA after a previous intertrochanteric valgus osteotomy and we report on dislocation measures. [Methods] We studied 13 joints with hip osteoarthritis who underwent THA using the S-ROM after a previous intertrochanteric valgus osteotomy. The mean follow-up period after THA was 7 y. The mean age at THA was 57 y. Our clinical evaluation included calculating a JOA score and noting the postoperative complications. The component impingement measures examined the presence of version adjustments and the adjustment angle between the stem and proximal sleeve during the operation. We measured the cup abduction angle from the postoperative X-ray, the neck anteversion angle and the cup anteversion angle from the postoperative CT. [Results] The mean JOA score was 53 in the preoperative period and 80 at the follow up. There were no post-operative dislocations. Six joints had an adjusted version between the proximal sleeve and the stem during the operation, and all joints had a reduced version (mean, 30°). The mean cup abduction angle was 43°. The mean neck anteversion angle was 33° and the mean cup anteversion angle was 14°. [Conclusion] The S-ROM can be useful in cases that require adaption of the proximal femur after previous intertrochanteric valgus osteotomy.

W67-4

A case of alkaptonuric arthritis treated with total knee arthroplasty

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Conflict of interest: None

We report a case of alkaptonuric arthritis treated with total knee arthroplasty. The patient was 50-years-old woman who complained severe pain of the bilateral knee and dyabasia. She had the past of diabetes and the cervical myelopathy. Total knee arthroplasty carried out by the diagnosis of charcot's joint. The articulr cartilage and meniscus displayed black pigmentation. And homogentisic acid was detected by her urine. Therefore we diagnosed as arcaptonuria. Alcaptnuria is rare hereditary metabolic disorder that results from a deficiency of the enzyme homogentisic acid oxidase. A buildup of dark pigment in connective tissues such as cartilage and skin, is also characteristic of the disorder. People with alkaptonuria typically develop arthritis, particularly in the spine and large joints, beginning in early adulthood. In the late stage of arthritis, arthroplasty is undergone.

W67-5

A case of warfarin-induced hemarthrosis treated with intra-articular injection of tranexamic acid

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Conflict of interest: None

【Case】The case was 61 years old woman who had suffered from rheumatic fever in childhood and underwent artificial aortic and mitral valve replacement surgery, and pacemaker implantation at the age of 51. She suffered from hemorrhage of right knee while car driving and bleeding stopped after 3 days of warfarin cessation and rest. 3 months later, recurrent hemorrhage of her right knee appeared and admitted to our hospital. Hemorrhage of right knee continued after 3 days of warfarin cessation and rest, and next we performed selective angiography and arterial embolization of right knee. Bleeding stopped by this procedure and she discharged from the hospital. 5 days after the discharge, she re-admitted the hospital by the subcutaneous hemorrhage of her right thigh. After 3 days of warfarin cessation and 2 weeks of rest and cooling, the subcutaneous hemorrhage was relieved and rehabilitation has started. On the next day, recurrent hemorrhage of her right knee appeared and we performed intra-articular injection of tranexamic acid. Hemorrhage stopped and the patient has experienced no recurrence of hemarthrosis and no side effect after this procedure.【Discussion and Conclusion】Intra-articular injection of tranexamic acid may be effective and safe procedure for recurrent hemarthrosis.

W67-6

A case of lower leg palsy caused thoracic pseudotomor

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Conflict of interest: None

[Objectives] The medical treatment of rheumatoid arthritis shows the fast effect by MTX or biological products. But we must pay attention the possibility of the malignant lesion due to decreased immunity by MTX etc. We report a case which was caused paralysis to the lower body due to developed pseudotumor in the thoracic spine after long-term administration of MTX and the salazosulfapyridine (SASP) [Methods] Case. The patient is a 59-year-old male with RA for 7 years. When a sneeze was come out, back pain occurred and electricity ran distally from the knee. Range of numbness expanded to the peripheral from both groin, he soon fell into a complete paralysis of both legs. MRI and CT showed a tumor lesion with a focus on vertebral arch of Th8 that compressed the spinal cord. The pathological finding was the pseudotumor. Although he was under MTX16mg per week, and SASP1000mg per day then, these internal use was stopped [Results] [Conclusion] The numbness and perception of the abdomen began to reduce by medication of steroid and the stop of SASP and MTX, and soon paralysis of the leg gradually recovered. Neurological symptoms were markedly improved. After 4 weeks MRI showed a significant decrease of the pseudotumor. And CT showed ossification of vertebral arch.

W68-1

Concordance between joint symptoms and ultrasonography findings in patients with rheumatoid arthritis

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Conflict of interest: None

Objective: Recently ultrasonography (US) has been prevalent as a valid and objective modality of joint examination. As a result, accumulating findings of the association between joint US observations and physical examination of the joints or a composite measure of disease activity of rheumatoid arthritis (RA) have been available. The association between patient-reported joint symptoms and US findings at each joint level has been rarely investigated. Therefore, we have examined the concordance between joint symptoms and US findings. Methods: Twenty-five patients with RA (80% female, the mean age 66 years) were asked for the self-evaluation of joint symptoms including pain and considerable stiffness in PIP, MCP, wrist, elbow, shoulder, knee and ankle joints. Those joints were evaluated by US for the presence of synovitis defined as either GS≥2or PD≥1. Results: The overall concordance rate was low (κ coefficient = 0.37). The concordance rate was especially poor in small joints (PIP, MCP and wrist; κ=0.32), compared with large joints (shoulder, elbow, knee and ankle; κ=0.50). Conclusion: The concordance between patient-reported joint symptoms and US synovitis was poor, especially in small joints, suggesting the importance of complete joint examinations including asymptomatic joints.

W68-2

A study on prediction of remission maintenance and diagnosis of RA by joint ultrasonography

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Conflict of interest: None

[Objectives] To determine the therapeutic strategy and diagnosis of RA, composite measures and ACR / EULAR classification criteria are used, both is required for precise evaluation of joint findings. Accurate evaluation of articular findings is needed both. Joint ultrasound was to investigate whether allowing accurate diagnosis. By the enforcement of joint echo, or for accurate diagnosis? We did consider whether more predictable maintained for the case in the remission state. [Methods] I We went to a total of 1165 cases of the joint echo. In the 186 cases that made the joint echo evaluation during the initial visit, I examined the sensitivity of the ACR / EULAR classification criteria, the specificity. We examined the joint echo findings RA, in the non-RA patients. Also in remission, we examined the joint echo findings. In the ACR / EULAR classification criteria, specificity was 87.9% sensitivity is 81.6%. In 13.7 ± 14.7 in the RA group, the total GS score 3.1 ± 4.5 in the non-RA group at the first visit. PD total score 2.3 ± 3.9 in the non-RA group and 11.1 ± 11.2 in the RA group at the first visit [Conclusion] Were able to correctly diagnose by enforcing joint echo. And even in remission, showed an example that can not be maintained remission with a total score high PD cases.

W68-3

Ultrasonographic findings in first metatarsophalangeal joints in patients with gout

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Conflict of interest: None

[Objectives] To determine first metatarsophalangeal (MTP1) joint findings with ultrasonography (US) in patients with gout. [Methods] US was performed in patients with gout who visited our clinic for regular visits. Each patient was assessed for US findings such as crystal deposition, synovitis, and bone damage. [Results] Total of 125 patients (250

MTP1 joints) were evaluated. Crystal deposition was found in 122 joints (49%), of which 44 joints had no history of acute attack in the past. US synovitis was found in 39 joints (16%), and 37 out of 39 joints revealed no synovitis clinically. Bone damage was found in 88 joints (35%). Presence of bone damage was statistically correlated with history of clinical gouty attack and US-detected crystal deposition, respectively. [Conclusion] US can detect subclinical pathological findings in MTP1 joints.

W68-4

Quantitative evaluation of knee cartilage degeneration by T1ρ and T2 mapping (comparing rheumatoid arthritis and osteoarthritis)

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Conflict of interest: None

[Objectives] To study the cartilage degradation in rheumatoid arthritis (RA) and osteoarthritis (OA) we evaluated knee cartilage using T1rho and T2 MRI mapping. [Methods] Sagittal T1rho maps of the femorotibial joint were obtained in 26 patients with RA and OA. Four regions of interest (ROIs) were placed on images of the cartilage in the medial and lateral femoral condyle (MFC, LFC) and the medial and lateral tibia plateau (MTP, LTP). The T1rho and T2 values (ms) of each ROI were recorded and differences between RA and OA cartilage were evaluated. [Results] T1rho values of each condyle were similar between groups. The T2 values of MF C47.1 and LFC 49.1 in RA cartilage were significantly higher than those of MFC 41.4 and LFC 43.0 in OA cartilage. The T2 values of MTP and LTP were not different between groups. Values of T1rho and T2 of each condyle were correlated with the osteoarthritic grade assessed by MRI. [Conclusion] RA subjects had significantly higher T2 values than OA subjects of similar morphologic grade in contrast to no differences of T1rho values between groups. These results suggest that an increase in the water content of articular cartilage of RA caused by the inflammatory changes is more than OA cartilage.

W68-5

Study on usefulness of joint ultrasonography in patients administered with tocilizumab

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Conflict of interest: None

[Purpose] The examination of usefulness in performing joint ultrasound (US) with clinical assessment on rheumatoid arthritis patients (RA) who administered with TCZ. [Method] Patients who are capable to follow 24 weeks from administeration with TCZ. At 0th week, 12th week and 24th week respectively, we have performed US on the 40 joints along with DAS28-ESR (4), CDAI, and HAQ, and evaluated by semi-quantitative method using GS /PD. In addition, we have performed a limbs XP at 0 week and 24th week, and evaluated them using Total Sharp Score (TSS). We divided a total of 400 joints from the 10 patients into 4 groups in accordance with the presence/absence of tenderness/swelling and PD, namely A group (observation+ /PD+), B group (+/-), C group (-/+) and D group (-/-), and compared any relationships with ΔTSS (0 to 24th week). [Result] Joints on which radiological progression (RP) was observed at 24th week were, 18% in A group (4/22), 0% in B group (0/28), 2.6% in C group (1/39) and, 1.3% in D group (4/311). [Conclusion] Almost joints on which bone destruction were observed after the initiation of TCZ had both tenderness/swelling and PD at 0 week. It is suggested that US is useful with complement of examination findings.

W68-6

Ultrasonography can detect PD signal related to radiographic progression even under biologics therapy

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Conflict of interest: None

[Objectives] To clarify whether PD signal detected by US predicts joint destruction of RA patients under biologics therapy. [Methods] We retrospectively analyzed the relationship between radiologic progression and clinical and US data among 76 RA patients who had been initiated and continued biologics for more than six months. We sequentially examined 22 joints of hands by US using PD scoring. Hand X-ray at baseline and at the last of observational period were assessed by mTSS and we also examined whether destruction of the individual joints of each patient progressed. [Results] During 798±470 days of continuing biologics, joint destruction was observed in 36% of the patients including those who achieved clinical remission and in 2.9% of all the assessed joints. Longer treatment period and having histories of switching biologics were risk factors for patient-based radiologic progression, whereas clinical data and total PD score during observational period were not associated with joint destruction. On the contrary, the existence of PD signals at the first and last US assessment were strongly related to the destruction of each joint (odds ratio; 11.3, 21.2, respectively). [Conclusion] To achieve radiologic remission, monitoring joints by US is helpful even under biologics treatment.

W69-1

The accuracy of musculoskeletal ultrasound (MSUS) static image grading by participants of JCR MSUS advance course

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Conflict of interest: Yes

[Objectives] To examine the accuracy of MSUS static image grading. [Methods] Participants of the 2013 JCR MSUS advance course were tested. Typical static images of 6 joint lesions including dorsal/ventral MCP, radiocarpal joint, dorsal/ventral humeroulnar joint (HUJ), glenohumeral joint (GHJ) were shown to the participants. Images included normal, mild, moderate and severe synovial pathologies of gray scale and power Doppler images. Images were selected by 5 of the members of JCR CoSMUS. To study the intraobserver variability, all the images were randomly shown twice. [Results] Answers were collected from 38 participants. The average rate of correct grading (accuracy) of all the images were 63.0% (GS 55.0%, PD 71.1%) before lecture and 65.1% after lecture. The accuracy among each severity was GS normal/mild/moderate/severe 53.7/49.1/45.2/72.1% respectively, PD normal/mild/moderate/severe 71.9/67.3/69.3/75.7%. Accuracy among different joint lesions was highest in dorsal MCP (75.1%) lowest in dorsal HUJ (58.6%). Intraobserver variability was moderate (k=0.569). [Conclusion] Accuracy was higher in PD than GS images, severe/normal than mild/moderate. Accuracy varied among different joint lesions. The joint lesion and severity of the images might affect the accuracy of MSUS static image grading.

W69-2

Residual ultrasound joint inflammation in sustained clinical remission: Is there a propensity to persist at radiographically progressed joints in patients with rheumatoid arthritis?

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Matsuki[1], Nagachika Sugisaki[1], Yusuke Yamada[1], Takuya Nemoto[1], Seiichiro Ando[1], Kentaro Minowa[1], Takayuki Kon[1], Kurisu Tada[1], Masakazu Matsushita[1], Ken Yamaji[1], Naoto Tamura[1], Shigeki Makino[2], Yoshinari Takasaki[1]
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Conflict of interest: None

[Objectives] Investigation of the correlation between subclinical synovitis and bone destruction in rheumatoid arthritis patients (RA) in sustained clinical remission. [Methods] Forty-four RA in sustained remission at least for 3 months were enrolled in this study. Clinical examination, hand X-ray (Genant's sharp scoring, SS), ultrasound examination (US) were conducted. [Results] Residual power Doppler signals (PD) were observed in 59.1% (26/44) of patients and %PD of each joints were 36.4% (32/88) at wrist, 2.95% (13/440) at MCP, and 2.05% (9/440) at PIP. Comparative analysis between patients with and without residual PD showed that SS had the highest difference (p=0.0057), and followed by swelling joint count (p=0.016). There were no patients without residual PD in patients with high SS. Although there was tendency the longer duration of clinical remission related to the larger %patients without residual PD, did not show statistical difference. [Conclusion] Residual PD was observed in patients with clinical remission, particularly in high SS patients. Sustained clinical remission was considered not to be effective to those residual PD. It is important that patients should be in clinical remission before bone destruction to achieve the clinical remission without residual PD.

W69-3

Sonographic semi-quantitative evaluation of the shoulder synovitis in polymyalgia rheumatica and elderly-onset rheumatoid arthritis mimicking PMR

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Conflict of interest: None

[Objectives] To compare the severity of the shoulder syonvitis between polymyalgia rheumatica (PMR) and elderly-onset RA mimicking PMR (polymyalgic-EORA, pm-EORA) using semi-quantitative ultrasound (US) evaluation. [Methods] We analyzed consecutive records of 14 PMR and 14 pm-EORA patients in our hospital in 2010-12, in whom adequate US images of both shoulders before treatment-start were available. The severity of tenosynovitis of the long-head of the biceps (LHB), bursitis including subdeltoid, subacrominal and subcoracoid bursitis, and synovitis of grenohumeral joint (GHJ) were subjectively graded and scored for GS and PD on a four-point scale: 0 = absent, 1 = mild, 2 = moderate or 3 = severe. [Results] There was a tendency that shoulder synovitis in PMR was milder than that in pm-EORA. There were statistically-significant differences in the PD-grade of LHB, GS-grade of bursitis and GS-grade of GHJ. There were also significant differences in GS-score of bursitis (1.18±1.28 vs 0.36±0.56, p=0.004), PD-score of bursitis (1.00±1.22 vs 0.36±0.73, p=0.021) and the sum of the 3 GS- and 3 PD-scores (6.43±5.45 vs 4.29±2.51, p=0.046) (mean±SD, pm-EORA vs PMR). [Conclusion] US semi-quantitative assessment revealed that shoulder synovitis in PMR tends to be milder than that in EORA mimicking PMR.

W69-4

Ultrasonographic evaluation of the thickness of articular cartilage - comparing normal subjects and rheumatoid arthritis subjects -

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Conflict of interest: None

<Introduction> Nowadays ultrasonographic examination of joint has been increasing for rheumatoid arthritis. Very useful advantage of ultrasonography is high resolution. <Material and Method> Estimation site was articular cartilage of distal metacarpal joint of second and third finger of right and left hand (R2,R3,L2,L3). There were 109 normal subjects (male 32 female 77) and 72 rheumatoid arthritis (male 15 female 57). The thickness of the articular cartilage of the the R2,R3,L2,L3 joint was measured and compared about the gender, age, body weight, height, disease duration, treatment free duration. <Results> The thickness of articular cartilage of normal subjects were R2:0.55mm R3:0.48mm L2:0.53mm L3:0.51mm, all cartilage of the normal patient could be observed clearly. The thickness of articular cartilage of rheumatoid arthritis were R2:0.36mm R3:0.35mm L2:0.37mm L3:0.36mm, and could be observed clearly in 170 cartilages, but was irregular in 68 cartilages, and were unclear in 50 cartilages. The thickness of normal subjects were significantly thicker than rheumatoid arthritis ($p<0.0001$ r: -0.286). The thickness was decreased according to the disease duration and treatment free duration ($p<0.0001$ r: -0.286, $p<0.0002$ r: -0.228), but not changed according to the gender nor age.

W69-5

Usefulness of Tomosynthesis in the Diagnosis of Early Rheumatoid Arthritis

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Conflict of interest: None

[Objectives] To clarify the validity of tomosynthesis for evaluation of joint space narrowing and bone erosions in rheumatoid arthritis. [Methods] 24 patients with early RA diagnosed by ACR/EULAR2010 (female 18, male 6), underwent radiography and tomosynthesis of hands and wrists, were included in this study. Mean age was 57.3 years old and mean duration of disease was 3.71 months. Rheumatologists in our hospital scored joints of the hands and wrists using modified Total Sharp Score from two imaging modalities. [Results] Scores for total joints evaluated were 112 vs 143 for joint space narrowing and 60 vs 142 for bone erosion in radiography and tomosynthesis respectively. Using Steinbrocker's staging system, 11 cases were Stage I and 13 cases Stage II assessed by radiography and 2 cases Stage I and 22 cases Stage II by tomosynthesis. In cases double negative for rheumatoid factor and anti-cyclic citrullinated peptide antibody, 3 cases in 6 were classified for Stage I by radiography, while all 6 cases were classified for Stage II by tomosynthesis. [Conclusion] Tomosynthesis may be useful for evaluation of bone erosions in patients with early RA, especially bone erosions of wrists.

W69-6

The effects of reactive hyperemia on power Doppler signals in rheumatoid arthritis patients: A preliminary study

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Conflict of interest: None

[Introduction] Power Doppler (PD) imaging is useful in early diagnosis and therapeutic assessment of rheumatoid arthritis (RA). PD signals are related to angiogenesis, but few studies have examined the effects of hyperemia on PD signals. [Objectives] To evaluate changes in PD signals by using brachiocephalic artery reactive hyperemia test (BART) [Methods] We included 3 healthy female volunteers and 3 RA patients. After occluding the brachiocephalic artery at systolic pressure +50 mmHg for 5 min with a tourniquet, PD signals were evaluated at 2 cross-sections in the wrist's dorsal aspect 1 min after releasing the tourniquet. [Results] While no PD signals were observed at rest in the healthy individuals, spot-pattern PD signals were observed in soft tissue and bone surface after BART. PD signals were evidently high in a patient with poor RA inflammation control. Spot-pattern PD signals increased in the 2 patients with favorable control of inflammation. [Conclusion] PD signals were observed in healthy individuals owing to reactive hyperemia. Thus, for

early diagnosis, PD signals in healthy individuals and RA patients in remission should be cautiously examined. Also, owing to reactive hyperemia in active arthritis, the level of angiogenesis in RA patients can be more accurately assessed.

W70-1

Statistical analysis between ultrasonography and pathological confirmation for the diagnosis of Giant cell arteritis (GCA): a cut-off value of intima-media thickness (IMT) in superficial temporal artery

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Conflict of interest: None

[Objectives] Ultrasonography (US) of the superficial temporal arteries was introduced in the 1990s. The diagnostic value of US of the superficial temporal artery wall in GCA has been extensively reported. In order to clarify the effectiveness of US preceding pathological diagnosis, we examined cut-off values of ultrasonography-derived halo signs (IMT). [Methods] Twenty-four patients with suspected GCA were examined by US before biopsy from October 2010 to October 2013, inclusive. US was performed unilaterally or bilaterally by two ultrasonographer and the greatest analyzed. Superficial temporal artery biopsy was used as the reference standard. [Results] Unilateral halo sign had a sensitivity of 78.9 % and specificity of 80.0 %. In ROC analysis, a cut-off of greatest dimension of halo > 0.78 mm was the most accurate for prediction with a sensitivity of 80.0 % and specificity of 87.5 %. The diagnostic odds ratio was 28.0 (95% CI, 2.59 – 303). [Conclusion] This is the first report that examined the cut-off values of IMT in diagnosing GCA. The measurement of the greatest dimension of the ultrasonography-derived halo sign (IMT) increased the diagnostic yield for pathological diagnosis.

W70-2

The assessment of echo findings in the heel of pediatric polyenthesitis

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Conflict of interest: None

[Objectives] Polyenthesitis is chronic inflammatory disease on the bone attachment sites of tendon or ligaments, which is a main pathogenesis of spondyloarthritis or psoriatic arthritis. Specific markers remain unknown, making early diagnosis difficult. Recently, it has been shown that imaging exams are effective in the diagnosis of adult cases. We assessed echo findings of pediatric polyenthesitis. [Methods] Twenty two children with polyenthesitis were subjected. An echo examination of heel was performed using linear probe (LOGIQ P6). [Results] Sixteen cases had abnormal signs: 12 power Doppler positive calcaneal tendon, 1 calcaneal bone erosion, 1 punctate ossification in calcaneal tendon, and 3 anterior Achilles tendon bursitis. [Conclusion] It has been reported that power Doppler positive sign is sensitive in detecting adult spondyloarthritis. Our analysis may show that power Doppler positive sign is also sensitive to detect polyenthesitis in children. However, in school-age cases, it might be difficult to differentiate between pathologic blood flow in entheseal inflammation and physiologic blood flow in developing endochondral ossification. It is important to standardize echo findings of heel, based on many more examinations.

W70-3

18F-FDG and NaF PET/CT demonstrate coupling of inflammation and accelerated bone metabolism in rheumatoid arthritis

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Conflict of interest: None

【Objective】Synovitis causes joint destruction that is associated with accelerated bone metabolism in rheumatoid arthritis (RA). We evaluated relationship of 18F-FDG and NaF PET/CT uptake with joint destruction. 【Methods】12 patients who started to receive biologic agents were enrolled. We examined association of FDG- and NaF-PET/CT of the bilateral hands with clinical findings at the baseline and interval changes of hand X-rays for the following 6 months according to according to the Genant-modified Sharp score. These imaging findings were comparatively assessed in individual joints, 【Results】The standard uptake value (SUV) of FDG was well correlated with that of NaF in individual joints (r=0.62), though NaF was accumulated in osteoplastic lesions without FDG signals. FDG were strongly accumulated in swelling joints and the total accumulation was correlated with DAS28. NaF accumulation was associated with DAS28, HAQ, progressive erosion in individual joints, and deterioration of total Sharp score (p=0.66).【Conclusion】FDG-PET detects synovistis sensitively, whereas NaF accumulation is more closely associated with bone destructive and plastic lesions. Simultaneous accumulation of the both molecules suggest coupling of inflammation and accelerated bone metabolism in RA joints.

W70-4

Joint power Doppler signals with anti-citrullinated peptide antibody predicts joint destruction in rheumatoid arthritis

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Conflict of interest: None

[Objectives] To ask whether synovial PD signals in musculoskeletal ultrasound (MSUS) collerate with progressive joint destruction in RA. [Methods] We retrospectively enrolled 413 RA patients (F:345, M:68, age 57.9±13.5 y.o) who underwent MSUS from 2002-2013. Correlations between yearly progressions of modified Sharp score on 2nd and 3rd MP joints, clinical profiles, and semi-quantitative analysis of synovial PD signals were determined by univariate and mixed model logistic regression analysis. [Results] Patients' characteristics were as follows: mean disease duration 2047±2785 days, RF (+) 79.4%, ACPA (+) 77%. Observation period was 1534±1004days. Significant association between positive PD signals and the subsequent joints destruction was found. Joint destruction in the PD (+) joints in presence of ACPA was significantly more prevalent than in the PD (-) joints in absence of ACPA, with the odds ratio of 20.8 (95% CI 8.0-54.2). Mixed effects logistic regression analysis of joints showed PD signal, ACPA, and MP2 joints were determined as independent risks for joint destruction. [Conclusion] Synovial PD signals in MSUS are predisposed to progressive joint destruction in RA patients, especially with positive ACPA. These patients may require more intensive anti-rheumatic therapy.

W70-5

The clinical and prognostic significance of the location of power Doppler signal in the joints of RA patients

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Conflict of interest: None

[Objectives] We can see the power Doppler signal (PD) of ultrasonography (US) in the joints which are in the locations of 1) synovial hypertrophy 2) intra-articular 3) extra-articular (feeding vessel). We examined the relation between the location of power Doppler signal and destruction of bone. [Methods] 25 patients of RA were examined by US

with 10 MCP joints and 10 PIP joints. We evaluated them with gray-scale (GS) and PD. X-ray of both wrist and finger joints were also examined. After 1 year, we examined same. [Results] In total 500 joints, we could have 141 PD positive joints in the area of 1) or 2), and 359 PD negative joints. After 1 year, bone damage of PD positive joints were progressed significantly than that of PD negative joints. There are no significant difference between the location of PD 1) and 2). [Conclusion] In RA patients, PD signal of the area 2) is important same as the signal of 1).

W70-6

The influence of joint space narrowing and bone erosion on functional disability in rheumatoid arthritis

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Conflict of interest: Yes

[Objectives] This study is aimed to investigate how joint space narrowing and erosion affect functional disability in rheumatoid arthritis (RA). [Methods] We chose 365 consecutive RA patients in our clinical cohort study and assessed age, disease duration, disease activities, HAQ-DI, joint space narrowing score (JSNs) and bone erosion score (BEs) of mTSS. [Results] HAQ-DI correlated with all variables (age $r=0.31$, $p<0.0001$; disease duration $r=0.45$, $p<0.0001$; DAS28 $r=0.47$, $p<0.0001$; BEs $r=0.47$, $p<0.0001$; JSNs $r=0.49$, $p<0.0001$). In the logistic regression analysis, predictors of HAQ-DI>0.5 (functional non-remission) were age ($p=0.01$, OR=1.02), DAS28 ($p<0.0001$, OR=2.13) and JSNs ($p=0.03$, OR=1.03). [Conclusion] Our results suggested that the functional disability was affected by disease activity most, and related to joint space narrowing than bone erosion in RA.

W71-1

IL-6, IL-8 and IL-10 are Associated with Pathophysiology of Hyperferritinemia in Interstitial Lung Disease with Polymyositis/Dermatomyositis

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Conflict of interest: None

Objectives: We previously reported that hyperferritinemia are associated with the prognosis of interstitial lung disease (ILD) in polymyositis (PM) /dermatomyositis (DM). Hyperferritinemia could be associated with a cytokine storm in rapidly progressive ILD (RP-ILD). We investigated the associations between the serum ferritin levels and various cytokines in PM/DM. ***Methods:*** This study included 38 patients (21 patients had ILD) with PM/DM. The disease activity of ILD was evaluated by the visual analogue scale (VAS) which the IMACS proposed. We measured serum cytokines (IL-1β, IL-2, IL-4, IL-6, IL-8, IL-10, IL-12, IL-13, IL-17, IL-18, TNF-α, INF-α, INF-γ and IP-10), and analyzed the associations between ILD activity, ferritin and cytokines. ***Results:*** The VAS of ILD was significantly correlated with serum ferritin, IL-8, IL-10, IL-18, TNF-α and IP-10. In a multiple linear regression analysis, IL-6 ($t=2.9$, $p<0.05$), IL-8 ($t=3.6$, $p<0.01$) and IL-10 ($t=4.0$, $p<0.001$) were significantly correlated with the ferritin levels. Serum levels of ferritin, IL-6, IL-8 and IL-10 were higher in the RP-ILD subset than other subsets. ***Conclusion:*** Serum ferritin was correlated with the disease activity of ILD in PM/DM. IL-6, IL-8 and IL-10 were significant factors contributed to the serum ferritin levels.

W71-2

The Evaluation of the Clinical Condition of Outpatients with Polymyositis/Dermatomyositis Using the Myositis Disease Activity Core Set

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Conflict of interest: None

Objectives: The Myositis Disease Activity Core Set (MDACS) is proposed by the International Myositis Assessment and Clinical Studies Group in the evaluation of the disease activity of PM/DM. We assessed the clinical condition of our outpatients using the MDACS. ***Methods:*** A total of 72 outpatients were enrolled. We evaluated the disease activity using the MDACS, which included patient global assessment (PGA), evaluator global assessment (EGA), manual muscle test (MMT8), the J-HAQ-DI and assessment of extra-muscular disease activity by physicians (MYOACT). ***Results:*** The mean age was 54±15 years old, and 80% of the patients were female. The mean disease duration was 9±6 years, and the percentages of PM/DM/CADM were 48/43/9%. Although the disease activity was considered to be in remission in half of the patients by the EGA and in 60% of those by the MYOACT, the PGA score was 0 in only 10%. Muscle weakness was not present in 60%. The J-HAQ-DI score was 0 in half of the patients and ≥ 1 in 20% of the patients. There were no differences in the PGA, EGA, J-HAQ-DI and MYOACT between PM, DM and CADM. ***Conclusions:*** Although half of the patients were considered to be in disease remission by physicians, half of the patients showed muscle weakness or impairment in completing daily activities.

W71-3

Clinical features of 5 patients with positive anti-PL-12 antibody

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Conflict of interest: None

【Objectives】To investigate the clinical features of patients with positive anti-PL-12 antibody (PL-12).【method】Five patients were found positive to anti-PL-12 (which was detected using a kit supplied from Orgentec Diagnostika) among patients who admitted to our hospital from January 2007 to December 2012.【result】Four of 5 patients with positive anti-PL-12 were diagnosed with rheumatoid arthritis (RA), and 3 of the 4 were positive for both rheumatoid factor (RF) and anti-citrullinated peptide antibody (ACPA). Among 4 RA patients, 2 were overlapped with Sjögren's syndrome (SS) and systemic sclerosis (SSc), respectively. Remaining 1 without RA was diagnosed with clinically amyopathic dermatomyositis (DM). All patients had interstitial pneumonia (IP). Elevation of creatine kinase levels was observed in 2 of 5. Two of 3 ACPA-positive RA patients developed rapidly progressive IP (one of them died), and 1 developed organizing pneumonia during treatment with etanercept. ACPA-negative RA patient overlapped with SS developed DM 12 years after the diagnosis of IP.【conclusion】Antibody to PL-12 could be positive in patients with not only DM, but also RA or SSc. Three of 5 with positive anti-PL-12 (60%) were diagnosed with ACPA-positive RA in our patients.

W71-4

Clinical study of patients with dermatomyositis (DM) and polymyositis (PM) complicated by interstitial pneumonia (IP)

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Conflict of interest: None

[Objectives] We examined the clinical course of patients with polymyositis (PM) and dermatomyositis (DM) complicated by interstitial pneumonia (IP). [Methods] We analyzed retrospectively PM and DM patients of 37 cases complicated with interstitial pneumonia. Evaluation of interstitial pneumonia was made by chest CT. [Results] The mean age of the patients is 58.6 ± 14.2 years, female patients 26 cases (70%), male patients is 11 cases (30%). Amyopathic Dermatomyositis (ADM) was 10 cases. 14 cases (38%) were anti-Jo-1 antibody positive. We will make the image classification of IP, 27 cases are NSIP pattern, six cases is a UIP pattern, four cases was a pattern of the other. 2 cases complicated with pneumomediastinum. Both patients were anti-CADM-140 antibody-positive. Five cases were hospitalized with infection in the course of treatment. 7 cases died, two patients died of exacerbation of IP. 5 cases died due to non-IP. [Conclusion] It is necessary to powerful immunosuppressive medical treatment for the treatment of patients DM and PM complicated with interstitial pneumonia. Then, it is necessary to perform a more powerful immunosuppressive medical treatment prognosis is so bad that cases of anti-CADM-140 antibody-positive and the case complicated by pneumomediastinum.

W71-5

Renal damage due to calcineurin inhibitors in interstitial pneumonia with dermatomyositis patients

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Conflict of interest: None

[Objectives] To investigate the renal damage due to calcineurin inhibitors (CNI) in interstitial pneumonia with dermatomyositis (DM-IP) patients and the possibility that angiotensin receptor blocker (ARB) prevent renal damage from CNI. [Methods] We assessed the change of serum creatinine (Cr) by the treatment of PSL and CNI in DM-IP, and the association between change of Cr and clinical factors. The change of serum Cr was defined as the ratio of serum Cr before to 1 year after the therapy (Cr 1y/ Cr 0y). [Results] The mean age, KL-6 were 56.1±11.8 years old, 1198±774U/ml, respectively. Of the 44 patients, 39 patients were treated with Cycrosporine-A (CsA) and 5 patients Tacrolimus (TAC). The mean dose of CsA and TAC were 204±41mg, 3.3±0.9mg, respectively. The mean Cr 1y/Cr 0y was 1.7±0.4, and Cr was significantly elevated after the treatment (P<0.0001). There was a tendency to correlate positively between Cr 1y/Cr 0y and age (P=0.0629). Between the groups treated with CsA and TAC, there was no significant difference in Cr 1y/Cr 0y. Although ARB was used in 11 patients, their renal damege was not reduced. [Conclusion] It is an important problem that ARB cannot prevent renal damage from CNI.

W71-6

Aggravating factors due to medication change from cyclosporine-A to tacrolimus in interstitial pneumonia with dermatomyositis

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Conflict of interest: None

[Objectives] We evaluate the aggravating factors of interstitial pneumonia (IP) in patients with dermatomyositis (DM) made the medication change from cyclosporine (CyA) to tacrolimus (Tac). [Methods] 21 patients treated with prednisolone (PSL) and CyA for more than 6 months were enrolled. We assessed the factors involved in IP exacerbation such as laboratory findings and treatment 6 months after change from CyA to Tac. The concentration of Tac was measured 1, 3, and 6 months after the medication change. IP exacerbation was defined as the increase of KL-6 of more than 1.5 times and/or a new shadow on chest CT. [Results] Of 21 patients, 4 patients had IP exacerbation during an observation period in. Two patients hospitalization, and one patient was died. Two outpatients showed the reduction of KL-6 by the increase of Tac in exacerbation group was significantly lower. The average blood concentration of Tac than that in non exacerbation group. (p=0.0487) [Conclusion] It is necessary to careful contorl of blood concentration of Tac when the attenuation from CyA to Tac is needed in DM-IP.

W72-1

Identification of autoantibodies to tyrosyl-transfer RNA synthetase associated with anti-synthetase syndrome

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Conflict of interest: None

[Objectives] A preliminary report has described the detection of an autoantibody to tyrosyl-tRNA synthetase (TyrRS) in only one patient. We aimed to identify further patients with anti-TyrRS autoantibodies using other assays than previously reported methods and elucidate their clinical significance. **[Methods]** Multiple assays were performed to detect anti-TyrRS antibodies in the sera of patients with active polymyositis/dermatomyositis (PM/DM) patients: enzyme-linked immunosorbent assay (ELISA), Western blot, and immunoprecipitation using TyrRS-transfected HeLaS3 cells. **[Results]** Among 141 samples from patients with PM/DM, sera from three patients with PM/DM showed significantly high O.D. values in ELISA, significant bands of 59 kDa protein of TyrRS at the same place as anti-His tag antibody in Western blot, and significant bands at the same place as the recombinant human TyrRS in immunoprecipitation assay. These data strongly suggest that these sera had autoantibodies to TyrRS. These patients had some features of myositis, interstitial lung disease, arthritis, Raynaud's phenomenon, and fever. **[Conclusion]** This study reconfirmed the presence of anti-TyrRS antibody in the setting of the anti-synthetase syndrome and strengthens the association of anti-synthetases with these conditions.

W72-2

Clinical Evaluation of Anti-Aminoacyl-tRNA Synthetase Antibodies in Patients with Interstitial Lung Disease Associated with Polymyositis/Dermatomyositis

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Conflict of interest: None

Objectives: In polymyositis/dermatomyositis (PM/DM) associated-ILD patients, we sought to determine whether the presence of anti-aminoacyl-tRNA Synthetase (ARS)-antibodies correlate with progression-free survival (PFS) as a parameter reflecting long-term outcome, and response to pharmacological therapies. ***Patients and Methods***: Determination of anti-ARS antibodies was carried out using Myositis Profile 3 euroline Blot Test Kit. Nine anti-ARS-antibodies-positive and 13 negative patients were analyzed retrospectively. PFS was defined as the period from the day of initiation of the treatment to the final observation day or the first day that events as death or decline of vital capacity occurred. We compared clinical data including pulmonary function, KL-6, and the extent of abnormal shadows on chest HRCT (HRCT scores). ***Result***: The mean observation period was 1249.3 ± 1706.2 (range; 29-6847) days. Multivariate analysis showed that independent poor predictors for shortened PFS were acute onset of ILD and the absence of anti-ARS-antibodies. ***Conclusion***: These results suggested that the presence of serum anti-ARS antibodies is clinically usuful as prognostic factor in patients with ILD complicated by PM/DM.

W72-3

Association between physical dysfunction and disease activity in daily clinical practice for outpatients with polymyositis/dermatomyositis

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Conflict of interest: None

[Objectives] The aim of this study is to clarify the present state of physical function and the association between physical function and disease activity in outpatients with polymyositis (PM)/ dermatomyositis (DM). [Methods] A total of 72 outpatients with PM/DM were enrolled in this study. We evaluated physical function and disease activity using the myositis disease activity core set as proposed by the IMACS. [Results] The J-HAQ found physical dysfunction in 39 of the patients evaluated (54%). The age at disease onset was higher in patients with physical dysfunction than those without physical dysfunction, although there was no difference in disease duration between the two subsets. The patient global assessment was higher and the manual muscle testing score was lower in patients with physical dysfunction than in those without physical dysfunction, although no significant differences were found in the physician global assessment between the two subsets. Many of the patients demonstrated difficulty with "Reach," "Grip" and "Activities" in the J-HAQ. [Conclusion] One half of the outpatients were found to have some difficulties completing daily activities. This finding may result from irreversible cumulative damage rather than from reversible disease activity.

W72-4

The analysis of prognostic factors in patients with inflammatory myopathies complicated with interstitial lung disease

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Conflict of interest: None

[Objectives] Because interstitial lung disease (ILD) is one of the most lethal causes in inflammatory myopathies (IM), especially amyopathic dermatomiositis (ADM), it is important to determine prognostic factors for survival. We investigated clinical features with fatal events in IM patients having ILD. [Methods] We retrospectively analyzed clinical features, laboratory and HRCT findings, and therapeutic regimens with clinical outcomes in 144 patients diagnosed with IM at 2 Yokohama City University hospitals from 1993 to 2012. The distribution and extent of ILD lesions were evaluated in each divided four zone (A to D) of HRCT. [Results] Among 83 of 144 IM patients with ILD, 12 patients (myopathic DM 8, ADM 4) died within 7 months after the diagnosis due to respiratory failure and infections. The early lethal events were associated with male, administration with tacrolimus, combined immunosuppressive therapies, low PCO2, low P/F ratio, and extended ILD in the upper lung fields. PCO2 and lesions in zone B were independent prognostic factors analyzed by Cox proportional hazard model. [Conclusion] Rapid and intensive therapies including prophylactic procedures against infections are necessary to manage IM patients with hypocapnia and ILD expanding to upper lung field.

W72-5

Retrospective study of 88 cases with idiopathic inflammatory myositis (IIM)

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Conflict of interest: None

[Objectives] We evaluated the survival rate (all over and without relapse), and functional impairment of patients with Polymyositis (PM), Dermatomyositis (DM), and Amyopathic DM (ADM). [Methods] Clinical data of IIM patients who received induction therapy from April 2002 to July 2013 in our hospital were collected from the medical charts. Survival rate were modeled Kaplan-Meier estimation. Functional impairment was evaluated with Health Assessment Questionnaire (HAQ). [Results] Eighty eight IIM patients (38 with PM, 40 with DM, and 10 with ADM) were included. Interstitial lung disease (ILD) was diagnosed in 63% of PM, 82% of DM, and all the ADM patients. Rapidly progressive ILD (RP-ILD) were found none of PM, 6% of DM, and 70% of ADM patients. Ten years all over survival rate of PM and DM were 79%, 76% respectively. Half of ADM patients had fatal clinical course of RP-ILD within 4 months after onset. Ten years survival rate without relapse were 75% for PM and 55% for DM. Patients treated with immunosuppressive agents (ISA), 68% of PM, 61% of DM, and 90% of ADM, tended to have lower relapse rate than those without ISA (P=0.053). Over 60 years-old patients had significantly higher HAQ-score (P<0.01). [Conclusion] Early administration of ISA might reduce the risk of relapse.

W72-6

Intravenous immunoglobulin therapy for refractory interstitial lung disease associated with clinically amyopathic dermatomyositis: analysis of 6 cases

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Conflict of interest: Yes

[Objectives] To investigate the efficacy of intravenous immunoglobulin (IVIG) for refractory interstitial lung disease associated with clinically amyopathic dermatomyositis (ILD-CADM). [Methods] Six admitted patients (mean age: 57.5 years; 5 men and 1 woman) were treated with IVIG for refractory ILD-CADM resistant to high-dose corticosteroid, tacrolimus and cyclophosphamide in our hospital from 2011 to 2013. We investigated the efficacy of IVIG by comparing the clinical picture of each case. [Results] Of the six patients, three patients survived and the others died. In survival cases, clinical response to IVIG was obtained a week after. IVIG tended to have efficacy for ILD-CADM especially when it had a certain level of response to triple immunosuppressive therapy. [Conclusion] IVIG is safe and could be an effective salvage therapy for refractory ILD-CADM.

W73-1

Synovial CXCL13-producing CD4+ T cells under inflammatory environment contribute to the formation of ecotopic follicle in rheumatoid arthritis

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Conflict of interest: Yes

[Objectives] Ectopic lymphoid follicles are frequently formed in synovium of rheumatoid arthritis (RA). Although CD4+ T-cells in RA synovium were reported to produce CXCL13, a chemokine crucial for the formation of germinal center, there relevance to known CD4+ T-cell subsets or proinflammatory cytokines had been largely unknown. [Methods] We analyzed character and function of CXCL13+CD4+ T-cells obtained from RA patients. [Results] Synovial CXCL13+CD4+ T-cells were a population distinct from known CD4+ T-cell subsets such as Th1, Th2,

Th17 and Tfh subset, and TNF-α and IL-6 maintained the CXCL13 production. In a transwell chemotaxis assay using supernatant of RA synovial cells, the neutralizing antibodies against CXCL13 blocked the migration of cell expressing CXCR5, which was receptor of CXCL13, to the supernatant. [Conclusion] Because proinflammatory cytokines were strongly involved in the function of synovial CXCL13+CD4+ T-cells, we named this population inflammatory CXCL13-producing helper T (iTh13) cells. iTh13 cells were induced in the inflammatory condition and thought to recruit lymphocytes to inflamed joint, and to participate in the formation of ectopic lymphoid follicle. Thus, it is suggested that iTh13 plays a key role in pathology of RA and other inflammatory disease.

W73-2

Unbiased detection of candidate pathogenic CD4$^+$ T cell clones in rheumatoid arthritis patients based on TCR repertoire and single-cell trasnscriptome analysis

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Conflict of interest: None

[Objectives] The purpose of this study is to detect candidate pathogenic CD4$^+$ T cell clones in RA patients in unbiased way. [Methods] We obtained peripheral blood from 5 RA patients, and synovial tissues from 4 of them. We used peripheral blood from 5 healthy volunteers as control samples. We performed T cell receptor (TCR) repertoire analysis by combination of single-cell and next-generation sequencer (NGS). We also performed single-cell transcriptome analysis of expanded clones (ECs) detected by TCR repertoire analysis. [Results] We detected significantly higher number of ECs in memory subset of CD4$^+$ T cells in RA peripheral blood compared with control, and a part of those ECs were also detected in synovial tissues. One EC had high level of clonality in both of peripheral blood and synovial tissues and showed high expression of Th1-associated genes, CD5, CXCR4 and JAK3, which suggested a pathogenic role of this clone. [Conclusion] We detected candidate pathogenic CD4$^+$ T cell clones in RA patients by using NGS for TCR repertoire analysis and single-cell transcriptome analysis. By increasing the size of this unbiased experimental system, we might be able to elucidate pathophysiology of RA and to detect new auto-antigens in RA.

W73-3

The synovial proliferative effect of RasGRP4 (Ras guanine nucleotide-releasing protein 4) in fibroblast-like synoviocytes from patients with rheumatoid arthritis

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Conflict of interest: None

[Background] RasGRP4 is a guanine nucleotide exchange factor expressed predominantly in the mast cells, monocytes and neutrophils. RasGRP4-null mice are resistant to serum-transfer model of arthritis. We have reported that fibroblast-like synoviocytes (FLSs) from rheumatoid arthritis (RA) patients express RasGRP4 more abundantly compared with those from osteoarthritis patients. [Objectives] To clarify the role of RasGRP4 in the pathogenesis of RA. [Methods] FLSs were isolated from the synovial tissues of ten RA patients and ten osteoarthritis patients, and the expression of RasGRP4 in FLSs was evaluated by real-time quantitative PCR. The RasGRP4-dependent proliferation potency of FLSs was evaluated by exposing FLSs to a RasGRP4-specific RNAi. Type II collagen-induced arthritis rats were intra-articularly injected with RasGRP4-specific RNAi and the effects were evaluated. [Results] The levels of the RasGRP4 transcript were correlated with the proliferation potency of the FLSs. Proliferation of FLS was abrogated by RasGRP4-specific RNAi. Intra-articular injection of RasGRP4-specific RNAi reduced arthritis in collagen-induced arthritis rats. [Conclusion] RasGRP4 is a possible target for proliferative synovitis.

W73-4

Enhanced RANKL expression in switched memory B cells from patients with rheumatoid arthritis

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Conflict of interest: None

[Objectives] RANKL plays a key role in osteoclastogenesis and inflammatory bone loss. A recent study suggested that B cells are a major source of RANKL in the joints of patients with RA. We have elucidated underlying mechanisms of RANKL expression in B cells from normal subjects and RA patients. [Methods] Levels of RANKL mRNA and protein in B cells from peripheral blood were evaluated using quantitative RT-PCR and flow cytometry, respectively. Highly pure B cell subsets were enriched using cell sorter. The osteoclast formation was assessed by tartrate-resistant acid phosphatase (TRAP) staining. [Results] Combined stimulation of B cells with anti-Ig and anti-CD40 significantly induced RANKL expression. Among B cell subsets, switched-memory (CD27 +IgD-) B cells expressed RANKL at the highest levels. Consistent with these findings, these subsets induced osteoclast formation as assessed by TRAP staining. Finally, switched-memory B cells from RA patients expressed RANKL at higher levels than normal subjects. [Conclusion] Our current findings shed the light on a pathogenic role of switched-memory B cells in bone damage associated with RA via production of RANKL.

W73-5

Appearance of CD14+CD15$^+$+population during the differentiation from RA iPS cells into monocytes

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Conflict of interest: None

[Background] CD14+CD15+abnormal cell population with both myeloid and monocyte lineage phenotypes has been reported to exist in the bone marrow of rheumatoid arthritis (RA) patients. We have established differentiation method of induced pluripotent stem (iPS) cells into monocytes under feeder-free conditions. This method can provide us observation of the differentiation stage without influences of any environmental factors such as drugs. [Objectives] To confirm whether CD14+CD15$^+$+ cells appear during the differentiation of iPS cells into monocytes in RA patients. [Methods] Monocytic cells were induced from iPS cells (RA patient and 2 health individuals [one from the RA patient family]) using a previously reported method (Niwa et al. Plos one, 2011). These cells were collected and stained with CD14 and CD15 antibodies for FACS analysis on the 15th, 18th and 21th day after induction treatment. [Results] CD14+CD15+cells were detected on the 15th day during the differentiation of RA iPS cells. Furthermore, CD14+CD15+population from RA iPS cells was larger than those from healthy individuals. [Conclusion] We successfully differentiated RA iPS cells into monocytes and identified CD14+CD15+cells during the differentiation. Appearance of CD14+CD15+cells may be characteristic to RA.

W73-6

$CD4^+CD25^-LAG3^+$ regulatory T cells in patients with rheumatoid arthritis

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Conflict of interest: Yes

[Objectives] Lymphocyte activation gene 3 (LAG3) is a membranous protein having structural homology with CD4. We reported murine $CD4^+CD25^-LAG3^+$ T cells as a new regulatory T cell subset in 2009. Moreover, Roncarolo et al. recently reported $CD4^+LAG3^+CD49b^+$ T cells in PBMC as type1 regulatory T cells in human. We focused on $CD4^+CD25^-LAG3^+$ T cells ($LAG3^+$ T cells) and investigated them in patients with rheumatoid arthritis (RA). [Methods] PBMC from 48 RA patients and healthy donors were investigated using Flowcytometry to measure various cells subsets, and correlation with clinical information was analyzed. [Results] $LAG3^+$ T cells were significantly reduced in RA patients compared to healthy donors. DAS28 did not have a demonstrable relationship to the percentages of $LAG3^+$ T cells. Intriguingly, $LAG3^+$ T cells increased in some patients treated with abatacept for 6 months. Large amount of IL-10 production of $LAG3^+$ T cells was detected in healthy donor, which did not depend on CD49b. [Conclusion] $LAG3^+$ T cells are IL-10 high producer. We suppose that $LAG3^+$ T cells may suppress the occurrence of autoimmune disease. The meaning of the effect of abatacept was still to be elucidated, therefore we are planning to clarify the function and accumulate data of $LAG3^+$ T cells.

W74-1

The investigation of MTX induced Liver dysfunction (MTXLD) in RA patients

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Conflict of interest: None

[Objectives] We often experience some liver dysfunction induced by MTX treatment in RA patients. Therefore, we analyzed in order to elucidate the factors generating MTXLD. [Methods] We have surveyed 69 RA patients who could finish period from MTX introduction to the end of observation. Respectively, we classified Rapid Escalation Group (REG) that was increased by treatment target dose within two months from start of MTX therapy, and Common Escalation Group (CEG) that was other way. Next, we have set the following three end points. 1) First onset of liver dysfunction 2) Onset of prolonged liver dysfunction 3) First time of MTX dosage reduction And we analysed factors associated to liver dysfunction by logistic regression analysis. [Results] We showed a statistically significant difference in liver dysfunction agenesis period between CEG and REG ($p<.001$). Next, we calculated OR of each factor to the three events. And MTX (mg/kg), related to the onset of Liver dysfunction, had a statistically significant difference ($p<.05$). [Conclusion] We suggested that MTX. 30mg/kg or more use might cause the onset of the liver dysfunction.

W74-2

A prediction of toxity/efficacy of methotrexate (MTX) by comprehensive analyze for polymorphisms of drug-metabolizing enzymes

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Conflict of interest: None

[Objectives] To investigate whether adverse events/efficacy of MTX can be predicted by detection of the polymorphisms of genes concerning in drug-metabolism enzymes. [Methods] Among RA patients taking MTX, 33 with hepatotoxicity and 38 without were selected. We used Drug Metabolizing Enzymes and Transpotors Plus array (Affymetrix) for genotyping 1,934 variants in 231 genes, and also direct-sequence method for the other 37 variants in 17 genes associated with MTX efficacy/toxicity. We firstly compared frequencies of genotypes between two groups by Fisher's exact test and constructed a prdiction model using multiple logistic regression analysis. [Results] Forty nine SNPs were extracted from a total of 1,971 variants with a significance level of $p<0.1$. We established a prediction model in which combination of 12 SNPs could discriminate patients between with and without hepatotoxicity (sensitivity/specificity; 97.0%/89.5%). By cross varidation procedure, a prediction model of 7 SNPs were also obtained (92.0%/83.0%). We tried to make a prediction model of MTX efficacy using these 49 SNPs. [Conclusion] We established a prediction model by a combination of 12 SNPs from 49 SNPs related to hepatotoxity of MTX. We are now validating this model for another cohort by real time PCR.

W74-3

Adverse reactions of methotrexate (MTX) is corelated with intracellular concentration and also mutation of MTX related enzyme genes with rheumatoid arthritis

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Conflict of interest: None

Objectives: Methotrexate (MTX) is an anchor drug for treatment of rheumatoid arthritis (RA). We investigated the association among dose-dependent adverse reactions (ARs) and single-nucleotide polymorphisms of MTX related enzyme genes. Methods: 335 patients with RA (58.3±9.8 y,o, M±SD) were entered into this study. The intracellular concentration of MTX in red blood cells (RBC) was measured by fluorescence polarization immunoassay after extraction and deglutamation procedure. The polymerase chain reaction-restriction fragment length polymorphism assay was applied to determine the genotypes of *SLC19A1* and *GGH*. Results: 114 patients were suffered from dose-dependent ARs. Adjusted intracellular MTX concentration in patients who received decreased doses of MTX by these ARs (n=83) was significantly ($p<0.01$) increased (15.6±0.88 nmol/ml/mg) when compared to that in patients undergoing stable doses of MTX without ARs. Minor allele frequency of *GGH* (14269G>T) in patients (12.0±0.66) with ARs including those who discontinued MTX was significantly ($p<0.03$) higher than that in patients without ARs. Conclusion: Dose-dependent ARs of MTX mightn be influenced at least in part by intracellular MTX concentration and/or mutation of *GGH* in patients with RA.

W74-4

The present status of treatment for rheumatoid arthritis of more than 80 years of age

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Conflict of interest: None

The rate of ageing (more than 65 years of age) in Japan is 24%, but is approximately 35% in the south Boso area in Chiba. Accordingly the age of patients with RA is also rapidly increasing, and approximately 15% of RA patients in our Rheumatology Clinic are more than 80 years of age. Because the present status of treatment for RA of more than 80 years of

age is rarely described in the reports of mega-studies of RA, we report how we treat such patient group. We picked up clinical charts and extracted clinical data. There were 62 patients visiting our outpatient clinic at present. The mean disease duration was 14.5 years (0.5 – 53 years). The stage and class 1/2/3/4 were 24/17/7/14 and 12/25/21/4, respectively. The rate of other complications was 69%, and that of ILD was 45%. The percentage of administration of PSL, MTX, SSZ, bucillamine and biologics were 82 % (mean 5.4 mg), 31 % (mean 4.9 mg), 26 %, 21 %, and 11 %, respectively. Specific biologics were IFX 1, ETN 2, TCZ 2 and ABT 2, respectively. The median of SDAI and the mean of DAS28ER were 6.59 and 2.83, respectively, and 68 % and 54 % of the patients were in the low disease activity or remission. In conclusion, the treatment was light compared with younger patients but the disease control seems to be comparable.

W74-5

Management of liver impairment and gastrointestinal symptoms in patients on MTX treatment~Usefulness of daily administration of Foliamin 1mg/day~

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Conflict of interest: None

[Background] From February 2012, use of MTX up to 16 mg/week became possible. However, dose-dependent adverse events such as liver impairment and gastric disorders posed challenges. Interventions such as increased foliamin dose were routinely applied. [Objectives] Clinical efficacy of changing foliamin dose from 5 mg/week to 1 mg daily for liver impairment and gastric disorders in MTX-treated patients was investigated at the author's institution. [Methods] Among rheumatoid arthritis (RA) out-patients on MTX, 34 with liver impairment and 20 with gastric disorders were studied. Mean age was 54 years, mean MTX dose 12 mg/week, mean AST (GOT) at the change was 56, and mean ALT (GPT) 88. Changes in symptoms were assessed up to 3 months. [Results] 1) Liver impairment symptoms improved significantly at 1 month, and continued uneventfully up to 3 months. MTX dose decrease was needed for 1 patient while an increase was possible for 6. 2) Gastric symptoms disappeared in 12 patients after 1 month, in 6 after 2 months, and 1 after 3 months with no decrease in MTX dose, the remaining 1 patient applied self control but the symptom persisted. [Conclusion] Changing the foliamin dose to 1 mg daily was shown to be an effective intervention option for such gastric and liver adverse reactions of MTX.

W74-6

Disease activity of patients who newly treated with MTX in our hospital have ameliorated after it have approved high dosage of MTX for RA management

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Conflict of interest: None

Objectives: High dosage of MTX for RA management was approved at February 2011 in Japan. We examined how to have used MTX in our hospital bordering on that time. Method: We compared the patients who had newly treated with MTX from January 2008 to December 2010 (Group 1: G1) with that from January 2011 to December 2012 (Group 2: G2) in the starting dose of MTX, disease duration, disease activity, and the number of patients treated with any biologic agents for one year. The change of disease activity at one year later were also examined. Result: 147 patients were included in G1 and 152 patients in G2. Average disease duration was 4.0 years in G1 and 3.8 years in G2. The starting dosage of MTX were 5.7 mg/W and 6.0 mg/W, and average disease activity at the time of MTX introduction was 4.84, 4.88, respectively. We could observe 145 patients in G1 and 143 patients in G2 for one year after. Average MTX dose at one year after was of 7.2mg/W and 8.0mg/W, and Average disease activity was 3.63 and 3.19, respectively. The number of the patients treated with any biologic agents within the observation period were 10 (6.8%) in G1, 13 (9.1%) in G2. Conclusion: A period to treat with MTX tended to shorten. And disease activity at one year after treatment in Group 2 was lower than that in Group 1.

W75-1

Interim report of Iguratimod all-patient surveillance in patients with rheumatoid arthritis (first report)

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Conflict of interest: Yes

[Objectives] We observed patients with rheumatoid arthritis (RA) being treated with Iguratimod (IGU). Here, I report the results of an interim analysis of RA patients who were observed for 24 weeks. [Methods] This surveillance included 2,699 patients who had received IGU up to April 14, 2013. The analysis set with data collected until September 2013 included 357 patients (mean age, 64.9 ± 11.8 years; mean disease duration, 10.76 ± 10.02 years). A total of 321 patients were receiving other antirheumatic drugs when IGU treatment was initiated, including Methotrexate (MTX) in 169 patients, non-MTX disease-modifying antirheumatic drugs (DMARDs) in 139, biological agents in 41, and steroids in 215 (some receiving multiple drugs). [Results] The incidence of adverse drug reactions (ADRs) was 42.58% (152/357 patients). Major ADRs included gastrointestinal disorders, hepatobiliary disorders, and abnormal laboratory values. [Conclusion] The major ADRs observed during this surveillance are comparable to those observed in clinical studies.

W75-2

Influences of disease activity at initiation of iguratimod on efficacy of iguratimod in patients with rheumatoid arthritis

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Conflict of interest: Yes

[Objectives] To investigate efficacy of iguratimod (IGU) in patients with rheumatoid arthritis (RA) with focus on disease activity (DA) at initiation of IGU. [Methods] Data of multicenter study (TBC) was used. 34 cases (29 female and 5 male) were included. These patients were divided into two groups (high DA group; HG and moderate and low DA group; MLG) using DAS28-CRP at initiation of IGU. 17 cases were included in HG and 17 cases were included in MLG. Patients' characteristics, time course of disease activity, drug retention rate at 24 weeks and change value in DA parameter s from 0w to 24w were compared with each other. [Results] MTX use rate was significantly low in HG compared with in MLG (35.3% vs. 76.5%). Mean DAS28-CRP at 0, 4, 8, 12 and 24w was 5.23, 4.64, 4.41, 4.21 and 3.60 in HG and 3.20, 3.22, 3.01, 2.90 and 2.65 in MLG. DAS28-CRP was significantly decreased in only HG. Same finding was observed in SDAI. Drug retention rates at 24w were 70.6% in HG and 88.2% in MLG. Delta DAS28-CRP from 0w to 24w were 1.77 in HG and 0.58 in MLG (p=0.03). Delta SDAI were 16.1 in HG and 3.5 in MLG (p=0.03). [Conclusion] This study suggests that IGU is one of the options not only in RA patients treated with sufficient MTX but also in RA patients with high DA treated with insufficient MTX.

W75-3

Long-term efficacy of tramadol hydrochloride/acetaminophen combination tablet in rheumatoid arthritis patients with chronic pain

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Conflict of interest: None

[Objectives] Recently, it is reported that weak opioids are effective for chronic musculoskeletal pain. We previously reported the clinical efficacy of tramadol hydrochloride/acetaminophen combination tablet (TRAM/APAP) in rheumatoid arthritis (RA) patients with chronic pain which were inadequately controlled by DMARDs, biologics and/or NSAIDs. In this presentation, we investigated efficacy and safety of the long-term administration of TRAM/APAP in RA patients. [Methods] Of 38 RA patients receiving TRAM/APAP, 10 patients (male, n=1; female, n=9) were administered for long-term (52 weeks) in our hospital. An average age was 69 years (range 55-89 years) and the mean disease duration was 11 years. The clinical response was assessed by VAS and HAQ-DI. [Results] The mean VAS score decreased from 68.9 mm at the start of TRM/APAP to 39.4 mm, 30.2 mm and 29.5 mm at week 4, 28 and 52, respectively. The mean HAQ-DI score improved from 1.58 to 1.07, 1.05 and 1.11 at week 4, 28 and 52, respectively. Adverse events (drowsiness and nausea) were decreased or improved during administration. [Conclusion] Long-term administration of TRAM/APAP was highly effective for chronic pain and improved ADL in RA patients. Use of TRAM/APAP is valuable treatment option for RA patients with chronic pain.

W75-4

Tolerability of Tcilizumab (TCZ) and Leflunomide (LEF) combination therapy in daily clinical practice

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Conflict of interest: None

[Objectives] To evaluate tolerability of LEF / TCZ combination therapy in RA patients. [Methods] Ten patients with intractable RA patients (mean age 71±13age, mean disease duration14.5±7.3ys, 9 females and 1male) were evaluated retrospectively. All patients were Stage4 and Class3 in the functional class. Ten patients did not reach enough effects by MTX/TCZ combination (nine) and Cyclophosphamide (Cy)/TCZ combination (one). We changed MTX and Cy to LEF (10 mg/day). Patient's complications consisted of cutaneous vasculitis in five, lupus nephritis (Type4) in one and scleroderma in two. Patients with scleroderma had pleural effusion and interstitial pneumonia respectively. Average observational period was 147days (range 11~255days). [Results] 6 cases showed moderate response improvement of EULAR criteria (4.51 to 3.55). Four was no response. Cutaneous vasculitis were improved in four, but relapse in one, unchanged in one. Two patients who discontinued combination were due to rash, deranged liver test and pruritis. It was not observed bone marrow suppression in all. In comparison with 56 cases of LEF alone, the LEF/TCZ combination did not show any differences in adverse effects incidence. [Conclusion] Our findings show that LEF/TCZ combination therapy is well tolerated by many severe RA patients.

W75-5

The efficacy of iguratimod on patients with rheumatoid arthritis

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Conflict of interest: None

Objective: Iguratimod inhibits the production of immunoglobulins and various inflammatory cytokines, and arthritic inflammation of the synovium in collagen-induced arthritis. Some patients with rheumatoid arthritis (RA) were refractory to disease-modifying antirheumatic drugs (DMARDs), and was not able to use methotrexate (MTX) and biological agents for complications. The purpose of this study was to evaluate the efficacy of iguratimod on them. Method: 8 patients with RA, mean of age 67.7 years and disease duration 13.8 years were treated with iguratimod. RA disease activity was evaluated by DAS28-CRP. We discussed adverse reactions associated with Iguratimod. Result: Iguratimode was effective in 4 patients and mean of DAS28-CRP decreased from 3.87 to 1.87 after six months. 4 patients had to stop iguratimod for adverse reactions. 2 patients with positive QuantiFERON-TB Gold In Tube had severe drug-induced pneumonitis. 1 patient who had experienced MTX-induced liver dysfunction had liver dysfunction. 1 patient had bloody feces. Conclusion: Iguratimod was effective for 4 patient, conversely 4 patients had drug-induced pneumonitis and liver dysfunction. Patients with past history of tuberculosis infection or liver dysfunction need pay attention to treated with iguratimod.

W75-6

A clinicalstudy of usefulness of SASP for potent inhibitor of PCP in RA patients

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Conflict of interest: None

[Objectives] Pc is fungal respiratory pathogen that cause life-threatening pneumonia in RA patients who receive immunosuppressive therapy. Prophylaxis against PCP with trimethoprimsulfamethoxazole is failed as often as not by adverse effects og TMP-SMX. OC cekk wakk beta-glucans initiate macrophage inflammatory responses through NF-kappaB activation while SASP modulates immune response as a potent inhibitor of NF-kappaB while SASP modulates imuune responses as a potent inhibitor of NF-kappaB. so we evaluate usefulness of SASP which is pootent inhibitor of PCP in RA patients by retrospective study. [Methods] 216 RA patients who did not prevent PCP by using TMP-SMX and received continuously MTX from 2005.1 to 2013.10 at follow up period were evaluated. They were divided into 2 groups whether patients combined use of NTX and SASP (n=61) or not (n=155). we evaluate usefulness of SASP for potent inhibitor of PCP by using Fisher's exact test. [Results] All patiants who developed PCP was is non SASP group (n=11). incidence of PCP in SASP group was significantly lower than non SASP group (P=0.036). [Conclusion] Our study suggests that SASP is potent inhibitor of PCP in RA patients.

W76-1

Presence of 'red complex' bacteria in oral microbiota associates with treatment-resistance in rheumatoid arthritis

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Conflict of interest: Yes

[Objectives] 'Red complex' is a group of bacteria that are associated with severe forms of periodontitis. The purpose of the study is to determine whether the presence of 'red complex' bacteria in oral microbiota is associated with treatment-resistance in rheumatoid arthritis (RA). [Methods] We conducted a prospective cohort study in the KURAMA cohort. Buccal swab samples were obtained from RA patients and the presence

of 'red complex' was determined by Taqman PCR. Ninety six patients who did not fulfill either SDAI remission or low disease activity (LDA) at the time of enrollment were followed up and the reduction in the disease activity (ΔSDAI) after 1 year was analyzed for their association with 'red complex'. [Results] Among the study subjects, 19 (19.8%) patients harbored all three species of 'red complex'. ΔSDAI was smaller in these patients than the others (1.01±1.28 vs 5.15±0.79, p=0.0353). As a consequence, SDAI remission or LDA rates after 1 year was different between these two groups (0 % vs 10 % for remission, 35.2 % vs 45.7% for LDA). ΔSDAI was not different among the patients who have 1 or 2 'red complex' bacteria or those without 'red complex'. [Conclusion] Presence of 'red complex' bacteria in oral microbiota is associated with treatment-resistance in RA.

W76-2

Midkine co-relates disease activity of rheumatoid arthritis

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Conflict of interest: None

Objective: Midkine (MK) is a heparin-binding protein, which increases in several malignant tumors and considered to play an important role in proliferation and invasion. MK is also known to increase inflammatory conditions such as rheumatoid arthritis (RA) and considered to enhance inflammation and also promotion of cell survival and repair. In RA, MK is expressed in synovial cells, however, the relation between MK and RA activity has not been examined well so far. In this study, we analyzed MK in RA serum and examined statistical analysis with RA activity. ***Method:*** Serums from 94 patients with RA in our hospital were obtained, and compared with several disease activity index, such as serum CRP, serum MMP-3, DAS28 and HAQ. MK concentration in serum was also compared with that of healthy donors. ***Results:*** MK in RA serum was apparently increased compared with healthy donors (752.6±50.59 (M±SD) pg/mL vs 180.36±26.19 pg/mL, Mann-Whitney U analysis, P=0.0000). MK concentration was correlated with CRP (P=0.0284) and HAQ (P=0.0043), but not with MMP-3 and DAS28 (multiple regression analysis). ***Conclusion:*** MK was increased in serum of RA patients and MK was correlated with disease activity, CRP and HAQ. These results suggest the possibility of MK as a therapeutic target.

W76-3

Residual synovial inflammation determined by comprehensive ultrasound assessment predicts relapse after discontinuation of biological treatment in patients with rheumatoid arthritis in clinical remission

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Conflict of interest: Yes

[Objective] To determine whether the comprehensive ultrasonographic assessment of synovial inflammation predicts relapse after discontinuation of biological treatment in patients with RA in clinical remission. [Methods] RA patients in clinical remission (DAS28<2.6) receiving biological treatment who agreed to discontinue the biological treatment were recruited. Patients underwent a comprehensive ultrasound scan on 134 synovial sites in 40 joints and were prospectively followed up for 6 months. [Results] Forty-two patients were enrolled. Using the optimal cut-off values determined by ROC analysis, relapse rates were significantly higher in patients whose total ultrasound scores at discontinuation were high than in those whose scores were low (P<0.001 for both total gray-scale (GS) and power Doppler (PD) scores), whereas the difference between high and low DAS28 was not statistically significant (P=0.158) (log-rank test). PPV and NPV were 80.0% and 73.3% for the total GS score and 88.9% and 74.2% for the total PD score, respectively. [Conclusion] In RA patients in clinical remission receiving biological treatment, residual synovial inflammation determined by comprehensive ultrasound assessment predicts relapse within a short term after discontinuation of the biological treatment.

W76-4

Change of patient satisfaction and disease activity after introducing a novel touch-panel system combined with RAPID3 (Hybrid MiRAi-RAPID3)

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Conflict of interest: None

[Objectives] We upgraded computerized touch-panel system for facilitating the assessment of RA (MiRAi) to allow patients to track their disease activity (RAPID3) independently on their monitor even before consulting their physician. (Hybrid MiRAi-RAPID3) We evaluated change of patient satisfaction and disease activity after introducing this novel touch-panel system. [Methods] Nurses asked RA patients who visited between 2/6/2012 and 3/9/2012 to fill out the anonymous questionnaires including patient satisfaction VAS and RAPID3 before and 6 months after introduction of this system. We also asked "Can you track your disease activity more easily after using this system?" and patients answered either "Agree", "Neither agree nor disagree", or "Disagree". [Results] The initial and second evaluation was obtained from 302 and 271 pts. Patient satisfaction VAS (median, IQR) improved from 84 (67, 96) to 87 (73, 98) (p=0.004). RAPID3 (median, IQR) improved from 6.7 (3.2, 12.3) to 6.3 (2, 12.8) (p=0.0039). "Agree" group (92 pts) exhibited better patient satisfaction and RAPID3 improvement than "Disagree" group (35 pts). [Conclusion] Patients who agreed to track their disease activity more easily after using Hybrid MiRAi-RAPID3 may achieve higher patient satisfaction and better disease activity.

W76-5

Anti-tumor necrosis factor biologics in anti-human T-lymphotropic virus type-1 antibody positive patients with rheumatoid arthritis

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Conflict of interest: None

[Objectives] To investigate clinical response to anti-tumor necrosis factor (TNF) therapy in anti-human T-lymphotropic virus type-1 (HTLV-1) antibody-seropositive rheumatoid arthritis (RA) patients. [Methods] We retrospectively surveyed the HTLV-1 seroprevalence in RA patients to whom anti-TNF therapy was newly introduced in Nagasaki University Hospital between January 2009 and August 2013. Therapeutic response was evaluated in anti-HTLV-1 antibody-seropositive and same number of seronegative patients at six months after the beginning of anti-TNF therapy by using 28-joint Disease Activity Score (DAS28ESR). [Results] 120 patients were enrolled in the study, and positivity of anti-HTLV-1 antibody was investigated in 88 patients among them. There were 13 HTLV-1-seropositive patients, and DAS28ESR before treatment was 5.45±1.35. After 6months treatment, DAS28ESR was significantly decreased to 4.01±1.83 (p=0.048). As control group, DAS28ESR for anti-HTLV-1 antibody-seronegative 13 patients was examined. It was 5.02±1.22 before

treatment, and significantly reduced after the therapy (5.02±1.22, p=0.003). [Conclusion] These data suggested that anti-HTLV-1 antibody-seropositive patients had greater resistance to anti-TNF therapy than anti-HTLV-1 antibody-seronegative patients.

W76-6

Prognostic factors for rapid radiographic progression are different between Adalimumab and Tocilizumab

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Conflict of interest: None

[Objectives] To analyze prognostic factors for rapid radiographic progression (RRP). RA patients were treated 1 year with adalimumab (ADA: TNF inhibitor) and tocilizumab (TCZ: non-TNF inhibitor). [Methods] Modified total sharp score (mTSS) were assessed to find RRP (ΔmTSS/year>3) in 50 ADA and 35 TCZ treated RA. DAS28-ESR, HAQ-DI, CRP, ESR, MMP3, RF, and anti-CCP antibody were measured and compared with RRP and non-RRP to investigate predictor of RRP in ADA and TCZ. The chi-squared test and the Wilcoxon test were used for the statistical analysis. [Results] Among baseline clinical factors in ADA treated patients, baseline serum MMP-3 (592.3 ng/ml vs 323.2 ng/ml, $p<0.05$) was significantly increased in RRP group compared with non-RRP group and in TCZ treated RA patients, mTSS/year (14.2 vs 8.6, $p<0.01$), serum CRP level (8.5mg/dl vs 3.2 mg/dl, $p<0.05$), DAS28-ESR (6.5 vs 5.7, $p<0.05$) and SJC (15.9 vs 11.0, $p<0.05$) were significantly increased in RRP group compared with non-RRP group. [Conclusion] Prognostic factors for RRP in ADA and TCZ were different - baseline MMP-3 for ADA, baseline mTSS/year, CRP, DAS28-ESR, and S.J.C for TCZ.

W77-1

Effect of patient global assessment in maintenance of Boolean remission criteria to lead better functional outcome in RA in daily practice, based on the IORRA cohort

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Conflict of interest: None

[Objectives] To investigate the effect of patient global assessment (PtGA) in Boolean remission criteria to lead long-term functional outcome in RA patients. [Methods] RA patients enrolled in IORRA from2009 to2012 were selected. Tentative remission criteria was defined fulfillment of SJC≦1, TJC≦1 and PtGA (/10cm) ≦1 (T1=Boolean practice) ≦1.5 (T1.5), ≦2 (T2) and ≦2.5 (T2.5), respectively. All patients were evaluated whether they achieved the remission criteria or not from 2009 to 2012. The proportions of patients with J-HAQ score progression from2009 to2012 were calculated according to the number of times in which each remission criteria was achievd. [Results] A total of 3,233 patients were selected (females 86%, mean disease duration 11.7 years, J-HAQ 0.65). The proportion of patients whose J-HAQ score progressed was higher in the group according to less frequently fulfilled each criteria. The proportions of patients whose J-HAQ score progressed during the period in each group continuously achieving T1, T1.5, T2 and T2.5 criteria were 6.7%, 6.8%, 8.6% and 10.3%, respectively. [Conclusion] Continually achievement of Boolean remission criteria is important to prevent physical functional. Re-evaluation for the cut off point of PtGA in Boolean remission criteria might be needed.

W77-2

Evaluation of physical Health Assessment Questionnaire (HAQ) in Elderly Patients with Rheumatoid Arthritis

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Conflict of interest: None

[Objectives] Health Assessment Questionnaire (HAQ) is widely used to measure disability in RA, and is known to be higher in elderly patients. This study is to investigate the influence of aging upon aggravation of HAQ in RA. [Methods] In 777 patients with RA, JHAQ score was compared among six groups: patients younger than 60 years with disease duration shorter than 60 months (A) and longer than 60months (B), 60 to 69 years patients with shorter duration (C) and longer (D), patients older than70 years with shorter duration (E) and longer (F). [Results] There were 103, 122, 93, 166, 119 and 174 patients and average score of JHAQ was 0.168, 0.307, 0.276, 0.404, 0.544 and 0.783 in group A, B, C, D, E and F, respectively. [Conclusion] Major factors aggravate JHAQ score in RA are thought to be disease activity, joint damage and aging. Elevation of HAQ score seems to be majorly caused by disease activity in group A, and the effect of joint damage were added to it in B. The effect of aging on JHAQ score could be identical with the difference between C and A, 0.108, in 60s and between E and A, 0.376, over 70s. The increase of JHAQ score by aging accounts for 69.1% of total in group E and 48.0% in F. We must consider the effect of aging on the evaluation of HAQ in RA patients over age 70 years.

W77-3

Combination of MRI-proven osteitis with 2010 RA classification criteria improves the diagnostic probability of early RA

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Conflict of interest: None

[Objectives] To investigate whether the MRI features improves the diagnostic performance of 2010 RA classification criteria. [Methods] One hundred sixty-four early arthritis patients whose duration less than 6 months were enrolled. All of the subjects underwent physical examination, blood tests, and enhanced MRI on the same day. Gold-standard early RA was defined based on being treated with DMARDs during the first year. We investigated the diagnostic performance of 2010 RA criteria with or without the finding of MRI-proven joint injury. [Results] 2010 RA criteria classified early RA with sensitivity of 62.4%, specificity of 83.1%, PPV of 82.9%, NPV of 62.8%, and accuracy of 71.3%. Osteitis was the most specific MRI finding in the gold-standard early RA patients. We used a decision-tree algorithm that involves initially applying 2010 RA criteria, and if not fulfill these criteria, the MRI-proven osteitis rule is introduced. The tree algorithm has been shown to differentiate patients more efficiently than the 2010 RA criteria alone, exhibiting sensitivity of 79.6%, NPV of 74.0%, and accuracy of 78.0%. [Conclusion] The present data indicate that the combination of MRI-proven osteitis with the 2010 RA classification criteria improves the diagnostic probability of RA at early stage.

W77-4

The efficacy and limitation of tight control for patients with long-standing rheumatoid arthritis

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Conflict of interest: None

[Objectives] To investigate the efficacy and limitation of tight control for patients with long-standing rheumatoid arthritis (RA). [Methods] Forty-three RA patients who met the criteria; more than 2 years disease duration, moderate or high disease activity, and over a consecutive 6-month follow-up, were enrolled into this study. We practiced "tight control" and compared treatment status, CRP, ESR, MMP-3, SDAI, and HAQ-DI between at the initial and last visit. We also investigated the induction rate of remission/low disease activity at the last visit. [Results] The median of disease duration was 10 years. At the last visit, MTX dose and induction rate of biologics were statistically high, and CRP, ESR and MMP-3 were improved significantly. The median SDAI was improved from 22.2 at the first visit to 6.5 at the last, and the induction rate of remission/low disease activity was 23.3%/74.4%, respectively. Although, the median HAQ-DI of all patients was improved from 0.63 to 0.50 significantly, the patients whose disease duration exceeded 10 years showed no significant improvement. [Conclusion] The tight control for established RA improved disease activity, whereas showed poor improvement of HAQ-DI, especially in the patients who had long-term disease duration more than 10 years.

W77-5

Correlation of serum MMP-3 level with the inhibitory effect of tacrolimus on progression of joint damage

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Conflict of interest: None

[Objectives] To assess the significance of serum MMP-3 level with the inhibitory effect of tacrolimus on progression of joint damage. [Methods] We examined 27 patients with rheumatoid arthritis (RA) who continued tacrolimus treatment over 2 years. We measured CRP, ESR, MMP-3 and each parameter of DAS28-CRP. Progression of joint destruction was assessed as a yearly change in mTSS (ΔmTSS). We assessed a correlation between clinical variables including serum MMP-3 level and ΔmTSS. [Results] The mean ΔmTSS was 2.63 in the first year and then decreased to 0.69 in the second year. The baseline clinical variables were not correlated with the ΔmTSS in the first year nor the second year of tacrolimus treatment. However, the MMP-3 levels at 12-month was well correlated with the ΔmTSS in the first year ($r = 0.39$, $p < 0.05$) and in the second year ($r = 0.53$, $P < 0.01$). Analysis of the receiver operating characteristic curve (ROC) indicated the MMP-3 cut off value to be 113 ng/ml at 12-month for the radiographic non-progression in the second year. [Conclusion] Our results showed that serum MMP-3 levels at 12-month could predict the progression of joint damage during tacrolimus treatment.

W77-6

Analysis of predictive biomarker which reflects the efficacy of Tocilizumab treatment for bio-naive RA patients

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Conflict of interest: None

【Background】The efficacy of biologics is different on individual RA patients, therefore we can never recommend the best biologics for each RA patient. Additionally, there is a little report about good predictive biomarker for the efficacy of biologics before administration. We suggested that the serum levels of IL-10, IL-17A, IL-6 and IP-10 were possible to become predictive biomarkers for the efficacy of TCZ. However we have the limitation that the influence of prior biologics to these biomarkers is not clear.【Objectives】We focused on serum cytokines expression with Bio-naïve RA patients to identify the predictive markers for TCZ.【Methods】We analyzed several cytokines from Bio-naïve RA patients treated with TCZ. Serum cytokines were measured using ELISA kit before TCZ administration. We classified the disease activity at 24 weeks into responder and non-responder group, and investigated the influence of these biomarkers in two groups.【Results】Among serum cytokines measured by ELISA kit, IL-10 was high in responder group ($P<0.05$).【Conclusion】In this study, the levels of IL-10 were different between effective cases and ineffective cases. We suggest that these cytokines are possible to become predictive biomarkers for the efficacy of TCZ in Bio-naïve RA patients.

W78-1

A case study, quickly administration of SFPP therapy was very effective for TTP complicated with MCTD

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Conflict of interest: None

【Case】female, 21 years old【Present Illness】She was doubted collagen disease on February 2010, because of positivity of antinuclear antibody, anti RNP Ab, and Raynaud phenomenon. March in 2011, she complained high fever, pharyngeal pain and headache, and several days later she admitted to our hospital because of purpura. Thrombocytopenia occurred, so that she was hospitalized on emergency.【Progression after hospitalization】We diagnosed MCTD because Raynaud phenomenon, anti RNP Ab positivity, butterfly eruption, leukopenia and low grade of % DLCO. We doubt for TTP because of thrombocytopenia, spallation with hemolytic anemia and fever. Activity of ADAMTS13 was less than measurement activity. We administered Single Filtration Plasmapheresis (SFPP) to her for 4 days continuously, and improved dramatically.【Consideration】We had followed up her for three years and thrombocytopenia happened 36 week pregnancy in October 2013. We considered recurrence of TTP, so administered SFPP as soon as possible that condition of a disease was improved and could be administered cesarean operation successfully. We report this case consideration with literature because we could dramatically improved TTP both first time activity and recurrence of activity by administration of SFPP very quickly.

W78-2

Effects of esomeprazole (EPZ) on gastroesophageal reflux disease (GERD) in patients with connective tissue diseases (CTDs) treated with NSAIDs (Non-Steroidal Anti-Inflammatory Drugs) or steroids

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Conflict of interest: None

【Objectives】In the patients with CTDs, GERD often occurs although proton-pump inhibitors (PPIs) are widely used. Effect of EPZ, a newly developed PPI on GERD, was studied.【Methods】513 patients (male: 136, female: 377) with CTDs treated with steroids or NSAIDs, and antacid drugs including PPIs. When any gastrointestinal symptoms were persisting, the antacid drugs were changed to EPZ, and gastrointestinal symptoms were evaluated by using GERD questionnaire before and 8 weeks after switch to EPZ.【Results】The percentage of patients taking PPIs and NSAIDs were 56.3% and 25.6%, respectively. The average prednisolone dosage was 7.8 mg/day. At baseline, 416 (81%) patients had no symptoms, and 97 (19%) had remaining gastrointestinal symptoms. In 34 out of 97 GERD patients with remaining symptoms, antacids were changed to EPZ. After 8 weeks, GERD symptoms improved in 14 (41%) patients and disappeared in 9 (32%) patients.【Conclusion】The patients with CTDs on steroids or NSAIDs frequently have various gastrointesti-

nal symptoms despite the use of antacids. Switch from current antacid drugs to EPZ improved their symptoms in some patients. Thus, EPZ might be more useful in some patients with remaining gastrointestinal symptoms.

W78-3

Effective multiple medicine combined therapy for Fibromyalgia

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Conflict of interest: None

[Objectives] Multiple medicine (Fluvoxamine+Chlorpphenesine Car bamate+Etizolam+Neurotropin+Zolpidem) are comfirmed to be effective forpain of Fibromyalgia (FM). This examination can evaluated the effect and make a comparative study between Pregabalin. [Methods] In 80 case diagnosised as FM, 40 subjects have treated with multiple medicine: Fluvoxamine + ChlorpphensineCarbamate +Etizolam+ Neurotropin +Zolpidem. And other subjects have treated with Pregabalin. After 2 months, the some efficacy of each group can be evaluated. Furthermore the subjects which showed no response to pain were changed into the other therapy (multiple medicine or Pregabalin). The symptom was evaluated using original scale. [Results] In the group using multiple medicine (n=40), 31 subjects (77.5%) showed symptom are improved. The other 9 subjects' medicinehave changed to Pregabalin. This result showed Pregabalin was effective for only 2 subjects. Whereas in the group using Pregabalin (n=40), 24 subjects (60%) showed symptom are improved. [Conclusion] Multiple medicine (Fluvoxamine+Chlorpphenesine Carbamate+Etizolam +Neurotropin+Zolpidem) are confirmed to beeffective. Side effects were confirmed slightly. So this combined multiple medicine can be effective for some symptom of FM.

W78-4

Adverse effects of mycophenolate mofetil - Analysis of 52 Japanese patients -

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Conflict of interest: None

[Objectives] Mycophenolate mofetil (MMF) is a standard concomitant drug for the remission induction in the patients with active lupus nephritis in Western countries. Several reports demonstrated the effectiveness of MMF for Japanese patients with various collagen diseases while safety of MMF has not been well-evaluated. [Methods] We analyzed 52 patients (SLE 30, ANCA-associated vasculitis 15, others 7) administered with MMF between January 2006 and December 2012. [Results] During 1 year, adverse events (AEs), required to reduce or discontinue MMF, occurred in 23 patients (44.2%). Common AEs were relapse (9 cases), cytopenia (9 cases) and infection (5 events). Seven patients (13%) discontinued MMF during 1 year. The patients with AEs were administered more dosage of MMF than without AEs, whereas age, renal function and blood cell counts were similar between 2 groups. Especially the patients administered over 1000 mg/day of MMF (N=30) experienced more AEs than 1000 mg/day or less (N=22) (60.0% vs. 22.7%, P=0.006). [Conclusion] Previous reports revealed that lower dosage of MMF might be preferable in Asians and the comparable dosage used in clinical settings in Western countries caused more AEs. In Japanese patients, it may require the reduction of dosage of MMF for safety use.

W78-5

Evaluation of the utility of Interferon-gamma Release Assays (IGRA) in the rheumatic disease center, comparison between QFT and T-SPOT test

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Conflict of interest: None

[Objectives] Early diagnosis of tuberculosis is important for the immunocompromised hosts including patients on immunosuppressive therapy, and to prevent the tuberculosis reactivation, we must diagnose latent tuberculosis infection (LTBI) as early as possible. Because of its lower specificity, classical diagnostic method, tuberculin skin test, is not enough for diagnosis, and the use of Interferon-gamma Release Assays (IGRA) which measure IFN-gamma production from stimulated antigen-specific T cells are recommended in tuberculosis related guidelines. In such situations, we evaluated two commercial interferon-gamma assays, Quantiferon (QFT) and T-SPOT test, mainly for immunocompromised patients. [Methods] We reviewed clinical records of 439patients who were performed IGRA testing 2012-2013. [Results] QFT and T-SPOT tests were performed for 260 and 179 patients respectively, and were negative in 174 (66.9%) and 165 (86.7%) patients, doubtful positive in 31 (11.9%) and 8 (0.04%), positive in 24 (9%) and 13 (0.76%). 31 (11.9%) and 3 (0.02%) patients had an indeterminate results respectively. [Conclusion] Compared with the QFT test, the percentages of indeterminate patients were less in T-SPOT test. We report the utility of IGRA and the relation to details of the backgrounds of patients.

W78-6

The American College of Rheumatology 2010 diagnostic preliminary criteria and 2011 revised criteria for fibromyalgia (FM) would be changed the concept of disease entity, evaluating by the Japanese patients with FM

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Conflict of interest: None

[Objectives] To evaluate the concept of disease entity of fibromyalgia (FM) classified or diagnosed by ACR 1990 criteria, 2010 criteria, or 2011 criteria using Japanese patients with FM. [Methods] 65 patients with FM diagnosed by ACR 1990 criteria were enrolled at the time diagnosed as FM. American Psychiatric Association (APA) proposed the new classification criteria for psychiatric disorders as DSM-5, deleted somatoform disorders, and presented a new concept of somatic symptom disorder (SSD). We evaluate the concept of SSD, comparing with FM. [Results] In ACR 1990 criteria FM is one of chronic widespread pain disorders, as rheumatic disorders, however in 2010 and 2011 criteria FM would be changed as multi-somatic symptom disorder. Moreover, in result of eliminating the tender points FM changed to a functional disorder, as psychosomatic or psychotic disorders. All of FM patients met the criteria od SSD, proposed by APA DSM-5. [Conclusion] A new concept of SSD and changing of diagnostic criteria (2010 or 2011criteria) would be more confused in the FM clinic.

W79-1

Down-regulation of β-2-microglobulin mRNA in peripheral blood by leukocytapheresis for rheumatoid arthritis

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Conflict of interest: None

[Objectives] Leukocytapheresis (LCAP) is a safe, unique therapy for rheumatoid arthritis (RA) patients even in case of drug allergy or infectious state. Various findings have been reported estimated to concern with LCAP efficacy, but the details are still unknown. We reported the reductions of mRNAs in peripheral blood associated with antigen presenting and cell adhesion just after the LCAP treatment for RA patient. To confirm these findings, we investigated serum β-2-microglobulin (B2M)

mRNA expression and protein levels by RT-PCR and enzyme linked immunesorbent (ELISA) assay in the LCAP treatment. [Methods] Peripheral blood samples were collected immediately before and after treatment from RA patients who received LCAP (n=6 for mRNA expression, n=14 for ELISA assay). Serum B2M levels was measured by ELISA assay. The expression levels of B2M mRNA was evaluated using real-time RT-PCR. The datasets was analyzed with IBM SPSS Statictics version21. [Results] The B2M mRNA expression level was down-regulated after the LCAP treatment (before; 0.84±0.87, after; 0.43±0.49, $p<0.05$). Peripheral blood concentration of B2M by ELISA was also decreased (before; 2.28±0.82μg/ml, after; 2.12±0.70μg/ml, $p<0.05$). [Conclusion] These findings may relate with previously unknown LCAP efficacy for RA patients.

W79-2

Analysis of the large intestinal perforation cases associated with connective tissue disease treated by PMX-DHP

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Conflict of interest: None

[Objectives] There were rarely seen to be complicated with the large intestinal perforation during treated with steroid for the connective tissue disease (CTD), and we analyzed the factor which influenced the prognosis. [Methods] We analyzed the 16 cases with CTD operated for the large intestinal perforation and treated by PMX-DHP in our hospital. [Results] As for the breakdown of CTD, SLE cases were seven, the most (43.8%), RA were two (12.5%), other PN, MPA, MRA, MCTD, AOSD, PMR were for each one case (6.3%). The mean contraction from these CTD developed was 11.7 years. The blood pressure of pre-operation, the number of the platelets after the operation, and the PaO2/FiO2 ratio after PMX-DHP were lower statistically significantly in non-survival group than in survival group. There were no difference with the survival group and the non-survival group in the number of times of PMX-DHP and the time required for until PMX-DHP started. [Conclusion] The CTD patients with the large intestinal perforation had long-term contraction of the CTD developed, and the non-survival rate was high (31.3%).

W79-3

Searching for the factors of rapid eGFR decline in RA patients

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Conflict of interest: None

[Objectives] We examined our outpatients to find the factors which associate the decline. [Methods] We retrospectively examined the subjects, who admitted our RA department between April and September in 2009. Subjects were 20 years or older. After checking the distribution of the estimated glomerular filtration rate (eGFR) at observation initiation, we picked up the cases that we were able to evaluate eGFR between April and September in 2013, and calculated the rate of decline in the four years. And we examined the group “Rapid decliner”, which showed 3% / year or more decline of the eGRF, to find contribution factors of the decline. [Results] 361 subject (89 male, 272 female, average age 61.2±12.1 years old). The mean eGFR was 76.8 ml/min/1.73mm^2. In the 25% of the male and the 15% of the female, the eGFR were under 60 ml/min/1.73mm^2. Among the subjects, we examined the rate of eGFR decline in 215 cases, which was 4.4 ml/min/1.73mm^2 in four years. CRP value at the begining was significantly high, and Hb and Alb value at the end were significantly low in the “Rapid decliner”. [Conclusion] In RA patients, eGFR decline tends to be faster, and CRP Alb Hb may be the associated factors.

W79-4

Long-term follow-up outcome of patients with rheumatoid arthritis following filtration leukocytapheresis therapy

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Conflict of interest: None

[Objectives] To determine the long-term efficacy of leukocytapheresis (LCAP) using Cellsorba® column for rheumatoid arthritis (RA), we performed case analysis. [Methods] Five apheresis procedures were performed in 72 drug-resistant RA, with 1-week intervals between procedures. The efficacy of filtration LCAP was evaluated according to ACR and EULAR definition of improvement of RA. [Results] Corticosteroid and/or disease-modifying antirheumatic drugs could be maintained or tapered in 28 patients (39%) at 1 year after LCAP therapy. Sixty-eight and 44 % of these patients achieved more than ACR 20 and 50, 83 and 36 % achieved more than moderate and good response at that time, respectively. [Conclusion] LCAP treatment is an effective and well-tolerated treatment for patients with drug-resistant RA.

W79-5

Efficacy of leukocytapheresis for Rheumatoid arthritis

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Conflict of interest: None

[Objectives] To evaluate the efficacy of leucocytapheresis (LCAP) for rheumatoid arthritis (RA). [Methods] We enrolled 85 RA patients from 2006 to May 2013. All patients continued drug therapy and were treated with LCAP weekly up to 5 times. The clinical response was evaluated at baseline before starting LCAP, finished 5 times, and 4 weeks later using the American College of Rheumatology (ACR) criteria and the 28-joint disease activity score (DAS28) of European League Against Rheumatism (EULAR). [Results] The tender joints counts, swollen joints counts, and C-reactive protein (CRP) levels decreased remarkably. DAS-28 CRP was significantly improved by LCAP. A 20%, 50%, 70% improvement in ACR was observed 30%, 14%, 7% of subjects. According to the EULAR improvement criteria based on DAS-28, 17% patients exhibited good and moderate response. And furthermore, the efficacy lasted at least 4 weeks after the completion of LCAP. [ConclusionThe results suggested that LCAP would be a beneficial therapy, and did not contradict several trials which had reported the effect of LCAP. The efficacy has shown to last several weeks and the resumption of LCAP might be a promise therapy to refractory RA.

W79-6

Experience of the plasma exchange (PE) treatment in our cases for the secondary thrombotic thrombocytopenic purpura (TTP)

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Conflict of interest: None

[Background] The cure using the PE in idiopathic and drug-related TTP is established and is proved effective. However, sometimes PE is not effective for secondary TTP with colloagenous vascular diseases (CVD). [Objectives and Methods] To clarify how to be performed PE for TTP with CVD, we report about 9 cases. [Results] The activity of ADAMTS13 was ranged from 18.3 with 115%. The ADAMTS13 inhibitor was negative in 5 cases. The number of PE was performed from 2 to 21 times. PE was effective for 5 cases which were observed raising numbers of platelets counts, disappearance of crushed red blood cells and im-

provement of anemia. [Summary] For TTP with CVD, PE is performed until raising numbers of platelets counts, disappearance of crushed red blood cells and improvement of anemia are confirmed. The ADAMTS13 activity level may be hard to be to an index.

W80-1

Detection of new lupus nephritis autoantigens by using wheat germ cell-free protein synthesis

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Conflict of interest: None

[Objective] To detect new autoantigens involved in the progression of lupus nephritis. [Methods] We screened for autoantigens with the AlphaScreen method using paired serum taken during the active and inactive stages, from 3 patients with SLE; thrombocytopenia, nephritis and serositis. The proteins used were created using the 2296 cDNA library from the Ehime University cell-Free sciences and technology research center. Sixty-six proteins characteristic to nephritis were selected and immunoprecipitation was performed using serum from patients with SLE, SSc and PM/DM. [Results] Immunoprecipitation of serum from patients with lupus nephritis, using 43 biotinylated proteins, yielded 17 proteins, including HIST1H1C and KIAA0409, which were positive in at least 1 subject. Of these, ten proteins showed strong reaction specifically to SLE serum with immunoprecipitation. Furthermore, immune complex deposition was confirmed by immunohistochemical staining of autopsy renal tissue of lupus nephritis. [Conclusion] The AlphaScreen method using antigens created using wheat germ cell-free protein synthesis proved useful for autoantibody screening. Lupus nephritis-specific autoantigens were confirmed using immunoprecipitation and renal tissue staining.

W80-2

The contribution of TLR7 to the progression of proliferative lupus nephritis

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Conflict of interest: None

Toll-like receptor (TLR) signals has been implicated in the development of pathogenic autoantibodies in systemic lupus erythematous. However, it is still unclear whether TLR7-mediated interactions in the kidney affect the development of lupus nephritis (LN) or not. Herein, we investigated renal TLR7 expressions in LN of human. We found renal TLR7 expressions were significantly increased in proliferative LN (class III+IV, n=22), compared with mesangial proliferative and membranous LN (class II+V, n=23). Immunohistological study showed glomerular TLR7+ cells were significantly increased in LN of class III and IV, compared with that of class II and V, and were almost included among CD68+ macrophages. Then, we investigated TLR7 expressions in LN model SCID mice injected with a nephritogenic IgG3-producing hybridoma clone, 76.8 or 2B11.3, from a MRL/lpr lupus mouse, which induced wire loop-like or cell-proliferative glomerular lesions respectively. We also found renal TLR7 expressions significantly increased in SCID mice infected with 2B11.3, compared with 7B6.8. In addition, TLR7 inhibitor administrations significantly suppressed the progressions of proliferative glomerulonephritis in LN SCID mice. In conclusion, TLR7 may contribute the progression of cell-proliferative LN.

W80-3

Role of calcium/calmodulin-dependent kinase type IV of podocyte function in lupus nephritis

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Conflict of interest: None

[Objectives] Kidney podocytes and their slit diaphragms contribute to prevent urinary protein loss. We previously described functional changes of kidney podocytes by calcium/calmodulin-dependent protein kinase type IV (CaMKIV) in lupus nephritis. Here we examined the effect of CaMKIV on kidney podocyte function in lupus nephritis using purified immunoglobulin G (IgG) from healthy controls and lupus nephritis patients. [Methods] We treated the IgG with kidney podocytes for 24 h, then analyzed the gene alteration in a DNA microarray. In addition, treated podocytes were silencing *CaMKIV*, and we analyzed selected gene expression changes by real-time polymerase chain reaction. We also examined the expression of the gene CD86 in kidney podocytes of MRL/*lpr*, MRL/*lpr.camkiv*−/− and MRL/*MPJ* mice by in situ hybridization. [Results] In the DNA microarray, the genes that are related to the activation of immune cells and podocyte damage were upregulated, including CD86, PTPN22, PDE5A, CD47 and MALT1. These genetic expressions tended to be restrained in silencing *CaMKIV*. The in situ hybridization showed that the expression of CD86 was reduced in podocytes of the MRL/*lpr.camkiv*−/− mice. [Conclusion] These data indicate that CaMKIV may alter the function of kidney podocytes in lupus nephritis.

W80-4

Urinary T cells and macrophages reflect the disease activity and renal function in patients with systemic lupus erythematosus

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Conflict of interest: None

[Objectives] To examine the utility of urinary immune cell analysis in patients with systemic lupus erythematosus (SLE). [Methods] Sixty-five samples from 56 patients with SLE, who had been referred to Niigata University Hospital between 2004 and 2013, were recruited. The numbers of urinary CD3-positive cells (T cells) and CD14-positive cells (macrophages), laboratory markers, and SLEDAI, were examined in each subject and compared according to their urinalysis. The data were also analyzed by Spearman's rank correlation coefficient to determine the relationship with urinary T cells and macrophages. [Results] The number of urinary CD3-positive cells was significantly elevated in patients with both proteinuria and abnormal urinary sedimentations, compared to patients with proteinuria-only or with normal urinalysis. The number of CD3-positive cells was positively correlated with serum Cr, abnormal urinary sedimentations, and SLEDAI, and was negatively correlated with serum CH50, while the number of urinary CD14-positive cells was positively correlated with serum Cr, abnormal urinary sedimentations, 24-hour urinary protein excretion, and SLEDAI. [Conclusion] These results indicated the usefulness of urinary immune cell analysis in the assessment of patients with SLE.

W80-5

Multitarget therapy using a combination of tacrolimus (TAC) and mycophenolate mofetil (MMF) in patients with active lupus nephritis (LN): A follow-up report

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ate School of Medicine

Conflict of interest: Yes

[Objective] Recently, we reported that multitarget therapy using TAC and MMF was effective as initial treatment for active LN, with CR achieved early and in a high percentage of patients (Mod Rheumatol, 2013). We conducted a follow-up study. [Methods] All 16 patients of the previous study were followed-up for a median of 31 months (range, 23-48) after the initiation of multitarget therapy. [Results] All the patients achieved a complete remission (CR) at a median of 3.6 months (range, 0.3-14.5). CR rates at 6 and 12 months were 81% and 94%, respectively. After achieving CR, MMF was switched to azathioprine (AZA) in 13 patients and to mizoribine in 2 patients. MMF was stopped in 1 patient, because of CMV gastric ulcer. Thirteen patients (81%) remained in remission without relapse of LN or recurrence of SLE. The mean dose of prednisolone was 4.4±2.5mg/day at the final observation in these patients. After switch to AZA, 3 patients experienced a serologic flare; 1 of them showed a relapse of LN. All the 3 flared patients were refractory LN, who had more than 1 relapse before multitarget therapy. [Conclusion] Although a few patients showed worsening of SLE or LN after switching MMF to AZA, most patients showed a favorable clinical course during 2 to 4 years follow-up after multitarget therapy.

W80-6

Analysis of associated factors of Therapeutic response of lupus nephritis

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Conflict of interest: None

[Objectives] We analyzed prognostic factors in lupus nephritis (LN). [Methods] Sixteen-three SLE patients (mean age 34.2 y.o, female n=56) who received renal biopsy (RBx) from 2004 to 2013 were enrolled. Histopathology was assessed by ISN/RPS classification and other pathological findings including glomerular sclerosis, crescent, thrombi, tubulointerstitial involvement (TII). Treatment regimens and clinical profiles including autoantibodies and complications were reviewed. Therapeutic responses were determined by SLICC. [Results] The RBx samples were classified into Class I/ II/ III/ IV/ V (2/7/15/25/11). Glomerular sclerosis, crescent, thorombi, and TII were found in 57.1%, 20.6%, 20.6% and 65.1%, respectively. mPSL pulse therapy and IVCY were conducted in 65.9% and 75.4% of the patients, respectively. Failure of complete remission was associated with Class IV(G), V, glomerular sclerosis, thorombi, hypertension, hyperlipidemia, diabetes mellitus and hyperuricemia. However, this study failed to show association between immunological findings including autoantibody profiles and clinical outcome. [conclusion] Besides ISN/RPS classification, pathological features such as glomerular sclerosis and thrombi and complications were predisposing factors to unfavorable clinical responses in LN.

W81-1

BAFF activates monocytes to produce IL-6 though BAFF receptor (BR3) for IgG production from peripheral B cells in patients with primary Sjögren's syndrome

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Conflict of interest: None

[Objectives] We have found that BAFF robustly increased IL-6 production by monocytes in patients with primary Sjögren's syndrome (pSS), and the expression level of a BAFF receptor (BR3) was significantly elevated in pSS monocytes compared to the controls. Since IL-6 promotes the differentiation of B cells, we investigated the possible involvement of monocytes producing IL-6 in the IgG production by B cells. [Methods] Peripheral monocytes were cultured with or without peripheral B cells and stimulated with soluble BAFF (sBAFF) in vitro. The production of IL-6 and IgG by the cells were measured by ELISA. FACS analysis of whole blood samples was employed to analyze the expression of BR3. [Results] The serum level of IgG and the proportion of BR3 positive monocytes ($BR3^+/CD14^+$) were elevated in pSS patients as compared to those in controls. Remarkably, the $BR3^+/CD14^+$ ratio was positively and significantly correlated with the serum IgG level and IL-6 production by pSS monocytes stimulated with sBAFF. Stimulation of co-culture of B cells and monocytes in pSS patients with sBAFF drastically enhanced IgG production by B cells. [Conclusion] Our data indicate that the abnormal expression of BR3 on monocytes is responsible for the overproduction of IgG by B cells in pSS patients.

W81-2

RORγt inhibit the expression of Foxp3 in $CD4^+CD25^+$ T cells in spontaneous development Sjögren's syndrome like sialadenitisRORgt inhibit the expression of Foxp3 in $CD4^+CD25^+$ T cells in spontaneous development Sjögren's syndrome like sialadenitis

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Conflict of interest: None

[Objectives] The aim of this study was to clarify the pathological role of RORγt in sialadenitis using RORγt transgenic (Tg) mice spontaneously developing Sjögren's syndrome like sialadenitis. [Methods] 1) Splenic $CD4^+$ cells from Tg mice were transferred into $Rag2^{-/-}$ ($CD4^+ \rightarrow Rag2^{-/-}$) mice and histological analysis was examined. 2) Compartment of Treg cells was investigated. 3) $CD4^+CD25^+$ (Treg cells) and $CD4^+25^-$ (Teff cells) from Tg or C57BL/6 (WT) mice were co-transferred into $Rag2^{-/-}$ mice in criss-cross manner, and histological analysis was examined. 4) IL-2 stimulated STAT5 phosphorylation in Treg cells was analyzed. [Results] 1) In $CD4^+ \rightarrow Rag2^{-/-}$ mice, sialadenitis was observed. 2) Foxp3 expression in $CD4^+CD25^+$ T cells was significantly decreased in Tg mice. 3) Co-transfer of Teff cells from Tg mice and Treg cells from WT mice could not develop any sialadenitis in $Rag2^{-/-}$ mice, whereas co-transfer of Teff cells from WT mice and Treg cells from Tg mice developed sialadenitis. 4) STAT5 phosphorylation was inhibited in IL-2 stimulated Treg cells of Tg mice. [Conclusion] These results suggested that the overexpression of RORgt in Treg cells induced downregulation of Foxp3 expression via repress IL-2 induced STAT5 phosphorylation, resulting in the spontaneous sialadenitis like SS.

W81-3

Correlation between salivary epidermal growth factor levels and refractory intraoral manifestations in patients with Sjögren's syndrome -A 3-year follow-up study-

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Conflict of interest: None

[Objectives] To assess changes of salivary epidermal growth factor (EGF) levels during three years and the correlation between these levels and the severity of intraoral manifestations in Sjögren's syndrome (SS). [Methods] 23 SS patients and 14 controls, followed up for three years, were enrolled. Salivary EGF concentration was measured using an ELISA kit, and intraoral manifestations were evaluated using a short version of the Oral Health Impact Profile (OHIP-14). The changes of salivary flow rate, EGF levels, and the severity of intraoral manifestations and associations among these factors were analyzed. [Results] In SS, the OHIP-14 score was significantly increased and total salivary EGF output was

significantly decreased after three years follow-up (10.2 vs 12.6, p=0.040, 10158.4 vs 8352.8 pg/10 min, p=0.032). A decrease in total EGF output was showed, especially in SS patients with long disease duration and poor oral QOL. Total salivary EGF output change was significantly correlated with the OHIP-14 score change in SS patients with poor oral QOL (r= –0.847, p= 0.008). [Conclusion] The salivary EGF levels are decreased with time in SS, and this deterioration in saliva quality causes refractory intraoral manifestations. Our findings have provided new therapeutic targets for SS.

W81-4

Long-term follow-up of patients with Sjögren's syndrome in pediatric age

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Conflict of interest: None

[Background] The natural course of Sjöregn's syndrome (SS) in children is not clear. [Objective] To discover whether children with SS will develop other autoimmune diseases we checked their clinical history and laboratory data. [Material and Method] Seventeen primary SS patients seen at Chiba University Hospital between 1989 and 2003, and followed up for the subsequent 10 years, were enrolled in the study. The data was collected retrospectively from clinical records. [Results] The anti DNA antibody changed positively in four patients. In three patients, the anti-RNP antibody also changed positively. Three patients fulfilled the criteria for juvenile systemic lupus erythematous, and two patients for mixed connective tissue disease, and needed immunosuppressants. All of them was positive for anti-SS-A antibody and had sicca symptoms. [Discussion] The patients who developed other rheumatic diseases were only 17.6%, and they were no different from other patients who did not. It is considered that they had SS and newly developed other rheumatic diseases. [Conclusion] We can diagnose pediatric patients have SS, however, we should consider whether they develop other rheumatic diseases. Further observation and analysis is needed to reveal any differences.

W81-5

Clinicopathological characteristics of anti-centromere antibody- and/or anti-SSA antibody-positive Sjögren's syndrome

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Conflict of interest: None

Objectives: We aimed to examine the clinicopathological characteristics of anti-centromere antibody (ACA)-positive Sjögren's syndrome (SS). Methods: We evaluated 13 patients with ACA-positive and SSA-positive SS (ACA+SSA+ group), 67 patients with ACA-negative and SSA-positive SS (ACA−SSA+ group), and 24 patients with ACA-positive and SSA-negative SS (ACA+SSA− group). We performed minor labial salivary gland biopsy, evaluated focus scores, and compared clinicopathological data of these 3 groups. Serum levels of many cytokines were also estimated using multiplex assays. Results: The 2 ACA-positive groups had a higher positive rate for Raynaud's phenomenon. No patient developed new skin sclerosis during the follow-up. Saxon's test results in the ACA+SSA+ group was lower than that in the ACA−SSA+ group. The 2 SSA-positive groups had lymphocytopenia and high serum IgG levels. The focus scores and fibrosis of the biopsy specimens did not differ significantly. Two ACA+SSA+ patients had pulmonary hypertension. Serum IL-12 was high in the ACA+SSA+ group; IFN-γ was high in the 2 SSA-positive groups. Conclusions: Clinicopathological data and serum cytokine profile in the 3 groups differed. Thus, measuring ACA is an important component in the management of SS.

W81-6

Musculoskeletal ultrasound and Magnetic resonance imaging of the wrists and finger joints in Sjögren's syndrome (SS) with articular manifestations

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Conflict of interest: None

【Objectives】Patients with sjögren's syndrome (SS) often complain polyarthralgia and prevalence of IgM-RF was high in SS. Therefore it is sometimes difficult for the clinician to differentiate cases of early-stage rheumatoid arthritis (RA) from SS. Musculoskeletal ultrasound (US) and MRI of the wrists and finger joints has been increasingly recognized as a useful method for diagnosis of RA. In contrast, there are not many studies evaluating the arthralgia in SS through US and MRI.【Methods】We retrospectively reviewed medical records of 63 SS patients with articular manifestiation.【Result】Among 63 patients, 35 were classified as primary SS or secondary SS complicated without RA. 12 of them underwent US and 30 of them underwent MRI. 7 (58%) showed synovitis on US, but their synovitis were detected no power doppler (PD) signals. As same as US findings, 20 (67%) showed synovitis on MRI. However MRI-proven bone changes (osteitis or bone erosion) were recognized in only 2 patients. On the other hand, there were high prevalence of PD positive synovitis on US and bone changes on MRI in the patients with secondary SS complicated with RA.【Disccusion】Our data suggests that MRI of the wrists and finger joints and musculoskeletal US are very useful for discrimination of SS and RA.

W82-1

Plantar pressure of the patients with rheumatoid arthritis (the first report)

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Conflict of interest: None

[Objectives] To investigate the difference between the preoperative plantar pressure of the surgically-treated forefoot and the pressure of the foot without surgery in the patient with rheumatoid arthritis. [Methods] Using F-Scan®, plantar pressure was measured at 175 feet in 91 inpatients. A foot radiograph under weight bearing was taken and HVA, M1M2, and M1M5 angles were measured. Distribution of the peak and the integrated pressures were measured in each section of the1st IPJ, the 1st through the 5th MTPJs, the medial and the lateral midfeet, and the hindfoot. [Results] Forefoot surgery was performed on 29 feet. More than one-half of the surgically treated foot had a painful plantar callosity at the 2nd and the 3rd MTPJs. The peak and the integrated pressures at the 1st MTPJ was high in the surgical group compared to those in the non-surgical group. Despite both pressures at the 5th MTPJ were low, the integrated pressure at the hindfoot was high in the surgical group. In the foot with mild HVA, the pressure at the 5th MTPJ was low, and in the foot with moderate to severe HVA, the pressure at the hindfoot was high. [Conclusion] Plantar pressure was high at the medial forefoot and the hindfoot in the patient who underwent forefoot reconstruction.

W82-2

Risk factors for delayed wound healing after forefoot surgery in rheumatoid arthritis

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Conflict of interest: None

[Objectives] The aim of this study is to identify the risk factors for delayed wound healing after forefoot surgery in RA. [Methods] From April 2010 through March 2012, 153 feet in 111 RA patients with rheumatic forefoot deformity were treated at our institution with toe arthroplasty. The mean disease activity score with 28-joint counts (DAS28) was 3.19, and the average operative time was 97.9 minutes. Delayed wound healing is defined as cases that required wound care more than 2 weeks after surgery. Logistic regression analysis was performed to define the risk factors for delayed wound healing (dependent variables: biological agents, diabetes mellitus, C-reactive protein, level of total protein, methotrexate dose, prednisolone dose, operative time, DAS28, Japanese version of Health Assessment Questionnaire score, body mass index, disease duration, age at surgery, and gender). [Results] Wound healing was delayed in 35 feet (22.9%) after surgery. The operative time significantly (P=0.026) impacted delayed wound healing after forefoot surgery in RA. ROC curve analysis showed that the predictive cut-off value of the operative time was 105.0 minutes. [Conclusion] Operative time was identified as a risk factor for delayed wound healing after forefoot surgery in RA.

W82-3

Swanson implant arthroplasty of great toe accompanied first metatarsal osteotomy and resection arthroplasty of lessor toes for forefoot deformity in rheumatoid arthritis

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Conflict of interest: None

[Objectives] To study mid-term results of swanson implant arthroplasty of great toe accompanied with first metatarsal osteotomy and resection arthroplasty of lessor toes for forefoot deformity in RA. [Methods] Twenty eight feet in 18 patients who had undergone aforementioned surgery were studied with minimal follow-up of 1 year. Patient characteristics, JSSF hallux scale, HVA, M1/2 angle, sesamoid position, implant breakage, implant sinking, and complications were examined. [Results] The average age and disease duration at the surgery was 65 years and 22 years, respectively. The average follow-up was 45 months. JSSF hallux scale improved significantly from 44 points preoperatively to 82 at the last follow-up. HVA and M1/2 decreased significantly from 50° and 16° preoperatively to 16° and 5° at the last follow-up, respectively. The position of the sesamoid improved in all cases. Implant breakage was not shown. However, 2 feet with implant sinking, 4 feet with recurrence of hallux valgus over 25°, 2 feet of infection, and 5 feet of delayed wound healing were observed. [Conclusion] Swanson arthroplasty of great toe with accompanied with first metatarsal osteotomy and resection arthroplasty of lessor toes for forefoot deformity in RA demonstrated excellent mid-term results.

W82-4

Swanson flexible hinge toe implant arthroplasty with grommets for rheumatoid arthritis of the first metatarsophalangeal joint: middle-term results

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Conflict of interest: None

[Objectives] To evaluate the middle-term results of Swanson type silicone prosthesis with grommets for rheumatoid arthritis of the first metatarsophalangeal joint. [Methods] Between 2002 to 2011, Swanson implant arthroplasty with grommets of the first metatarsophalangeal joint were performed on 97 feet in 68 patients (64 women and 4 men) in rheumatoid arthritis. Five patients who were followed up less than 2 years were excluded, so 92 feet (95%) were evaluated. Average follow-up period was 5.6 years. The survival rate of the implant and the integrity of each implant were examined. Using radiographs, we assessed whether the breakage of implant was influenced by preoperative and postoperative forefoot deformities. [Results] Early revision was required 2 joints (2 infections). Implant breakage was occurred in 6 joints (7.7%), and one of them was undergone revision. Implant breakage was not influenced by radiographic findings. [Conclusion] With revision as the endpoint, the survival rate of the implant was 97%.

W82-5

Surgical results of arthroplasty for forefoot deformity in theumatoid arthritis. -comparison of a shortening oblique osteotomy with a resection arthroplasty-

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Conflict of interest: None

[Purpose] To investagate the results of arthroplasty on rheumatoid forefoot deformity and to compare those of shortening oblique osteotomy (A group) and resection arthroplasty (B group). [Method] Postoperative findings of 91 RA patients who underwent arthroplasty between August 2000 and June 2013 were examined. Clinical results and radiological examinatons were carried out. Clinical results were evaluated by Japanese Society for Surgery of the Foot RA foot ankle scale (JSSF RA foot scale) and radiologically with the angle of HV (HVA), M1M2 (M1M2) and M1M5 (M1M5). [Results] JSSF RA foot ankle scale improved from 37.7 points to 72.4 points (A: 37.5 to 72.2, B: 40.0 to 72.9). Improvement were found in all subscales except for ROM. Preoperative and postoperative mean HV angle were 31.3 and 16.5 (A: 27.8 and 14.9, B: 33.4 and 17.4), M1M2 angle were 13.4 and 12.9 (A: 12.8 and 12.5, B: 13.6 and 13.1) and M1M5 angle were 31.3 and 29.4 (A: 32.2 and 26.1, B: 31.0 and 30.8), respectively. There were no statistical differences between group A and group B. [Conclusion] Whereas significant improvements were achieved in both procedures, A joint preservation arthroplasty was preferable and should be conducted as much as possible considering the function and appearance of resultant foot.

W82-6

The short term results of oblique osteotomies of lateral toes in RA patients

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Conflict of interest: None

[Objectives] The deformities of frontal foots often happens in the rheumatoid arthritis patients. In our hospital, shortening oblique osteotomies are performed to deformities of lateral toes. The objective of this study is to clarify the short-term results of this operation. [Methods] Between 2009 and 2013, these operations were done 25 foots in 16 patients (male: 2, female: 14). The mean age at the operation was 66.8 (47-84) yrs., and the mean follow-up period was 29.2 (6 -56) mos. Shortening oblique osteotomies of metatarsus to lateral toe are performed with sloping 45 degrees. Osteophyte is resected and bones are transfixed by a 1.5mm diameter Kirschner wire from the distal phalanx to the metatarsal shaft. The clinical outcomes were assessed using Japanese Society for Surgery of the Foot (JSSF) score. In X ray, we checked the rate of nonunion and recurrence. [Results] The average scores of JFFS changed from 41.4 to 68.1 ($P<0.05$). In X ray, there were 14 non-unions of metatarsus bones, but there was no pain in patients. There was 1 recurrence of calluses and 3 Mallet toes. [Conclusion] We keep MTPJ, so it is easy for patients to walk with strong weight. We remove the osteophyte and there weren't so many recurrence of callus. Short-term results of this operation were favorable.

W83-1

Long- term results of anke arthrodesis for rheumatoid arthritis patients using intramedullary nail

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Conflict of interest: None

[Objectives] We investigated long-term results of ankle arthrodesis for RA patients using intramedullary nail. [Methods] Twenty seven patients, 29 feet with rheumatoid arthritis who had undergone surgical treatment at our hospital between 1998 and 2008, and who had been followd 5 months to 15 years (mean 7 years) were included in the study. All patients were women (mean age 60 years; range 27-79 years). We used intramedullary nail with fin (Nakashima mdical, Japan) for 24 feet and Phenix Ankle Arthrodesis Nail (Biomet, USA) for 5 feet. [Results] At the time of last investigation, 9 patients was died. The complications were one pesudarthrosis (the patient had severe bone destruction, using intramedullary nail with fin), 2 paties needed removal of nail because of skin touble. At the time of a first walking was 4-40 days (mean 19 days) using intramedullary nail with fin, 30-40 days (mean 34 days) using Phenix Ankle Arthrodesis Nail. JSSF RA foot ankle scale was 45.7 poits preoperetively, and 61 points at the time of final follow up [Conclusion] Ankle arhtrodesis using intramedullary nail is useful for RA patitents. The patients using intramedullary nail with fin can start walking early, but we need care for severe bone destructin cases.

W83-2

Total ankle arthroplasty for rheumatoid ankle

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Conflict of interest: None

[Objectives] We indicated ankle arthrodesis for rheumatoid ankle without severe varus-valgus deformity or bone loss in less than 60 years old patients. The purpose of this paper is to investigate short term result. [Methods] We retrospectively studied 10 ankles of 10 RA patients with severe ankle pain on walking. There were 6 males and 4 females. The mean age at the operation was 63.4 years old (range, 46-80), and the mean disease duration was 12.9 years. Pre-operative mean dorsi-flexion was 12 degrees and mean planter-flexion was 32 degrees. Larsen grade was classified II in 1, III in 2, IV in 5, and V in 2 ankles. We used Fine total ankle system®. The mean follow-up period was 4.6years (range, 2-11). [Results] No surgical complication was observed. All patients achieved full weight bearing walk after 3.7 weeks (range, 3-9) after surgery The mean JOA score significantly improved from 43.4 (range, 30-58) preoperatively to 63.4 (range, 52-76) postoperatively. Clear zone more than 1mm was observed 9 ankles in tibial side and 1 ankle in talar side. Remarkable sinking of tibial component occurred in an obese female case. [Conclusion] Total ankle arthroplasy is a useful surgical treatment for rheumatoid ankle, however indication in obese cases requires circumspection.

W83-3

Treatment for Knee Joint Lesion of Rheumatoid Arthritis: Total Knee Arthroplasty Improves Body Dysfunction and Disease Activity Better than Enforced Medication

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Conflict of interest: None

[Objectives] The aim of this study is to compare the effect of TKA and medication for knee joint lesion of RA. [Methods] From the RA patients enrolled in IORRA, prospective observational cohort study, from 2000 (Phase1) to 2010 (Phase20), we selected 1488 participants who had experienced knee monoarthritis in any Phase. From each of their datum, we extracted 2 Phases when they had knee monoarthritis and one year later from then. Based on the datum, the patients were divided into 3 groups. TKA Group is composed of those who underwent TKA in the first 6month. Enforced Group consists of those only medicated and enforced in 1 year, and Control Group is the medicated only with the same drugs. We used multi regression analysis to assess the significant difference among the three groups, of the changes of DAS28 (ΔDAS28), J-HAQ (ΔJ-HAQ), VAS (ΔVAS) and CRP (ΔCRP). [Results] The number of patients in TKA Group was 33, Enforced Group, 198, and Control Group was 483. We found that ΔJ-HAQ was significantly improved in TKA Group better than the other groups. In ΔDAS, we could find the significant difference only between TKA Group and Control Group. [Conclusion] It appears that TKA improves body dysfunction and disease activity of RA patients with knee joint lesion better than enforced medication.

W83-4

Clinical results of PFCΣRP total knee arthroplasty in patients with rheumatoid arthritis

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Conflict of interest: None

[Objectives] To demonstrate the clinical results of PFCΣRP total knee arthroplasty (TKA) in patients with rheumatoid arthritis (RA). [Methods] One-hundred fiftynine arthroplasties in 125 patients with RA were performed from January 2004 to December 2012 at Rheumatic StateThere were 13 men and 112women; the mean patients age at the surgery was 61.9 years (range 38-86 years). The mean follow-ed period was 5.4 years (0.5-15.4 yeas). We measured RA Japanese Orthopedic associatio (JOA) knee score, presence of loosening and preoperative and postoperative knee ROM. [Results] Afracture was present in two cases, looseing was absent. 9 patients was died. The mean preoprerative RA JOA knee score was 2., and the score at the final examination was 85.3. [Conclusion] The clinical results of PFC ΣRP total knee arthroplasty in RA patients was almost good.

W83-5

Clinical Results of TKA for RA Patients

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Conflict of interest: None

[Objectives] We report about the clinical results of TKA for RA patients in15 years from April in 1996 to March in 1996, with some comparisons with the performance of OA patients [Methods] Total number of operations in the same period was 280 knees. Primary cases (P group) were 261 Knees, 19 knees were revision cases (P group). Among them, 58 knees were the RA patients, 52 knees were in the P group (20%), 6 knees were in the R group (32%). About 60% of the RA patients were in Stage III, 35% of the RA patients were in Class II, 48% were in Class III. The average age was 66.4 years at the time of surgery. Average of preoperative JOA score was 45.3 points, FTA was 177.5 °. We used mainly Scorpio / Deltafit series of Stryker Corporation. PS type accounts for about 80%, cemented TKA also accounted for about 80%. [Results] Average of JOA score 86.2 points after surgery. Average of FTA is 173 °, average of flexion angle is 118 °. 3 cases in the P group were performed revision operation. [Conclusion] In TKA operation for RA patients, we have some technical problems; for example, sever deformation, poor bone quality, and compromised condition. It is important that we have preoperative preparation in cases of advanced deformation and bone defect and careful follow-up.

W83-6

The QOL study of total knee arthroplasy in patient with rheumatoid arthritis evaluated with use of the New Knee Society Score and the Japanese style of the Knee injury and Osteoarthritis Outcome Score

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Conflict of interest: None

【Objective】To investigate the QOL of total knee arthroplasy in patient with rheumatoid arthritis evaluated with use of the New Knee Society Score (NKSS) and the Japanese style of the Knee injury and Osteoarthritis Outcome Score (J-KOOS), attracting attentions as giving patient-based outcome scores.【Materials and Methods】A total of 72 TKAs were performed in 57 RA patients. All patients were over one year after operation. The NKSS (symptoms, patient satisfaction, patient expectation, functional activities) and J-KOOS (symptom, pain, ADL, QOL) were utilized to assess outcomes. 55 of TKAs of OA patients also assessed.【Results】The average of RA patients' NKSS were 18/25 (symptoms), 22/40 (patient satisfaction), 10/15 (patient expectation), 41/100 (functional activities). The average of RA patients' J-KOOS were 78/100 (symptom), 84/100 (pain), 71/100 (ADL), 73/100 (QOL). Each of ADL and QOL scores in RA patients were lower than OA patients.【Discussion】This study suggested that patient-based outcome score made it possible to evaluate the effectiveness of TKA for RA patients against the knee pain, symptom and QOL. But the other joint disturbance and spine disorder affected to RA patients' ADL.

W84-1

Predictive factors of lung disease progression in patients with rheumatoid arthritis

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Conflict of interest: None

[Objectives] Lung lesions in rheumatoid arthritis (RA) patients are various and their prognoses are unclear. The purpose of this study was to clarify the prognoses and risk factors of RA-related lung diseases. [Methods] This prospective study comprised 103 RA consecutive patients attending to our department from April 2005 to June 2009. All patients underwent high resolution CT scan (HRCT) regardless of their respiratory symptoms and we assessed the prognoses by follow-up HRCT from November 2012 to October 2013. [Results] 62 patients (15 males, 47 females) underwent follow-up HRCT. Mean age was 48.5 years and mean follow-up period was 98 months. RA-related interstitial pneumonia (n=15), RA-related bronchiolitis (n=10), rheumatoid nodules (n=5) and other lung diseases (n=20) were observed in the initial HRCT. Lung lesions improved in 3, remained in 29 and worsened in 32 patients during the follow-up period. Predictive factors for progression of lung lesions were bronchiectasis ($p=0.009$), centrilobular particulate opacity ($p<0.001$), interlobular septal thickening ($p<0.001$), cystic lesions ($p=0.004$) and worsening of DAS28-ESR ($p=0.036$). [Conclusion] The above abnormalities on HRCT and worsening of DAS28-ESR are significant predictors of lung diseases in RA.

W84-2

IL-18 plasma level correlates with the presence of interstitial pneumonia and the serum KL-6 level in rheumatoid arthritis

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Conflict of interest: None

[Objectives] IL-18 level is elevated in patients with interstitial pneumonia (IP). On the other hand, IL-18 is produced by activated synoviocytes and its level is associated with arthritis activity in rheumatoid arthritis (RA). This study aims to determine whether IL-18 level is increased in RA patients complicated with IP. [Methods] We conducted a cross-sectional study in the KURAMA cohort. Plasma IL-18 level was measured by ELISA in 352 consecutive RA patients. [Results] IP was complicated in 15 % of the study population. IL-18 level was higher in patients with IP than those without IP (517±54vs 427±17 pg/ml, $p=0.0151$). IL-18 level was significantly associated with serum KL-6 level ($r=0.325$, $p<0.001$). It also correlated with DAS28 ($r=0.154$, $p=0.012$) or CRP level ($r=0.348$, $p<0.001$), sex, age, serum LDH, GOT, CRE, ALB, MMP-3 levels and dose of glucocorticoid treatment. After adjustment with these confounding factors, IL-18 level remained significantly associated with KL-6 level (coefficient of correlation 2.3-2.7, P=0.01-0.02), but not with DAS-28 or CRP level. [Conclusion] IL-18 level is significantly associated with IP complication or KL-6 level in RA. Prospective study is necessary to determine the causal relationship between IL-18 and IP or KL-6.

W84-3

Analyze of the efficacy of tocilizumab in rheumatoid arthritis with interstitial lung disease

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Conflict of interest: None

[Objectives] To assess the clinical characteristics of rheumatoid arthritis (RA) with or without interstitial lung disease (ILD) patients treated with tocilizumab (TCZ). [Methods] Efficacy was evaluated by CDAI. Medical records of all the patients were systematically reviewed. [Results] 48 (6men, 42women, average age 50.1 years old) of RA patients were treated with TCZ and enrolled in this study. 6 out of 8 ILD patients showed fibrotic-ILD pattern and rest of 2 showed cellular-NSIP pattern on chest HRCT. No patients showed relapse or worsened of ILD in 48 patients. Before TCZ treatment, average serum KL-6 were 247.1+/-76.9U/ml in non-ILD group and 415+/-251.4U/ml in ILD group. After TCZ treatment, average serum KL-6 were 239.0+/-72.8U/ml in non-ILD group and 357+/-197.5 in ILD group. 6 out of 8 patients in ILD group showed improvement of KL-6 after TCZ treatment. There was no respiratory adverse effect to discontinue TCZ in all 48 patinets. [Conclusion] All patients must be aware of ILD associated with biologics, however there is a possibility to use TCZ safety in RA with ILD patients.

W84-4

The impact of abatacept therapy on interstitial lung disease associated with rheumatoid arthritis

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Conflict of interest: None

[Objectives] Interstitial lung disease (ILD) is one of the important complications in rheumatoid arthritis (RA), which affect its survival. We retrospectively studied whether ILD was exacerbated by abatacept (ABT) therapy in RA patients complicated with pre-existing ILD (RA-ILD). [Methods] Among 111 RA patients treated with ABT, 10 (9.0 %) had ILD. We retrospectively investigated the records of 10 Japanese RA patients complicated with ILD who was treated by ABT. Pulmonary function test, serum KL-6 and chest HRCT were evaluated at 52 weeks after administration of ABT. [Results] Five patients (50% were female) with

RA-ILD were included. At the enrollment, the median age was 64.6 years, and the median disease duration of RA was 72 months. ABT therapy leads to no significant exacerbation of %FVC (from 80.1±18 to 85.7±17 %) and KL-6 (from 1184±600 to 970±436 IU/ml) at 52-weeks, and there were no patients who showed exacerbation of ILD by the treatment with ABT. [Conclusion] ABT might be safe for RA patients having ILD. Further studies will be needed to establish proper guideline regarding the use of ABT in RA patients complicated with ILD.

W84-5

Clinical features, characteristics of pleural effusion and thoracoscopic and pathologic findings of rheumatoid pleuritis

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Conflict of interest: None

[Objectives] Rheumatoid pleuritis has been characterized by exudative sterile pleural effusion (PE) containing neutrophils or lymphocytes, low PH, low glucose levels, high LDH and ADAH levels, histology of which was granuloma resembling rheumatoid nodule. However, in clinical practice, we have experienced cases that did not meet the characteristics. The aim of this study is to reevaluate clinical features, characteristics of PE and thoracoscopic and pathologic findings of rheumatoid pleuritis [Methods] We reviewed medical records of 11 RA patients with sterile unknown PE who received thoracoscopic examination. [Results] Among 11 cases, 9 were female. PE was exudative and 2 of which were empyematous, 5 of which were lymphocyte dominant. Low PH, low glucose and high LDH in PE were found in 5, 5 and 5 in 11 cases, respectively. ADA levels in PE were elevated in 6cases. Thoracoscpic findings were empyematous in 2, pleural thickness in 2, nodules in 1 and diffuse granules, in 1 case (s). Histological examination showed non-specific inflammation in most caeses, but 3 cases of lymphocytic pleuritis and only one case of granulomatous change were found. [Conclusion] Rheumatoid pleuritis has varieties in clinical features, PE findings, pleural changes other than ones previously described.

W84-6

Resistin and leptin increase in pleural fluid in rheumatoid arthritis

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Conflict of interest: None

[Objectives] Pleuritis is one of the common extra-articlular complications in rheumatoid arthritis (RA), however, the precise etiopathology has not been clarified yet. On the other hand, we have clarified the role of several adipokines in the pathophysiology of RA. In this study, we examined several adipokine concentrations in the pleural fluid (PF) to clarify whether adipokines are responsible for the RA pleuritis. **[Methods]** PFs were obtained from five RA patients with pleural effusion and five patients with systemic autoimmune disease (SAD; 3 systemic lupus erythematosus and 2 systemic sclerosis) patients (all female). Resistin, leptin, HMW-adiponectin and chemerin in the PF were measured and compared with those of serum by ELISA. **[Results]** Resistin, leptin, HMW-Adipokine, chemerin in pleural fluid of RA were 56.7±11.5 ng/ml, 61.2±32.3 ng/ml, 47.1±51.5 μg/ml, and 131.9±174.2 ng/ml, respectively, whereas those of SAD were 46.4±25.2, 13.1±3.78, 31.5±16.1, and 63.8±10.9, respectively. The concentration of resistin and leptin were increased in pleural fluid compared with serum in RA patients. **[Conclusion]** Resistin and leptin were increased in PF compared with serum in only RA patients. These adipokines may have important roles in the pathophysiology of RA pleuritis.

W85-1

Clinical features of anti-aminoacyl tRNA synthetase antibodies in patients with rheumatoid arthritis

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Conflict of interest: None

[Objectives] Anti-Jo-1 antibody is an autoantibody specifically detected in sera from autoimmune myositis patients. The antigen corresponding to this autoantibody is histidyl-tRNA synthase, being an aminoacyl-tRNA synthase (ARS). We examined the positive rate of anti-ARS antibody in rheumatoid arthritis (RA) patients and evaluated the clinical characteristics of their symptoms. [Methods] This study included 235 RA patients treated at our hospital. Determination of anti-ARS antibodies was carried out using Myositis Profile 3 Euroline Blot Test Kit commercially available from EUROIMMUN. Then, we evaluate the positive rate and clinical features in these patients. [Results] Anti-ARS antibodies were detected in 8.1% patients. Specifically, anti-Jo-1 was detected in 3patients (1.3%), anti-EJ was detected in 6 patients (2.6%), anti-OJ was detected in 1 patient (0.4%), anti-PL-7 was detected in 7 patients (3.0%), and anti-PL-12 was detected in 2 patients (0.9%). The evaluation of clinical characteristics found concurrent IP in 42.8% of anti-EJ antibody-positive patients, 71.4% of anti-PL-7 antibody-positive patients, and all anti-PL-12 antibody-positive patients. [Conclusion] The results suggest anti-PL-12 antibody and anti-PL-7 antibody are IP-related autoantibodies in RA patients.

W85-2

Investigation of the association between gastroesophageal reflux disease and clinical factors in patients with rheumatoid arthritis

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Conflict of interest: None

[Objectives] Patients with rheumatoid arthritis (RA) frequently complicate gastroesophageal reflux disease (GERD). The purpose of this study was to investigate the association between GERD and clinical factors in RA patients. [Methods] We investigated 378 outpatients with RA (70 males, 308 females). The presence or absence of GERD was evaluated by using GerdQ. The correlation between GERD and clinical factors such as age, sex, height, weight, BMI, disease duration, DAS28/DAS28-CRP/SDAI, Pt-VAS, and medication drugs (NSAIDs, steroid, bisphosphonate, gatroprotective agents) were analyzed. [Results] The prevalence of GERD in RA (25.4%) was higher than that in the Japanese population (7.6-10.6%). SDAI and patient's VAS were significantly higher in the GERD positive group than the GERD negative group ($p<0.05$). DAS28 and DAS28-CRP were higher in the GERD positive group than the GERD negative group, but these differences did not reach statistical significances. [Conclusion] The prevalence of GERD in RA was high and associated with Pt-VAS. Therefore, we should pay attention to the complication of GERD when the evaluation of disease activity of RA.

W85-3

Active Rheumatoid Arthritis Is An Independent Risk Factor Of Chronic Kidney Disease

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Conflict of interest: None

[Objectives] To determine whether active RA is an independent risk factor for CKD. [Methods] This prospective study included 134 RA patients and 1156 non-RA individuals. When patients showed eGFR less

than 60 ml/min/1.73m^2 or positive for urinary protein test, they were judged as having CKD. [Results] Annual decline of eGFR and annual incidence of CKD were greater in RA group compared with control (-5.81±11.75 vs. 0.71±8.51, P = 0.000) (15.7 % vs. 4.6 %, P = 0.000). Logistic regression analysis showed RA is an independent risk factor of incident of CKD (P = 0.005, relative risk = 2.968, 95%CI. =1.393 to 6.327). Among RA patients, significant correlation was found between DAS28CRP at baseline and annual decline of eGFR (R = -0.238, P = 0.006). Active group had greater annual decline of eGFR compared to remission group (-8.9 ± 11.2 % vs. -3.5 % ± 11.7, P = 0.003). Multiple regression analysis showed that high DAS28 CRP is correlated with annual decline of eGFR in the patients with RA (B = -2.026, 95%CI. -3.909 to -0.142, P = 0.035). [Conclusion] RA is an independent risk factors of CKD incident. RA activity is correlated with annual decline of eGFR in patients with RA, suggesting that RA activity, presumably systemic inflammation, could contribute to development of CKD.

W85-4

Characterization of 4 patients with recurred-rheumatoid arthritis after treatment of methotrexate-associated lymphoproliferative disorders

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Conflict of interest: None

[Objectives] Methotrexate (MTX) serves as a key drug in treating patients (pts) with RA, but certain RA pts treated with MTX develop lymphoproliferative disorders (MTX-LPD). When RA recurred after treatment of MTX-LPD, the characterization and management was unclear. [Methods] We analyzed 4 pts (a male and 3 females) with recurred-RA, whose MTX-LPD was treated from January 2010 to July 2011. [Results] The mean age was 66, mean disease duration of RA 11 years, mean total dose of MTX 1,611 mg, and mean duration of MTX treatment 46 months. A patient had been administered with infliximab. Two pts were diagnosed to have diffuse large B cell lymphomas, one had Hodgkin lymphoma, and one T cell-rich large B-cell lymphoma. Esptein-Barr virus infection was detected in tumor tissues from 3 of 4 pts analyzed. All 4 pts received chemotherapy. RA recurred within mean 12 months after the end of chemotherapy. All pts were treated with prednisolone, two pt was bucillamine (BUC) and tacrolimus (TAC), one BUC, and one TAC or biologic DMARDs (etanercept, abatacept). Two pts achieved re-remission of RA. LPD did not recur in all pts during observation period. [Conclusion] When RA recurred after treatment of MTX-LPD, steroid and DMARDs except MTX were used effectively without recurrence of LPD.

W85-5

Investigation of Methotrexate-associated lymphoproliferative disorder (MTX-LPD) in our department

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Conflict of interest: None

Objectives: It is well recognized that patients of rheumatoid arthritis with MTX develop MTX-LPD. Spontaneous remission with MTX withdrawal is often seen, however the relapse cases after regression were reported. The objective of this study is to investigate MTX-LPD cases in our department and to identify predictive factors of relapse. Methods: We evaluated the clinical characteristics, pathological and laboratory findings, treatment and course in 13 MTX-LPD cases. Results: Average age of MTX-LPD onset was 71.5 years (52~85) and average time of its onset from administration of MTX was 7.9 years (2.2~19.8). Extranodal sites were occurred in 46% (6/13). 11 cases were includes in DLBCL (n=4), FL (n=1), PTCL NOS (n=1), AILD (n=1), PEL (n=1), no malignancy (n=4), two cases were not proceeded. MTX was stopped in all patients, and 4/13 (3: DLBCL, 1: PTCL-NOS) started chemotherapy. All lesions were regressed, but the relapse was observed in 23% (3/13). Relapse was associated with elevated sIL-2R (p=0.045). Conclusions: All cases of MTX-LPD in our department were improved, however 23% of cases were relapsed. We must follow the patients of MTX-LPD after remission especially in high risk relapse group whose sIL-2R was elevated.

W85-6

Analysis of DMARDs selection in rheumatoid arthritis patients with malignancies

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Conflict of interest: None

[Objectives] According to 2012 update of 2008 ACR recommendation for the use of DMARD, the panel recommends starting or resuming any biologic DMARDs for patients who have been treated for solid malignancies more than 5 years ago. This study analyzed the DMARDs selection in rheumatoid arthritis patients with malignancies. [Methods] 1872 patients was seen in our clinic, between 2013 April and September. Patient records were reviewed retrospectively and analyzed. [Results] Of the 1872 patients, 44 developed a malignancy (42 solid tumors, 1 lymphomas and 1 hematologic non-lymphomas). Of 44 patients, 27 patients were treated with methotrexate (MTX), and no patient was treated with biologic DMARDs. All of 27 patients treated with MTX were discontinuation of treatment with MTX. After diagnosis of malignancies, 14 patients showed relapse of RA (31.8%). After treatment of malignancies, 14 patients were restart to given for the treatment of RA (31.8%). 6 patients showed relapse or metastasis of cancers.

W86-1

The relationship between Serum cystatin C (CysC) levels and Rheumatic diseases activity

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Conflict of interest: None

Objective: CysC is a useful marker of GFR, whereas it is not fully elucidated. We examined the relationship between serum CysC and disease activity in SLE and RA. ***Methods:*** We enrolled 52 SLE patients (female: 50) and 189 RA patients (female: 157) who visited our hospital from 2012 to 2013. We measured SLEDAI, DAS28CRP, serum Cr, estimated GFR and serum CysC. ***Results:*** In the both groups, serum CysC significantly correlated with serum Cr (SLE: R=0.90, RA: R=0.78), and inversely correlated with estimated GFR (SLE: R=0.69, RA: R=0.67). Serum CysC levels in high disease activity group were significant higher in both SLE and RA patients regardless of renal damage. ***Discussion:*** The reason why serum CysC was higher in high disease activity group is that CysC may indicate subclinical renal damage. However, serum CysC may reflect disease activity, because there were reports that CysC involved in the inflammatory process.[1] ***Conclusion:*** CysC may be a useful marker for disease activity in rheumatic disease regardless of renal damage. ***Reference:*** 1. Keller CR, et al. Kidney Int. 2007; 71:239-44

W86-2

The significance of urinary podocyte number and urinary podocalyxin level in SLE

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Conflict of interest: None

[Objectives] To clarify the significance of urinary podocyte-related

biomarkers in SLE. [Methods] Numbers of urine podocytes (U-Pod) were determined by counting podocalyxin (PCX)-positive cells in urine sediments. Urine levels of PCX (U-PCX) were measured by ELISA, normalized to urine creatinine levels. Eighty three SLE patients with or without kidney diseases (KD) were enrolled. [Results] U-Pod and U-PCX of KD (+) group were significantly higher than those of KD (-) group in SLE (U-Pod KD (+): 7.9±24.9 cells/mL vs KD (-): 0.2±0.6 cells/mL, P<0.0001, U-PCX KD (+): 362.2±298.8 μg/gCr vs KD (-): 128.9±113.5 μg/gCr, P=0.0012). Among 36 patients with biopsy-proven lupus nephritis, U-Pod of patients with Class IV lesion was significantly higher than that of patients without (20.0±38.6 vs 0.7±0.6 cells/mL, P=0.0025). U-PCX of patients with Class V lesion tended to be higher than that of patients without (549.1±344.5 vs 347.8±274.0 cells/mL, P=0.058). ROC analysis showed that U-Pod>0.9 cells/mL predicted pure and mixed Class IV (sensitivity 81.0%, specificity 71.4%, P=0.004), and that U-Pod<1.25 cells/mL and U-PCX>686.0 μg/gCr predicted pure Class V (sensitivity 60.0%, specificity 96.7%). [Conclusion] U-Pod and U-PCX are high in lupus nephritis, and histological class might be predictable with U-Pod and U-PCX.

W86-3

A possible role of serum IL-6 quick measure system in RA patients

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Conflict of interest: None

[Objectives] Interleukin 6 is an important cytokine in Rheumatoid arthritis pathogenesis. Measurement of serum Il-6 needs a few hours and there is not measured in daily clinical setting. We created high sensitivity cytokine quick measure system, thus we investigated accuracy of the system in RA patients. [Methods] Our system can measure serum IL-6 titer using 100 μl whole blood in only 25 minutes. 70 RA patients were measured serum IL-6 by our system and CLEIA methods, we investigate their accuracy. We also examined the correlation between serum IL-6 and c reactive protein, ESR. [Results] The mean age was 64.3 years. Their disease length was 13.5 years, 19 cases was using biological agents. The average titer of quick measure system was 23.6pg/ml and CLEIA methods was 16.7pg/ml. Coefficient of correlation was 0.923. The mean value of quick measure system was little higher than CLEIA methods. There was no correlation between serum IL-6 and CRP, ESR. But, except using biological agent cases, Coefficient of correlation between IL-6 and CRP was 0.381, IL-6 and ESR was 0.37. [Conclusion] Our cytokine quick measure system was not inferior to CLEIA methods. Serum IL-6 is more essential inflammatory protein than CRP, our system contributes to RA treatment.

W86-4

Pentraxin-3 (PTX3) in Patient with Rheumatoid Arthritis (RA): High disease activity or Infection

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Conflict of interest: None

Infection is a critical complication in management of patient with rheumatoid arthritis (RA). When you examine a patient with high level of serum C-reactive protein (CRP), it isn't easy to distinguish worthing of RA and complicated with infections, in some time. If we have a biomaker which can distinguish the two easily, it is very helpful in daily clinical site. PTX3 is a novel biomaker which was reported in usefulness in some disease. [Objectives] To evaluate the diagnosability of PTX3 in RA patients with high level of CRP. [Methods] 21 RA patients with infections (infection RA: iRA), 20 with high disease activity of RA (flare RA: fRA), 23 healthy controls (HC) were enrolled in this study. We measured PTX3, CRP and procalcitonin (PCT) before and after the treatments (iRA and fRA), at any time (HC). [Results] In iRA, average levels of PTX3 significantly reduced pre- and post-treatment. In pretreatment iRA, PTX and PCT have correlation. In pretreatment, iRA's PTX3 level was higher than that of fRA, but both of level were higher than that of HC. In post treatment PTX3, there wasn't significant distinction in iRA and fRA, but both level were higher than that of HC. [Conclusion] PTX3 is a useful biomaker which can distinguish worthing of RA and complicated with infections.

W86-5

Bioelectrical impedance analysis for assessing skeletal muscle mass in patients with rheumatic diseases

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Conflict of interest: None

[Objectives] In patients with rheumatic diseases, movement disorders and glucocorticoid (GC) therapy reduce skeletal muscle mass (SMM) resulting in ADL disturbances. However, their epidemiological characteristics remain to be elusive. Although the computed tomography (CT) and magnetic resonance imaging (MRI) have high validity to evaluate SMM, it is desirable to decrease the absorbed radiation dose, time, and costs. We aimed to validate Bioelectrical Impedance Analysis (BIA) for quantification of SMM in rheumatic disease patients by comparison with cross sectional area (CSA) of thigh muscle using CT and MRI. [Methods] We retrospectively obtained the data from 22 rheumatic disease patients who treated with or without GC in our division. SMM was measured by a BIA device Tanita MC-190. CSA of the mid-thigh muscle was analyzed by CT/MRI and ImageJ software and corrected by the length of femur. [Results] There was a significant correlation between CT/MRI mid-thigh muscle CSA and BIA whole, trunk, arms and legs SMM each. Moreover, those correlations remain preserved regardless of the correction of BIA measurements by height and with or without GC. [Conclusion] Our study showed that BIA is a useful technique for assessing SMM in patients with rheumatic diseases.

W86-6

Usefulness of CLEIA for the determination of anti-dsDNA antibodies

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Conflict of interest: None

[Objectives] Anti-dsDNA antibodies are specific marker for systemic lupus erythematosus (SLE) and associated with disease activity. We examined the usefulness of chemiluminescent enzyme immunoassay (CLEIA) for anti-dsDNA antibodies. [Methods] Ninety six SLE patients were measured anti-dsDNA antibodies by CLEIA and enzyme-linked immunosorbent assay (ELISA). We analyzed the relationship between anti-dsDNA antibody values and SLE disease activity index (SLEDAI). [Results] Twenty four patients were positive for anti-dsDNA antibodies by CLEIA and ELISA, and 47 patients were negative by both assays. Though only 2 patients were positive by CLEIA and negative by ELISA, 23 patients were positive by ELISA and negative by CLEIA. The mean anti-dsDNA antibody levels of these 23 patients were 34.1 ± 33.0 IU/ml (ELISA), and 6.7 ± 3.3 IU/ml (CLEIA). The mean value of SLEDAI was 3.9 ± 3.2 (0-10), and 15 of these 23 patients were low disease activity (SLEDAI was under 4). [Conclusion] CLEIA for anti-dsDNA antibodies reflects more exact disease activity than ELISA and provide results within short time. Hence, CLEIA is the useful assay for the assessment of SLE.

W87-1

RORγt^{+}Foxp3^{+} CD4 T cells regulates the development of collagen induced arthritis

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Conflict of interest: None

[Objectives] To clarify the effect of RORγt expression on T cells in the development of autoimmune arthritis. [Methods] 1) Incidence and severity of collagen induced arthritis (CIA) were assessed in C57BL/6 (B6) and RORγt transgenic (Tg) mice. 2) Cytokine production from collagen type II (CII) reactive T cells was analyzed by ELISA. 3) Transcription factors and CCR6 expression on CII reactive CD4 T cells was analyzed by FACS. 4) Draining lymph node cells or CD4^{+} cells isolated from B6 or Tg mice were transferred into immunized B6 mice, and then clinical course of arthritis was assessed. [Results] 1) CIA was significantly suppressed in Tg mice. 2) IL-17 production from CII reactive T cells was significantly increased in Tg mice. 3) Foxp3 expressing CD4 T cells also expressed RORγt, and higher expression of CCR6 was observed in RORγt^{+}Foxp3^{+} CD4 T cells in Tg mice. 4) Transfer of lymph node cells harvested from Tg mice significantly suppressed CIA in B6 mice, and transfer of CD4^{+} cells harvested from Tg mice also tended to suppress CIA in B6 mice. [Conclusion] Overexpression of RORγt in T cells suppressed CIA in spite of higher IL-17 production. The results of cell transfer experiments showed the possibility that RORγt^{+}Foxp3^{+} regulatory T cells might regulate the development of CIA.

W87-2

CD4^{+}CD25^{-}LAG3^{+} regulatory T cell controls excessive B cell responses

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Conflict of interest: Yes

Recent case-control association study suggests that polymorphisms in the early growth response gene-2 (*EGR2*), a zinc-finger transcription factor, influence systemic lupus erythematosus (SLE) susceptibility in humans. We have previously reported the novel Foxp3-independent CD4^{+}CD25^{-} regulatory T cells (Tregs) that characteristically expressed both lymphocyte activation gene-3 (LAG3) and Egr2. Here, we demonstrated the role of CD4^{+}CD25^{-}LAG3^{+} Tregs (LAG3^{+} Tregs) in lupus pathogenesis. Adoptive transfer of LAG3^{+} Tregs from MRL/+ mice significantly suppressed the progression of nephritis and autoantibody production in MRL/*Fas^{lpr}* mice. In a C57BL/6 mice based *in vivo* transfer model, LAG3^{+} Tregs strongly suppressed antibody production and the development of germinal center B cells and follicular helper T cells. Interestingly, both Egr2 and Fas expression on LAG3^{+} Tregs were necessary for its suppressive activity. We also revealed that LAG3^{+} Tregs directly induced B cell apoptosis via regulation of BCL-X_L expression in a PD-1/PD-L1-dependent manner. These findings elucidate that LAG3^{+} Tregs play a crucial role in preventing the excessive B cell responses. By exploiting the capacity of LAG3^{+} Tregs, they may provide a new therapeutic method in autoantibody-mediated autoimmune diseases.

W87-3

The role of sphingosine-1-phosphate receptor 3 (S1P3) signaling in murine collagen-induced arthiritis

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Conflict of interest: None

[Objectives] To examine the role of S1P3 receptor signaling in the development of collagen-induced arthritis (CIA) in murine. [Methods] Wild-type (WT) and S1P3-deficient (KO) mice backcrossed 9 generations to DBA/1J mice were immunized with bovine type II collagen, and disease severity were assessed by arthritis scoring system of 0–4. Mice were sacrificed on the 42nd day and histopathological changes of their paws stained with H&E were scored based on synovial inflammation, cartilage destruction and bone erosion parameters of 0-3. The levels of anti-type II collagen antibodies were measured by ELISA. [Results] The severeity of arthritis in S1P3 KO mice was significantly lower compared with WT mice ($P<0.05$). Synovial inflammation and bone erosion parameters in S1P3 KO mice were siginificantly lower compared with WT mice ($P < 0.05$). The level of anti-type II collagen antibodies were not different between two groups. [Conclusion] These results indicate that S1P3 receptor signaling plays an important role in the development of murine collagen-induced arthritis model. This pathway could be a therapeutic target for rheumatoid arthritis, although further investigations are required.

W87-4

TIARP suppresses the migration of neutrophils in arthritis via the reduced CXCL2/CXCR2 expression

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Conflict of interest: None

[Aim] TIARP is dominantly expressed in macrophages (Mφ), neutrophils (Neu) and fibroblast-like synoviocytes (FLS). Recently, we found that TIARP$^{-/-}$ mice develop spontaneous arthritis with increased TNF-induced IL-6 production in Mφ, although the functional role of TIARP in Neu and FLS remains uncertain. The aim of this study is to elucidate the role of TIARP in Neu and FLS with arthritis. [Methods] 1) TIARP expression in FLS after TNFα stimulation were measured. 2) Using WT or TIARP$^{-/-}$ FLS, IL-6, MMP3 and CXCL2 expression were compared. 3) Cell proliferation of FLS by TNFα was analyzed by BrdU incorporation. 4) The chemoatractant activity of TIARP$^{-/-}$ Neu was tested by transwell chemotaxis assays. 5) The expression of CXCR2 on Neu was analyzed. [Results] 1) TIARP expression in FLS was significantly increased by TNFα. 2) TNFα stimulation induced higher expressions of IL-6, CXCL2 and MMP3 in TIARP$^{-/-}$ FLS. 3) TNFα stimulation induced much more cell proliferation in TIARP$^{-/-}$ FLS. 4) The recruitment was enhanced by CXCL2-dependent manner in TIARP$^{-/-}$ Neu. 5) CXCR2 expression was significantly higher in TIARP$^{-/-}$ Neu. [Conclusion] TIARP might downregulate the production of CXCL2 from FLS and the expression of CXCR2 in Neu, resulting in the protective ability of Neu migration in arthritic joints.

W87-5

***Peptidylarginine deiminase type4* (*Padi4*) role in murine arthritis model**

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Conflict of interest: None

[Objectives] *Peptidylarginine deiminase type 4 (PADI4)* was firstly identified as non-MHC risk factor of rheumatoid arthritis (RA). PAD4 protein has enzymatic activity, called citrullination. Recent report suggested that *Padi4* contributed to RA, regardless of ACPA status. It raise the possibility that *Padi4* associated with RA via unknown effects other than antigen citrullination. [Methods] We immunized DBA/1J wildtype (WT) and *Padi4* knockout (KO) mice with recombinant human Glucose-

6-phosphate isomerase (rhGPI) and scored arthritis/histological severity. Numbers and phenotypes of T cells, B cells and myeloid lineage cells in the spleen and inguinal lymph nodes were analyzed by FACS. Serum anti GPI antibodies (Abs) and IL-6 were measured by ELISA. *In vivo* viability of neutrophil were measures by annexin V and propidium iodide. [Results] In *Padi4* KO mice, arthritis severity was reduced. *Padi4* KO mice could produce anti-GPI IgG, but titer is low. The numbers/phenotypes of T cells were normal, however, T helper 17 (Th17) cells in iLNs and serum IL-6 concentration were reduced. Viability of neutrophil is decreased *in vivo*. [Conclusion] *Padi4* depletion showed the reduction of serum IL-6 concentration, Th17 cells and myeloid lineage cells, and resulted in the decrease of arthritis severity.

W87-6

Exacerbation of polymyositis model in interferon-gamma-deficient mice

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Conflict of interest: None

[Objectives] C protein–induced myositis (CIM) is a mouse model of polymyositis, in which activated antigen-specific $CD8^+$ T cells are essential. The purpose of the present study is to substantiate a pathogenic role of type1 and type2 cytokines, IFNγ and IL-4, in the development of CIM. [Methods] CIM was induced in $IFN\gamma^{-/-}$, $IL\text{-}4^{-/-}$, $IFNg^{-/-}IL\text{-}17A^{-/-}$, and wild-type (WT) C57BL/6 mice. IFNγ and IL-17A production from $CD4^+$ T cells of $IFN\gamma^{-/-}$ and WT mice were assessed with ELISA. [Results] $IFN\gamma^{-/-}$ mice developed severer myositis compared to WT mice. Histologic examination revealed abundant infiltration of neutrophils in the injured muscles, which was not seen in WT mice. In contrast, CIM in $IL\text{-}4^{-/-}$ mice was comparable to that in WT mice. $CD4^+$ T cells derived from $IFNg^{-/-}$ mice secreted more IL-17A compared to those from WT mice. $IFN\gamma^{-/-}IL\text{-}17A^{-/-}$ mice developed myositis comparable to $IFN\gamma^{-/-}$ mice, with comparable neutrophil infiltration. [Conclusion] Deficiency of type1 cytokine, but not type2 cytokine led to severer CIM. Histologic analysis showed neutrophils infiltrating in the muscles of IFNγ deficient mice, which were absent in WT mice. While lack of IFNγ leads to the activation of Th17 cells, it may not be involved in the exacerbation of CIM.

International Concurrent Workshop

ICW1-1

Genetic impact on the occurrence of hip fracture in Japanese patients with rheumatoid arthritis: results from the IORRA cohort study

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Conflict of interest: None

[Objectives] Patients with rheumatoid arthritis (RA) have a higher prevalence of osteoporosis and hip fracture than healthy individuals. Multiple genetic loci for osteoporotic fracture were identified in the recent genome-wide association studies. The purpose of our study was to identify genetic variants associated with the occurrence of hip fracture in Japanese patients with RA. [Methods] DNA samples of 1957 Japanese patients with RA were obtained from the Institute of Rheumatology Rheumatoid Arthritis cohort study (IORRA) DNA collection. Nineteen single nucleotide polymorphisms (SNPs) in the 18 genetic loci reported in the recent studies were selected and genotyped in the DNA samples. Thirty-nine hip fractures in 39 patients were identified and included into this study. The genetic risk for hip fracture was examined by using a multivariate Cox proportional hazards regression model in 1957 patients. [Results] The risk analyses revealed that patients who are homozygous for the major allele of SNP rs6993813, in the *OPG* locus, have a higher risk for hip fracture [HR (95% CI) = 3.04 (1.44 to 5.44), $P = 0.002$]. No associations were found with the other SNPs. [Conclusion] Our results indicate that an *OPG* polymorphism is a genetic risk factor for hip fracture in Japanese patients with RA.

ICW1-2

Ankylosing Spondylitis and ERAP1 gene; Epistasis between HLA-B*27 and ERAP1 gene Diplotypes

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[Objectives] Some extra MHC genes and its haplotype and diplotypes of susceptible genes might interfere with HLA-B27 to predispose HLA-B27 individuals to this disease. ERAP1 gene has the highest association with AS susceptibility after HLA-B27. This study's purpose is to investigate the role of epistases between HLA-B*27 and ERAP-1 gene diplotypes in AS susceptibility. [Methods] In present study 399 AS patients and 322 healthy controls were recruited. All 12 SNPs of *ERAP1* were genotyped using allelic discrimination real time PCR method. After genotyping, Diplotype analysis performed for these SNPs. HLA-B27 for patients and healthy controls determined using PCR-SSP. [Results] $\frac{\text{TTTCGCAAGCGA}}{\text{TTTCGCAAGCGA}}$ and $\frac{\text{TTCCCCAAGCGA}}{\text{TTCCCCAAGCGA}}$ diplotypes (rs1065407; rs2287987; rs30187; rs10050860; rs27044; rs26653; rs27434; rs469876; rs17481856; rs28366066; rs28096; rs13167972) found in 10 and 12 HLA-B27 positive patients, respectively; but these diplotypes were not found in any healthy controls. [Conclusion] HLA-B27 positive individuals with these patterns of ERAP1 diplotypes seemed to be doomed for developing ankylosing spondylitis. Further studies on other ERAP1 SNPs diplotypes and other genes can show us the dark points of contributor genes and SNPs in this disease.

ICW1-3

PPARγ controls mTOR/autophagy signalling in the articular cartilage

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Conflict of interest: None

Objectives: In this study we explored the role of peroxisome proliferator activated receptor gamma (PPARγ), a transcription factor, on chondroprotection by determining the effect of PPARγ genetic deletion in the cartilage on mammalian target of rapamycin (mTOR)/autophagy signaling pathway using mice model of OA. **Methods:** We created inducible cartilage-specific PPARγ knockout (KO) mice and subjected them to mice model of OA. **Results:** PPARγ KO mice exhibit accelerated cartilage destruction, chondrocytes apoptosis, synovial fibrosis and overproduction of OA inflammatory/catabolic factors as well as increased expression of mTOR and suppression of key autophagy genes compare to controls. *In vitro* rescue experiments using PPARγ expression vector reduced mTOR expression, increased expression of autophagy genes and reduced the expression of OA inflammatory/catabolic factors, thus reversing the phenotype of PPARγ KO mice chondrocytes. To validate our *in vitro* findings *in vivo* we created cartilage specific PPARγ-mTOR double KO mice. Loss of mTOR in PPARγ KO mice resulted in increased autophagy signaling and significant protection from OA in mice. **Conclusion:** These findings outline PPARγ and its signaling by mTOR/autophagy as a potential therapeutic target for the treatment of OA.

ICW1-4

Dynamic visualization of RANKL-mediated vascular permeability in living bones by intravital multiphoton microscopy

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Conflict of interest: None

Bone tissue is highly vascularized and a large number of fenestrations in the vessel walls increase vascular permeability in this region. These unique features of bone are assumed to affect the migration of cells. For example, various kinds of hematopoietic cells are differentiated in bone marrow cavity and migrate to the peripheral tissues through the blood circulation. Controlling vascular permeability must be very important for the recruitment and egress of these cells. However, it remains unclear how vascular permeability is regulated in bone marrow *in vivo*. To answer this question, we utilized an advanced imaging system for visualizing living bone tissues with intravital multiphoton microscopy that we have originally developed. By means of this technique, we found that the vascular permeability in bone marrow cavity was much higher than in other tissues and that it could be variable in pathological conditions. We also found that RANKL, which is known as a key molecule for osteoclastogenesis, could also regulate the vascular permeability in bone marrow. Furthermore, the vascular permeability in bone marrow was associated with the bone density. These novel approaches using intravital multiphoton microscopy are very useful for studying cellular dynamics in bone marrow *in vivo*.

ICW1-5

Density and microstructure at distal radius in patients with psoriatic arthritis: a case-control study ing high-resolution peripheral quantitative computed tomography

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[Objectives] To investigate volumetric BMD (vBMD) and bone microstructure at distal radius in psoriatic arthritis (PsA) patients using high-resolution peripheral quantitative computed tomography (HR-pQCT) [Methods] This cross-sectional study involved 65 PsA patients (30 males and 35 females, age: 55.0±10.7 years) and 65 age- and gender-matched healthy controls. Areal BMD (aBMD) of hip, lumbar spine and ultradistal radius was measured by DXA. HR-pQCT was performed at distal radius. [Results] aBMD at all sites were effectively the same between 2 groups. Compared to controls, patients had lower vBMD, albeit shy of statistical significance. Trabecular microstructure, including trabecular bone volume fraction, number, thickness and separation, was maintained in patients. The only measures indicating compromised bone quality were related to cortical porosity, where cortical pore volume and porosity index were 74% (p=0.023) and 103% (p=0.001) higher, respectively, in patients. [Conclusion] Our results suggest that major feature of compromised bone quality in PsA is accelerated cortical porosity. This underscores the inability of DXA to explain bone fragility in PsA. Microstructural deficits in cortical bone may play a central role in the pathophysiology of bone fragility in PsA.

ICW1-6

18F-FDG and NaF PET/CT demonstrate coupling of inflammation and accelerated bone metabolism in rheumatoid arthritis

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Conflict of interest: None

【Objective】Synovitis causes joint destruction that is associated with accelerated bone metabolism in rheumatoid arthritis (RA). We evaluated relationship of 18F-FDG and NaF PET/CT uptake with joint destruction. 【Methods】12 patients who started to receive biologic agents were enrolled. We examined association of FDG- and NaF-PET/CT of the bilateral hands with clinical findings at the baseline and interval changes of hand X-rays for the following 6 months according to according to the Genant-modified Sharp score. These imaging findings were comparatively assessed in individual joints, 【Results】The standard uptake value (SUV) of FDG was well correlated with that of NaF in individual joints (r=0.62), though NaF was accumulated in osteoplastic lesions without FDG signals. FDG were strongly accumulated in swelling joints and the total accumulation was correlated with DAS28. NaF accumulation was associated with DAS28, HAQ, progressive erosion in individual joints, and deterioration of total Sharp score (p=0.66). 【Conclusion】FDG-PET detects synovistis sensitively, whereas NaF accumulation is more closely associated with bone destructive and plastic lesions. Simultaneous accumulation of the both molecules suggest coupling of inflammation and accelerated bone metabolism in RA joints.

ICW1-7

A novel delivering system of mesenchymal stem cells using Nano-fiber scaffold for treatment of rheumatic arthritis

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Conflict of interest: None

[Objectives] Mesenchymal stem cells (MSCs) possess immunoregulatory ability with multipotency which makes them an ideal tool for treatment of rheumatoid arthritis (RA). In order to develop an effective delivery system of MSCs, we utilized a scaffold made of nano-diameter poly-

lactic-co-glycolic acid fiber sheet (Nano-fiber). [Methods] MSCs were injected intra-articularly (IA) or intra-peritoneally (IP) or seeded on Nano-fiber and implanted into ankles (Nano-MSCs) of collagen induced arthritis (CIA) rats. [Results] IA or IP treatment demonstrated no effects whereas Nano-MSCs significantly suppressed arthritis evaluated by arthritis score and body weight. X-ray, micro-CT and histological analysis revealed markedly suppressed joint destruction with Nano-MSCs but not with IA or IP. Furthermore, draining lymph nodes were decreased in size and pro-inflammatory cytokines expression, serum anti-type II collagen IgG and proliferation of T cells *ex vivo* was significantly suppressed. Culture of MSCs on Nano-fiber increased TGF-β1 production and gene expression compared to culturing on plate. [Conclusion] administration of MSCs with Nano-fiber efficiently suppressed arthritis and bone destruction and systemic inflammation, suggesting a novel MSCs delivery system for future RA treatment.

ICW1-8

Inhibitory effects of IL-17 on chondrogenic differentiation of human mesenchymal stem cells through the phosphorylation of Sox9

Masahiro Kondo[1,2], Kunihiro Yamaoka[1], Koshiro Sonomoto[1], Shunsuke Fukuyo[1], Koichi Oshita[1,2], Yosuke Okada[1], Yoshiya Tanaka[1]
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Conflict of interest: Yes

[Objectives] Mesenchymal stem cells (MSCs) can differentiate into chondrocytes. Therefore, MSCs are considered to contribute to cartilage homeostasis and expected as a new tool for cartilage repair therapy. IL-17contributes to cartilage matrix (CM) breakdown and chondrocytes apoptosis. However, the effects of IL-17 on chondrogenic differentiation remain unclear. [Methods] Pellet culture was performed with MSCs in chondrogenic induction media containing TGF-β3 (CIM). [Results] Elevation of CM and marker genes expression by CIM was inhibited by IL-17, meanwhile IL-17 receptor expression was increased. Expression and phosphorylation of Sox9 were up-regulated by CIM whereas IL-17 decreased phospho-Sox9 without affecting Sox9 expression. Protein kinase A (PKA), a kinase known to phosphorylate Sox9, was induced by CIM and suppressed by IL-17. CM and marker genes induced by CIM were selectively suppressed by a PKA-inhibitor H89. [Conclusion] Activation of SOX9 by PKA is important for chondrogenesis, and IL-17 shows inhibitory effect through the suppression of SOX9 activation. These results suggest that IL-17 induces cartilage disorder by disrupting homeostasis. Considering the cell based therapy, preoperative inactivation of IL-17 should be important for effective cartilage repair.

ICW1-9

Soluble Semaphorin 4D in Rheumatoid Arthritis

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Conflict of interest: None

Semaphorin 4D (Sema4D), which is a protein of the semaphorin family of guidance molecule, activates immune cells and inhibits osteoblast mediated bone formation. To elucidate the pathogenic role of Sema4D in rheumatoid arthritis (RA), we investigated the soluble Sema4D levels in sera and synovial fluid by ELISA. Surface Sema4D expression on cells from peripheral blood and synovial fluid was analyzed by FACS. Soluble Sema4D was increased in RA sera compared with sera from healthy individuals. In synovial fluid, the levels of soluble Sema4D were increased in RA compared with osteoarthritis. The levels of serum soluble Sema4D was correlated with disease activities of RA such as DAS28, CRP, rheumatoid factor, and urinary deoxypyridinoline. In addition, serum levels of soluble Sema4D were decreased after biologics treatments in RA patients. Interestingly, the cell surface expression levels of sema4D were not increased in PBMC and rather decreased in CD3+ cells in synovial fluid of RA patients. Collectively, these results not only indicate that the pathological roles of sema4D in RA, but also suggest that cell surface Sema4D might be a source of increased soluble Sema4D in RA synovium.

ICW1-10

S1P-mediated osteoclast precursor monocyte migration is a critical point of control in antibone-resorptive action of active vitamin D

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Conflict of interest: None

The migration and positioning of osteoclast precursor monocytes are controlled by the blood-enriched lipid mediator sphingosine-1-phosphate (S1P) and have recently been shown to be critical points of control in osteoclastogenesis and bone homeostasis. Here, we show that calcitriol, which is the hormonally active form of vitamin D, and its therapeutically used analog, eldecalcitol, inhibit bone resorption by modulating this mechanism. Vitamin D analogs have been used clinically for treating osteoporosis, although the mode of its pharmacologic action remains to be fully elucidated. In this study, we found that active vitamin D reduced the expression of S1PR2, a chemorepulsive receptor for blood S1P, on circulating osteoclast precursor monocytes both *in vitro* and *in vivo*. Calcitriol- or eldecalcitol-treated monocytoid RAW264.7 cells, which display osteoclast precursor-like properties, migrated readily to S1P. Concordantly, the mobility of circulating CX_3CR1^+ osteoclast precursor monocytes was significantly increased on systemic administration of active vitamin D. These results show a mechanism for active vitamin D in controlling the migratory behavior of circulating osteoclast precursors, and this action should be conducive to limiting osteoclastic bone resorption *in vivo*.

ICW1-11

Analysis of the Mechanism of Differentiation and Function of Osteoclast-like Cells Induced by Combination of Tumor Necrosis Factor α and Interleukin 6

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Conflict of interest: None

[Objectives] Local bone destruction associated with RA is partially controllable by biological agents targeting TNFα or IL-6. We elucidated the mechanism of differentiation and function of osteoclast-like cells (OLCs) induced by the combination of TNFα and IL-6. [Methods] We cultured osteoclast precursors from the femora of mice in the presence of M-CSF, TNFα, IL-6 and TNFα plus IL-6. The expression levels of c-Fos and NFATc1 were detected by Western blotting. The effects of anti-IL-1β antibody and JAK inhibitor were examined. The genetic ablation of STAT3 was also evaluated. These cytokines were administered into the supracalvariae in mice. [Results] The combination of TNFα and IL-6 induced TRAP-positive OLCs in an RANKL-independent manner. Stimulation with TNFα and IL-6 significantly induced the expression levels of c-Fos and NFATc1. The differentiation of OLCs was completely inhibited by JAK inhibitor but not anti-IL-1β antibody. We observed no difference in the induction of OLCs derived from STAT3-knockout mice and control mice. Bone resorption on the calvariae in mice was significantly increased, once the combination of TNFα and IL-6 was administered. [Conclusion] We have found a novel mechanism developing OLCs with the combination of TNFα and IL-6.

ICW1-12

Comparison of the effect of 18 months daily Teriparatide administration in RA or postmenopausal osteoporosis patients

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Conflict of interest: None

[Objectives] The aim of this study is to clarify the effect of 18 months administration of Teriparatide (TPTD) on RA osteoporosis patients (RA) by comparing with that of postmenopausal osteoporosis patients (Porosis). [Methods] Daily TPTD was administered to 69 RA patients (66 female, 67.7 years old, DAS28-CRP 2.9, 75.4% taking prednisolone (PSL) with average dose 4.0mg, 26.2% taking biologics, lumbar T-score -2.4, femoral neck T-score -2.6, previous vertebral fracture 2.4) and 62 postmenopausal osteoporosis patients (71.1 years old, lumbar T-score -3.1, femoral neck T-score -2.4, previous vertebral fracture 2.7) and followed up for 18 months. [Results] BMD change from baseline→6→12→18 months was as follows. Lumbar spine (RA: 0.7→4.4→6.6→7.3%/Porosis: -0.7→4.0→7.2→7.9%) Femoral neck (RA: -3.0→-1.1→3.2→4.0%/Porosis: -0.7→-0.2→0.1→-0.7%). There were no significant difference of lumbar spine BMD change between two groups, but femoral neck BMD significantly increased from 12 months only in RA group ($p<0.05$). Incidence of new fracture during this period was 5.6% in RA and 3.9% in Porosis. [Conclusion] Our findings indicate that 18 months administration of daily TPTD is more effective in increasing femoral neck BMD in RA compared to postmenopausal osteoporosis.

ICW1-13

Comparison of the effect of 6 months administration between Minodronate monotherapy and vitaminK2 or eldecarcitol combination therapy in postmenopausal, male, and RA osteoporosis patients

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Conflict of interest: Yes

[Objectives] Difference of the effect of Minodronate (MIN) monotherapy and combination therapy with vitaminK2 (VK) or eldecarcitol (ELD) in osteoporosis treatment remains unknown. [Methods] 138 postmenopausal, male, and RA osteoporosis patients were enrolled in this 6-months prospective study. 1) 48 treated by MIN (44 female 4 male 11 RA / 74.2 yo), 2) 40 treated by MIN+VK (37 female 3 male 11 RA / 73.0 yo), 3) 50 treated by MIN+ELD (39 female 11 male 14 RA / 76.4 yo). [Results] No significant difference was observed in initial age, BMI, eGFR, bone metabolism markers, bone mineral density (BMD), between 3 groups. Increasing rate (%) of the BMD were in lumbar 1) 2.9 2) 2.5 3) 3.7, in femoral neck 1) -0.8 2) 0.2 3) 1.5, in proximal femur 1) -0.1 2) 1.1 3) 2.3, and in forearm 1) -1.3 2) 2.3 3) 1.5, respectively. Compared to MIN monotherapy, MIN+ELD significantly increased BMD of proximal femur ($P<0.05$) and MIN+VK significantly increased BMD of forearm ($P<0.05$). No significant differences were observed in decreasing rate of bone metabolism markers after 3-months (TRACP-5b; 1) -42.0 2) -53.0 3) -52.0, P1NP; 1) -43.0 2) -51.2 3) -56.0, and ucOC; 1) -42.0 2) -50.0 3) -42.0). [Conclusion] 6-months combination therapy with MIN and VK or ELD may be useful in BMD increment compared to MIN monotherapy.

ICW1-14

Clinical Features and Treatment Results of Japanese Patients with SAPHO (synovitis-acne-pustulosis-hyperostosis-osteitis) Syndrome

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Conflict of interest: None

[Objectives and Methods] We investigated the clinical features and treatment results in 36 Japanese patients with SAPHO syndrome (M/F: 10/26) diagnosed and treated between 2003-2013. [Results] The avg. age at diagnosis was 53 y.o (16-74). The avg. FU period was 48 mo. Sternocostoclavicular hyperostosis was recognized in 32 cases (89%), spondylitis in 17 (47%). PPP and/or acne were seen in 31 cases (86%), Oral ulcer in 6 (17%). Most patients had intermittent attacks of pain and NSAIDs were needed in all cases. Oral PSL was used in 14 cases (39%). NSAIDs and/or PSL were effective for temporary pain-relief. SSZ was used in 16 cases and the pain-relief >50% was seen in 4 cases (25%). MTX was scarcely effective for pain-relief. In 2 refractory cases with severe spondylitis, adalimumab (ADA) was tried. Both cases showed immediate pain-relief and ADA was effective during at least 1 year. HLA typing in 30 cases showed the allele frequency of HLA-B27 was 0%. But the frequency of HLA-B61 was 27%, significantly higher than in healthy controls. [Conclusion] Mucosal lesions seem to be a rather frequent complication of SAPHO. The efficacy of DMARDs was limited. ADA was effective in refractory spondylitis. This study revealed HLA-B61 was significantly increased in Japanese patients with SAPHO.

ICW1-15

Risk factors influenced for post-operative infection in RA patients

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Conflict of interest: None

[Objectives] It was controversial that biologics agent increase the risk of post-operative infection. To reveal this matter, we investigated the operations for RA patients, retrospectively. [Methods] We researched the operations for RA patients followed over one year from 2006 to 2012. We analyzed the risk factors influenced for acute surgical site infection (SSI) of superficial and deep, delayed wound healing and chronic infection by multivariate logistic regression analysis. [Results] Total 408 operations for 227 patients (female 204, male 23) were performed. Average age was 64.9 years and disease duration was 16.8 years. The usage rate of biologics agent was 31.6% and that of DMARDs was 92.2%. The risk factors for superficial SSI were age and operation time (odds ratio (OR); 1.15, 1.01). These for deep SSI were operation time and disease activity OR; 1.05, 7.26). These for delayed wound healing were age, operation time and foot operation (OR; 1.15, 1.01 and 2.88). Biologics agents were not the risk factors for all parameters. [Conclusion] It was revealed that biologics agents were not the risk factors for postoperative infection in RA patients. Foot operation was the risk factor for delayed wound healing and it is necessary to be careful for the management.

ICW2-1

Targeted exon sequencing in rheumatoid arthritis

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Objectives. Although there have been many efforts to identify genetic causes of rheumatoid arthritis (RA) by common variants, most of around 60 loci identified have modest effect sizes. In order to identify rare to low frequency novel functional variants in RA, we performed targeted exon sequencing of 666 genes selected using a multifaceted approach. ***Methods.*** We performed targeted exon resequencing for candidate genes for

1,997 Korean RA cases-controls. Single-marker associations were calculated using PLINK. In a gene-based analysis of rare coding variants, we performed both non-burden testing [SKAT-O] and burden testing [SCORE-seq]. ***Results.*** In a meta-analysis (4,262 cases-7,910 controls) using the Korean RA GWAS and immunochip data in addition to our sequencing data, we did not find any novel variant with genome-wide significance in single-variant association test. Using a gene-based approach for rare nonsynonymous variants, we identified 17 genes with nominal signals. ***Conclusions.*** We were unable to identify rare coding variants with large enough effects to explain the missing heritability for RA. This study suggests that a large number of common and rare variants with small-effect may contribute to RA in combination rather than as large-effect rare variants.

ICW2-2

Changes in levels of circulating microRNAs as potential predictors of treatment response in early rheumatoid arthritis

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Objectives An early therapeutic intervention in rheumatoid arthritis (RA) can prevent joint destruction and influence long term clinical outcome. However, predictors of treatment response in early RA (ERA) are not established yet. Circulating miRNAs are considered potential diagnostic/prognostic biomarkers. We aimed to perform a comprehensive analysis of circulating miRNA in ERA. **Methods** Sera were obtained from treatment naïve ERA patients and after 3 and 12 months of therapy with DMARDs and corticosteroids. Total RNA was isolated and equal amounts of RNA were pooled from 5 patients. RNA was reverse transcribed and preamplified. TaqMan Low Density Array cards were used to measure the expression of miRNAs. **Results** Of the 377 miRNAs measured, 60 miRNAs were at least two fold up- or down-regulated. The expression of miR-16 was upregulated only after 3 months but not after 12 months of treatment. We detected a decrease in the levels of miR-223 and miR-155 after 12 months. **Conclusion** Here we show changes in the expression of 377 miRNAs in ERA patients after DMARD therapy. These changes can serve as a basis for the future identification of markers that predict treatment response in ERA. This work was supported by IMI BTCure, IAR, EU-TEAM, EU-Osteoimmune, IGA NT 14498, MHCR project no. 023728.

ICW2-3

The limited effects of smoking and shared epitope on the production of ACPA and RF in a Japanese adult population: The Nagahama Study

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Conflict of interest: None

[Objectives] To evaluate positivity of anti-citrullinated peptide antibody (ACPA) and rheumatoid factor (RF) in a general Japanese population and to detect correlates including genetic components for these autoantibody positivity. [Methods] ACPA and RF were quantified in 9,804 volunteers aged from 30 to 75. Logistic regression analyses were performed to evaluate the effects of candidates of correlates on the autoantibody positivity. Genome-wide association (GWA) study for the autoantibody positivity was performed using 394,239 SNPs for 3,170 subjects among the participants. HLA-DRB1 alleles were imputed based on the GWA data. [Results] 1.7% and 6.4% of subjects were positive for ACPA and RF, respectively, and the two showed a significant correlation ($p=2.0x10^{-23}$). Old age was associated with positivity of ACPA ($p=0.00062$). Sex, smoking, shared epitope (SE), and other candidates of correlates did not have significant effects on the positivity of ACPA or RF. Interaction between SE and smoking for the autoantibody positivity was not apparent. [Conclusion] ACPA and RF were suggested to share mechanisms even in healthy populations. Old age was associated with increasing ACPA positivity. Positivity of ACPA and RF was not associated with SE and smoking, either alone or in combination.

ICW2-4

Genetic architecture of Rheumatoid Arthritis Contribute to Novel Biological Insights and Drug Discovery

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Conflict of interest: None

[Objectives] We demonstrate a strategy to integrate genetic risk variants of rheumatoid arthritis (RA) with diverse genomic and biological datasets to provide insight into drug discovery. **[Methods]** We performed a trans-ethnic genome-wide association study in >100,000 subjects. We integrated RA risk loci with: functional annotation of SNPs; cell-specific eQTL analysis; pleiotropy analysis; Mendelian disease or cancer genes; epigenetic histone peaks and pathways. We evaluated connections of RA risk genes to target genes for approved RA drugs. **[Results]** We discovered 42 novel RA risk loci, bringing the total to 101 ($P < 5x10^{-8}$). These loci revealed: ethnically shared genetic architecture; many risk alleles altering gene expression; two-thirds of loci had pleiotropy on other human complex traits; overlap with genes of human primary immunodeficiency and hematological cancer somatic mutations; specific cell types (T_{reg} cells) and novel molecular pathways that contribute to RA pathogenesis. RA risk genes were significantly enriched in overlap with target genes of approved RA therapies, suggesting that overlapped drugs approved for other indications may be repurposed for RA. **[Conclusion]** Our study provides empirical evidence that the genetics of RA can contribute to drug discovery.

ICW2-5

Comprehensive Immunoclinical Analysis of Rheumatoid Arthritis

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Conflict of interest: None

[Objectives] Immunological overview of rheumatoid arthritis (RA) and its relation to clinical heterogeneity have not yet been answered. Therefore, we performed a comprehensive analysis of clinical information, immune cells classification, and HLA-DRB1 genotyping. [Methods] Fifty RA patients and twenty-five healthy volunteers were included. We performed FACS subset classification and HLA-DR quantitation of CD4+ T cells, B cells, NK cells, Monocytes, and dendritic cells. We also

analyzed clinical information and shared epitope (SE) positivity based on HLA-DRB1 genotyping. [Results] Positive correlations were observed between DAS28 and CD45RA-CXCR5-CCR6-CXCR3- cells ratio, RF and CD27high CD38high plasmablast ratio, and plasmablast and CD45RA-CXCR5+CCR6+CXCR3- (Tfh-Th17) cells ratios. New-onset untreated RA (NORA) patients showed increased plasmablast and Tfh-Th17 cells ratios. HLA-DRB1 expression on CD4+ T cells and NK cells was also increased in NORA patients. SE positive patients showed increased HLA-DR expression on B cells and monocytes. [Conclusion] These results suggest an association of CD45RA-CXCR5-CCR6-CXCR3- cells with disease activity, an association of plasmablast and Tfh-Th17 cells with autoantibody production, and reversible immunological changes in NORA.

ICW2-6

Monocarboxylate transporter (MCT)-4, associated with the decrease of synovial fluid pH, is a novel therapeutic target of rheumatoid arthritis

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Conflict of interest: None

[Objectives] Although it is well known that synovial fluid pH is decreased in rheumatoid arthritis (RA) patients, the mechanisms remain unclear. Here we investigate the correlation between synovial fluid pH and the disease activity of RA. We reveal the mechanisms regulating synovial fluid pH. [Methods] We measured the values of pH and the concentration of lactate in synovial fluid of RA patients. Next, we investigated the expression of monocarboxylate transporter (MCT)-4 in RA synovial fibroblasts (RASFs) obtained from the inflamed joints using quantitative RT-PCR and Western Blotting. Finally, we examined whether the proliferation of RASFs was inhibited by knockdown of MCT4 using small interfering RNA (siRNA). [Results] Synovial fluid pH correlated negatively with the disease activity score (DAS)-28 using CRP in RA patients, accompanied by increased level of lactate. The levels of MCT4 mRNA and protein were increased in RASFs. Knockdown of MCT4 induced apoptosis of RASFs and inhibited their proliferation. [Conclusion] Synovial fluid pH of RA patients correlated negatively with DAS28-CRP due to increased expression of MCT4 in RASFs. Silencing of MCT4 inhibit RASF proliferation, indicating that MCT4 could be a novel therapeutic target of RA.

ICW2-7

The Scaffold Protein p62 Regulates Caspase-3 Dependent and -Independent Cell Death and Autophagy in Rheumatoid Arthritis Synovial Fibroblasts

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Conflict of interest: None

[Objectives] To investigate the role of sequestosome 1/p62 in the regulation of autophagy and cell death in rheumatoid arthritis synovial fibroblasts (RASF). [Methods] Autophagy was induced by thapsigargin. Autophagy, poly-ubiquitinated proteins and p62 were evaluated by immunoblotting, immunofluorescence and immunohistochemistry. RASF were transfected with siRNA against p62. Cell death was analyzed by flow cytometry and caspase-3 activity. [Results] The expression of p62 was increased in synovial tissues from RA compared to osteoarthritis (OA) patients (p=0.01) and was decreased in RA patients treated with anti-TNFα agents compared to patients treated with non-biologics (p=0.006), tocilizumab (p=0.008) or abatacept (p=0.02). Consistently, p62 was induced in RASF by TNFα. p62 knockdown in RASF promoted TRAIL-induced apoptosis (p=0.02) and the activation of caspase-3. Autophagy induction upon ER stress promoted a caspase-3 independent autophagic cell death, the accumulation of p62-positive poly-ubiquitinated protein aggregates and large vacuole formation in RASF, but not in OASF. [Conclusion] Our data indicate that p62 regulates caspase-3 dependent and -independent cell death and autophagy. We conclude that p62 is regulated by TNFα and plays a protective role against apoptosis in RA.

ICW2-8

RORγt$^+$Foxp3$^+$ CD4 T cells regulates the development of collagen induced arthritis

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Conflict of interest: None

[Objectives] To clarify the effect of RORγt expression on T cells in the development of autoimmune arthritis. [Methods] 1) Incidence and severity of collagen induced arthritis (CIA) were assessed in C57BL/6 (B6) and RORγt transgenic (Tg) mice. 2) Cytokine production from collagen type II (CII) reactive T cells was analyzed by ELISA. 3) Transcription factors and CCR6 expression on CII reactive CD4 T cells was analyzed by FACS. 4) Draining lymph node cells or CD4$^+$ cells isolated from B6 or Tg mice were transferred into immunized B6 mice, and then clinical course of arthritis was assessed. [Results] 1) CIA was significantly suppressed in Tg mice. 2) IL-17 production from CII reactive T cells was significantly increased in Tg mice. 3) Foxp3 expressing CD4 T cells also expressed RORγt, and higher expression of CCR6 was observed in RORγt$^+$Foxp3$^+$ CD4 T cells in Tg mice. 4) Transfer of lymph node cells harvested from Tg mice significantly suppressed CIA in B6 mice, and transfer of CD4$^+$ cells harvested from Tg mice also tended to suppress CIA in B6 mice. [Conclusion] Overexpression of RORγt in T cells suppressed CIA in spite of higher IL-17 production. The results of cell transfer experiments showed the possibility that RORγt$^+$Foxp3$^+$ regulatory T cells might regulate the development of CIA.

ICW2-9

Synovial CXCL13-producing CD4+ T cells under inflammatory environment contribute to the formation of ecotopic follicle in rheumatoid arthritis

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Conflict of interest: Yes

[Objectives] Ectopic lymphoid follicles are frequently formed in synovium of rheumatoid arthritis (RA). Although CD4+ T-cells in RA synovium were reported to produce CXCL13, a chemokine crucial for the formation of germinal center, there relevance to known CD4+ T-cell subsets or proinflammatory cytokines had been largely unknown. [Methods] We analyzed character and function of CXCL13+CD4+ T-cells obtained from RA patients. [Results] Synovial CXCL13+CD4+ T-cells were a population distinct from known CD4+ T-cell subsets such as Th1, Th2, Th17 and Tfh subset, and TNF-α and IL-6 maintained the CXCL13 production. In a transwell chemotaxis assay using supernatant of RA synovial cells, the neutralizing antibodies against CXCL13 blocked the migration of cell expressing CXCR5, which was receptor of CXCL13, to the supernatant. [Conclusion] Because proinflammatory cytokines were strongly involved in the function of synovial CXCL13+CD4+ T-cells, we named this population inflammatory CXCL13-producing helper T

(iTh13) cells. iTh13 cells were induced in the inflammatory condition and thought to recruit lymphocytes to inflamed joint, and to participate in the formation of ectopic lymphoid follicle. Thus, it is suggested that iTh13 plays a key role in pathology of RA and other inflammatory disease.

ICW2-10

TIARP suppresses the migration of neutrophils in arthritis via the reduced CXCL2/CXCR2 expression

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Conflict of interest: None

[Aim] TIARP is dominantly expressed in macrophages (Mφ), neutrophils (Neu) and fibroblast-like synoviocytes (FLS). Recently, we found that TIARP$^{-/-}$ mice develop spontaneous arthritis with increased TNF-induced IL-6 production in Mφ, although the functional role of TIARP in Neu and FLS remains uncertain. The aim of this study is to elucidate the role of TIARP in Neu and FLS with arthritis. [Methods] 1) TIARP expression in FLS after TNFα stimulation were measured. 2) Using WT or TIARP$^{-/-}$ FLS, IL-6, MMP3 and CXCL2 expression were compared. 3) Cell proliferation of FLS by TNFα was analyzed by BrdU incorporation. 4) The chemoatractant activity of TIARP$^{-/-}$ Neu was tested by transwell chemotaxis assays. 5) The expression of CXCR2 on Neu was analyzed. [Results] 1) TIARP expression in FLS was significantly increased by TNFα. 2) TNFα stimulation induced higher expressions of IL-6, CXCL2 and MMP3 in TIARP$^{-/-}$ FLS. 3) TNFα stimulation induced much more cell proliferation in TIARP$^{-/-}$ FLS. 4) The recruitment was enhanced by CXCL2-dependent manner in TIARP$^{-/-}$ Neu. 5) CXCR2 expression was significantly higher in TIARP$^{-/-}$ Neu. [Conclusion] TIARP might down-regulate the production of CXCL2 from FLS and the expression of CXCR2 in Neu, resulting in the protective ability of Neu migration in arthritic joints.

ICW2-11

The synovial proliferative effect of RasGRP4 (Ras guanine nucleotide-releasing protein 4) in fibroblast-like synoviocytes from patients with rheumatoid arthritis

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Conflict of interest: None

[Background] RasGRP4 is a guanine nucleotide exchange factor expressed predominantly in the mast cells, monocytes and neutrophils. RasGRP4-null mice are resistant to serum-transfer model of arthritis. We have reported that fibroblast-like synoviocytes (FLSs) from rheumatoid arthritis (RA) patients express RasGRP4 more abundantly compared with those from osteoarthritis patients. [Objectives] To clarify the role of RasGRP4 in the pathogenesis of RA. [Methods] FLSs were isolated from the synovial tissues of ten RA patients and ten osteoarthritis patients, and the expression of RasGRP4 in FLSs was evaluated by real-time quantitative PCR. The RasGRP4-dependent proliferation potency of FLSs was evaluated by exposing FLSs to a RasGRP4-specific RNAi. Type II collagen-induced arthritis rats were intra-articularly injected with RasGRP4-specific RNAi and the effects were evaluated. [Results] The levels of the RasGRP4 transcript were correlated with the proliferation potency of the FLSs. Proliferation of FLS was abrogated by RasGRP4-specific RNAi. Intra-articular injection of RasGRP4-specific RNAi reduced arthritis in collagen-induced arthritis rats. [Conclusion] RasGRP4 is a possible target for proliferative synovitis.

ICW2-12

Cell cycle regulation therapy combined with cytokine blockade enhances anti-arthritic effects without increase of immune suppression

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Conflict of interest: None

[Objectives] Cytokine blockers to treat rheumatoid arthritis (RA) are to inhibit immune reactions involved in RA. However, they cannot induce complete remission in all patients. We revealed that cell cycle regulation by cyclin-dependent kinase (CDK) inhibitors exerted anti-arthritic effects by inhibiting synovial fibroblast proliferation. A new CDK4/6 inhibitor, palbociclib was reported to be well-tolerated and effective in clinical trials for breast cancer. We aim to reveal if palbociclib shows anti-arthritic effects and synergizes with cytokine blockers in preclinical studies. [Methods] Collagen (CII)-induced arthritis (CIA) of mice was treated with palbociclib, etanercept or anti-IL-6 receptor antibody alone, or with combinations of palbociclib and cytokine blockers. Clinical and radiographic scores, serum anti-CII antibodies and proliferative responses of lymph node cells to CII were quantified. [Results] Palbociclib and the cytokine blockers were effective in treating CIA. Furthermore, combinations of both enhanced the anti-arthritic effects, but did not affect the anti-CII antibody levels or T cell proliferative responses to CII. [Conclusion] A new CDK4/6 inhibitor exerted anti-arthritic effects and synergized with cytokine blockers without enhancing immune suppression.

ICW2-13

Evaluation of intracellular biomarkers of NKT cells in rheumatoid arthritis

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Conflict of interest: None

Objectives Natural killer T (NKT) cells in rheumatoid arthritis (RA) are under researched. Expression of cytolytic granules, cytokines and CXCL-8 in NKT cells were studied in RA patients. **Method** Disease severity of 40 patients was monitored using DAS28 index. Apoptosis were investigated in PBMCs by TUNEL assay. Perforin, granzyme A/B, IFN-γ, IL-4 and CXCL-8 were measured in NKT cells using flow cytometry. Results were analyzed by Mann-Whitney U test. **Results** Mean DAS28 were 5.45±1.06. Apoptosis were four times and were positively correlated with DAS28. NKT cells were significantly lowered in patients (0.44±0.18%) than control (0.83±0.29%). Perforin, granzyme A, IFN-γ and CXCL-8 expressing NKT cells were significantly enhanced in patients. Granzyme B^{+} NKT cells (70.8±6.48%) remained comparable in patients and controls (73.0±6.71%) and were not correlated with DAS28. However, IL-4^{+}NKT cells were remarkably low in patients and negatively correlated with DAS28. **Conclusions** Reduced NKT cells suggested the protective role of NKT cells. Correlation of intracellular biomarkers with DAS28 deciphers their involvement in the prognostic course of RA. Elevated apoptosis could be attributed to the elevated perforin/granzyme. A newer scoring system may be developed using these biomarkers

ICW2-14

Tofacitinib facilitates expansion of myeloid-derived suppressor cells and ameliorates arthritis in SKG mice

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Conflict of interest: None

[Objectives] Myeloid-derived suppressor cells (MDSCs) are a heterogenous population of cells that have an ability to suppress T cell responses. The aim of this study was to evaluate the effects of tofacitinib on MDSCs in a mouse model of rheumatoid arthritis. [Methods] Arthritis was induced in SKG mice by zymosan A injection. For adoptive transfer experiments, isolated MDSCs from the bone marrow (BM) of arthritic SKG mice were administered to arthritic mice. Tofacitinib was administered subcutaneously via osmotic pump. For a depletion assay, anti-Gr1 mAb was injected to mice treated with tofacitinib. BM cells were incubated in GM-CSF, with or without tofacitinib and the percentage of MDSCs was evaluated. [Results] Total and polymorphonuclear (PMN) MDSCs in spleen were significantly increased in mice. Adoptive transfer of MDSCs reduced arthritis compared to control. Significantly higher number of total and PMN MDSCs in BM was observed in tofacitinib-treated group. Furthermore, administration of anti-Gr1 mAb exacerbated the arthritis of tofacitinib-treated mice. Tofacitinib facilitated the differentiation of MDSCs and inhibited the differentiation of DCs *in vitro*. [Conclusion] Tofacitinib facilitates expansion of MDSCs both *in vivo* and *in vitro*, and ameliorates arthritis in SKG mice.

ICW2-15

Tofacitinib reduces IL-17, IFN-g production from CD4+T cells and improves disease activity

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Conflict of interest: None

Background: Tofacitinib suppress JAK, although its precise mechanism of action in patients are unknown. Method: CD4+Tcells were collected from 32 patients participating the clinical trial in our institute and stimulated with anti-CD3 and CD28 antibody. IFN-g/IL-17 production, clinical efficacy and modified total Sharp score (mTSS) were evaluated at baseline, year-1 and year-2. Results: Background; 53.9 years, disease duration 80.5 months, concomitant MTX 71.3 %, concomitant GC 25.0 %, SDAI 37.9, HAQ 1.4, mTSS 64.6, ΔTSS 15.7, CRP 2.3, ESR 51.0, RF 184.3, MMP-3 293.0. SDAI, HAQ, ΔTSS, CRP, ESR, RF and MMP-3 improved with significant difference from baseline at year-1 and was sustained to year-2. IFN-g production did not change from baseline at year-1 and -2 (1641.3 pg/ml, 1089.3 pg/ml, 1659.9 pg/ml) whereas IL-17 significantly decreased from 1760.5 pg/ml to 989.0pg/ml at year-1 and 748.2pg/ml at year-2. Univariate analysis revealed that IFN-g production at year-1 correlated with inflammation and IL-17 production at year-1 correlated with radiographic progression and MMP-3. Conclusion: IL-17 production was reduced from CD4+ T cells collected from patients treated with tofacitinib at year-1 and year-2 and contributed to suppression of MMP-3 and radiographic progression.

ICW3-1

Risk of Malignancy in Clinically Amyopathic Dermatomyositis and Anti-MDA5 Antibody

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Objective: To determine the association of cancer-associated myositis (CAM) with clinically amyopathic dermatomyositis (CADM) and anti-MDA5 antibody (Ab) in North America. **Method:** We analyzed data on CADM and 1:1 matched (gender and age ±10 yrs) classic DM controls. CAM was defined as a non-skin cancer within 5 yrs of myositis diagnosis. Anti-TIF1-γ and MDA5 Ab were measured by ELISA. Chi-square was used. **Results:** There were 61% females and 87% Caucasians with a mean age of 46.5 (17.8) in 59 CADM and 59 DM. CAM was seen in 8.5% (5/59) of CADM as compared to 16.9% (10/59) of the classic DM (p=0.15). Cancers in CADM included breast, brain, lymphoma, prostate and unknown while DM included 2 prostate and 1 each of breast, uterus, lymphoma, melanoma, renal, colon, thyroid and gastric. The frequency of MDA5 Ab was similar in CADM (13.5%, 8/59) and classic DM (13.5%, 8/59). Only 2 CAM were detected in MDA5 Ab+ (12.5%, 2/16) with similar frequency in MDA5 Ab^+ patients (12.7%, 13/102). TIF1-γ Ab was seen in 13.5% (8/59) CADM vs. 23.8% (14/59) classic DM (p=0.15) and was associated with CAM (27% in Ab+ vs. 9% in Ab^+, p=0.02). **Conclusion:** CADM and MDA5 Ab+ patients have a similar risk of malignancy as classic DM and Ab^+ patients, but TIF1-γ Ab is associated with cancer in CADM and classic DM.

ICW3-2

Fragment of type III collagen degradation may be a novel serological marker for interstitial lung disease in dermatomyositis and polymyositis

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Conflict of interest: None

Objectives To investigate whether matrix metalloproteinases-9-cleaved fragment of type III collagen (C3M) and the amino-terminal propeptide of procollagen type III (PIIINP) may be used as novel markers for ILD in polymyositis (PM) and dermatomyositis (DM). **Methods** Serum concentrations of C3M and PIIINP were determined by enzyme-1inked immunosorbent assay in 46 adult PM/DM patients (31 with ILD, 15 without ILD) and 19 healthy controls. **Results** The serum levels of C3M were 7.16±3.77ng/ml in PM/DM with ILD group, 4.56±0.84ng/ml in PM/DM without ILD group, and 4.63±0.85ng/ml, in healthy controls, respectively. Serum C3M level in ILD group was significantly higher than without ILD group and healthy controls (both $P < 0.01$). The sensitivity and specificity of positive C3M for ILD in PM/DM were 71.0% and 82.4%, respectively. The serum levels of PIIINP were 12.39±12.17 ng/ml in PM/DM with ILD group, 9.57±5.67ng/ml in PM/DM without ILD group, and 8.28±4.95ng/ml, in healthy controls, respectively. Serum PIIINP level in ILD group was higher than in without ILD group and healthy controls but with no statistical significance (both $P >0.05$). **Conclusions** C3M may be potential and useful serum marker for the diagnosis of ILD in PM/DM patients.

ICW3-3

IL-6, IL-8 and IL-10 are Associated with Pathophysiology of Hyperferritinemia in Interstitial Lung Disease with Polymyositis/Dermatomyositis

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Conflict of interest: None

Objectives: We previously reported that hyperferritinemia are associated with the prognosis of interstitial lung disease (ILD) in polymyositis (PM) /dermatomyositis (DM). Hyperferritinemia could be associated with a cytokine storm in rapidly progressive ILD (RP-ILD). We investigated the associations between the serum ferritin levels and various cytokines in PM/DM. ***Methods:*** This study included 38 patients (21 patients had ILD) with PM/DM. The disease activity of ILD was evaluated by the visual analogue scale (VAS) which the IMACS proposed. We measured serum cytokines (IL-1β, IL-2, IL-4, IL-6, IL-8, IL-10, IL-12, IL-13, IL-17, IL-18, TNF-α, INF-α, INF-γ and IP-10), and analyzed the associations between ILD activity, ferritin and cytokines. ***Results:*** The VAS of ILD was significantly correlated with serum ferritin, IL-8, IL-10, IL-18, TNF-α and IP-10. In a multiple linear regression analysis, IL-6 ($t=2.9$, $p<0.05$), IL-8 ($t=3.6$, $p<0.01$) and IL-10 ($t=4.0$, $p<0.001$) were significantly correlated with the ferritin levels. Serum levels of ferritin, IL-6, IL-8 and IL-10 were higher in the RP-ILD subset than other subsets. ***Conclusion:*** Serum ferritin was correlated with the disease activity of

ILD in PM/DM. IL-6, IL-8 and IL-10 were significant factors contributed to the serum ferritin levels.

ICW3-4

Identification of autoantibodies to tyrosyl-transfer RNA synthetase associated with anti-synthetase syndrome

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Conflict of interest: None

[Objectives] A preliminary report has described the detection of an autoantibody to tyrosyl–tRNA synthetase (TyrRS) in only one patient. We aimed to identify further patients with anti–TyrRS autoantibodies using other assays than previously reported methods and elucidate their clinical significance. **[Methods]** Multiple assays were performed to detect anti–TyrRS antibodies in the sera of patients with active polymyositis/dermatomyositis (PM/DM) patients: enzyme–linked immunosorbent assay (ELISA), Western blot, and immunoprecipitation using TyrRS–transfected HeLaS3 cells. **[Results]** Among 141 samples from patients with PM/DM, sera from three patients with PM/DM showed significantly high O.D. values in ELISA, significant bands of 59 kDa protein of TyrRS at the same place as anti–His tag antibody in Western blot, and significant bands at the same place as the recombinant human TyrRS in immunoprecipitation assay. These data strongly suggest that these sera had autoantibodies to TyrRS. These patients had some features of myositis, interstitial lung disease, arthritis, Raynaud's phenomenon, and fever. **[Conclusion]** This study reconfirmed the presence of anti–TyrRS antibody in the setting of the anti–synthetase syndrome and strengthens the association of anti–synthetases with these conditions.

ICW3-5

The analysis of prognostic factors in patients with inflammatory myopathies complicated with interstitial lung disease

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Conflict of interest: None

[Objectives] Because interstitial lung disease (ILD) is one of the most lethal causes in inflammatory myopathies (IM), especially amyopathic dermatomiositis (ADM), it is important to determine prognostic factors for survival. We investigated clinical features with fatal events in IM patients having ILD. [Methods] We retrospectively analyzed clinical features, laboratory and HRCT findings, and therapeutic regimens with clinical outcomes in 144 patients diagnosed with IM at 2 Yokohama City University hospitals from 1993 to 2012. The distribution and extent of ILD lesions were evaluated in each divided four zone (A to D) of HRCT. [Results] Among 83 of 144 IM patients with ILD, 12 patients (myopathic DM 8, ADM 4) died within 7 months after the diagnosis due to respiratory failure and infections. The early lethal events were associated with male, administration with tacrolimus, combined immunosuppressive therapies, low PCO2, low P/F ratio, and extended ILD in the upper lung fields. PCO2 and lesions in zone B were independent prognostic factors analyzed by Cox proportional hazard model. [Conclusion] Rapid and intensive therapies including prophylactic procedures against infections are necessary to manage IM patients with hypocapnia and ILD expanding to upper lung field.

ICW3-6

Association between physical dysfunction and disease activity in daily clinical practice for outpatients with polymyositis/dermatomyositis

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Conflict of interest: None

[Objectives] The aim of this study is to clarify the present state of physical function and the association between physical function and disease activity in outpatients with polymyositis (PM)/ dermatomyositis (DM). [Methods] A total of 72 outpatients with PM/DM were enrolled in this study. We evaluated physical function and disease activity using the myositis disease activity core set as proposed by the IMACS. [Results] The J-HAQ found physical dysfunction in 39 of the patients evaluated (54%). The age at disease onset was higher in patients with physical dysfunction than those without physical dysfunction, although there was no difference in disease duration between the two subsets. The patient global assessment was higher and the manual muscle testing score was lower in patients with physical dysfunction than in those without physical dysfunction, although no significant differences were found in the physician global assessment between the two subsets. Many of the patients demonstrated difficulty with "Reach," "Grip" and "Activities" in the J-HAQ. [Conclusion] One half of the outpatients were found to have some difficulties completing daily activities. This finding may result from irreversible cumulative damage rather than from reversible disease activity.

ICW3-7

Genome-wide DNA methylation patterns in naïve CD4+ T cells from patients with primary Sjögren's syndrome

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Conflict of interest: None

Objective: Primary Sjögren's syndrome (pSS) is an autoimmune disease with incompletely understood etiology. Very little is known about the role of epigenetic dysregulation in the pathogenesis of pSS. **Methods:** We performed a genome-wide DNA methylation study in naïve CD4+ T cells in eleven pSS patients compared to age, sex, and ethnicity-matched healthy controls. Cytosine methylation was quantified using the Illumina Infinium HumanMethylation450 BeadChip array and validated using bisulfite sequencing. **Results:** We identified 553 hypomethylated and 200 hypermethylated CpG sites in naïve CD4+ T cells from pSS patients compared to healthy matched controls, representing 311 hypomethylated and 115 hypermethylated gene regions. Hypomethylated genes in pSS include LTA, coding for Lymphotoxin α. Other relevant genes such as CD247, TNFRSF25, PTPRC, GSTM1 and PDCD1 were also hypomethylated. The interferon pathway was represented by hypomethylation of STAT1, IFI44L, USP18 and IFITM1. A group of genes encoding for members of the solute carrier proteins were differentially methylated. **Conclusion:** This is the first epigenome-wide DNA methylation study in pSS. Our data highlight a role for DNA methylation in pSS and identify disease-associated DNA methylation changes in several genes and pathways.

ICW3-8

The suppressive ability of altered peptide ligands to M3R induced autoimmune sialadenitis

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Conflict of interest: None

[Objectives] To evaluate the suppressive ability of altered peptide ligands (APLs), the peptides with substitutions in amino acid residues at TCR contact sites, in M3 muscarinic acetylcoline receptor (M3R) induced sialadenitis (MIS). [Methods] 1) Splenocytes of $M3R^{-/-}$ mice immunized with M3R peptides mixture were cultured with each peptide. The cytokines production was measured. 2) APLs of each N1 and 1st peptide were designed. Each APL was loaded to CD11c+ cells, isolated from

M3R$^{-/-}$ mice immunized with each N1 and 1st peptide, pre-cultured with suboptimal concentration of each peptide. CD4+ T cells were added and cytokines production was measured. 3) Antagonistic APLs were administered on day 7 and 10 after the cell transfer. [Results] 1) M3R reactive T cells produced IL-17 and IFN-g against N1 and 1st loop more highly than controls and other extracellular domains of M3R. 2) Seven APLs of N1 peptide (N1-APL 1-7) and eight APLs of 1st peptide (1st-APL 1-8) were designed. N1-APL5 (AA15 N→T), N1-APL6 (AA15 N→C) and N1-APL7 (AA15 N→S) significantly suppressed IFN-g. 1st-APL8 (AA140 A→M) significantly suppressed IL-17. 3) All the antagonistic APLs in vitro suppressed MIS in vivo, especially N1-APL7. [Conclusion] Antagonistic APLs *in vitro* suppressed the induction of MIS *in vivo*.

ICW3-9

RORγt inhibit the expression of Foxp3 in CD4$^+$CD25$^+$ T cells in spontaneous development Sjögren's syndrome like sialadenitisRORgt inhibit the expression of Foxp3 in CD4$^+$CD25$^+$ T cells in spontaneous development Sjögren's syndrome like sialadenitis

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Conflict of interest: None

[Objectives] The aim of this study was to clarify the pathological role of RORγt in sialadenitis using RORγt transgenic (Tg) mice spontaneously developing Sjögren's syndrome like sialadenitis. [Methods] 1) Splenic CD4$^+$ cells from Tg mice were transferred into Rag2$^{-/-}$ (CD4$^+$→Rag2$^{-/-}$) mice and histological analysis was examined. 2) Compartment of Treg cells was investigated. 3) CD4$^+$CD25$^+$ (Treg cells) and CD4$^+$25$^-$ (Teff cells) from Tg or C57BL/6 (WT) mice were co-transferred into Rag2$^{-/-}$ mice in criss-cross manner, and histological analysis was examined. 4) IL-2 stimulated STAT5 phosphorylation in Treg cells was analyzed. [Results] 1) In CD4$^+$→Rag2$^{-/-}$ mice, sialadenitis was observed. 2) Foxp3 expression in CD4$^+$CD25$^+$ T cells was significantly decreased in Tg mice. 3) Co-transfer of Teff cells from Tg mice and Treg cells from WT mice could not develop any sialadenitis in Rag2$^{-/-}$ mice, whereas co-transfer of Teff cells from WT mice and Treg cells from Tg mice developed sialadenitis. 4) STAT5 phosphorylation was inhibited in IL-2 stimulated Treg cells of Tg mice. [Conclusion] These results suggested that the overexpression of RORgt in Treg cells induced downregulation of Foxp3 expression via repress IL-2 induced STAT5 phosphorylation, resulting in the spontaneous sialadenitis like SS.

ICW3-10

BAFF activates monocytes to produce IL-6 though BAFF receptor (BR3) for IgG production from peripheral B cells in patients with primary Sjögren's syndrome

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Conflict of interest: None

[Objectives] We have found that BAFF robustly increased IL-6 production by monocytes in patients with primary Sjögren's syndrome (pSS), and the expression level of a BAFF receptor (BR3) was significantly elevated in pSS monocytes compared to the controls. Since IL-6 promotes the differentiation of B cells, we investigated the possible involvement of monocytes producing IL-6 in the IgG production by B cells. [Methods] Peripheral monocytes were cultured with or without peripheral B cells and stimulated with soluble BAFF (sBAFF) in vitro. The production of IL-6 and IgG by the cells were measured by ELISA. FACS analysis of whole blood samples was employed to analyze the expression of BR3. [Results] The serum level of IgG and the proportion of BR3 positive monocytes (BR3$^+$/CD14$^+$) were elevated in pSS patients as compared to those in controls. Remarkably, the BR3$^+$/CD14$^+$ ratio was positively and significantly correlated with the serum IgG level and IL-6 production by pSS monocytes stimulated with sBAFF. Stimulation of co-culture of B cells and monocytes in pSS patients with sBAFF drastically enhanced IgG production by B cells. [Conclusion] Our data indicate that the abnormal expression of BR3 on monocytes is responsible for the overproduction of IgG by B cells in pSS patients.

ICW3-11

Musculoskeletal ultrasound and Magnetic resonance imaging of the wrists and finger joints in Sjögren's syndrome (SS) with articular manifestations

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Conflict of interest: None

【Objectives】Patients with sjögren's syndrome (SS) often complain polyarthralgia and prevalence of IgM-RF was high in SS. Therefore it is sometimes difficult for the clinician to differentiate cases of early-stage rheumatoid arthritis (RA) from SS. Musculoskeletal ultrasound (US) and MRI of the wrists and finger joints has been increasingly recognized as a useful method for diagnosis of RA. In contrast, there are not many studies evaluating the arthralgia in SS through US and MRI.【Methods】We retrospectively reviewed medical records of 63 SS patients with articular manifestiation.【Result】Among 63 patients, 35 were classified as primary SS or secondary SS complicated without RA. 12 of them underwent US and 30 of them underwent MRI. 7 (58%) showed synovitis on US, but their synovitis were detected no power doppler (PD) signals. As same as US findings, 20 (67%) showed synovitis on MRI. However MRI-proven bone changes (osteitis or bone erosion) were recognized in only 2 patients. On the other hand, there were high prevalence of PD positive synovitis on US and bone changes on MRI in the patients with secondary SS complicated with RA.【Disccusion】Our data suggests that MRI of the wrists and finger joints and musculoskeletal US are very useful for discrimination of SS and RA.

ICW3-12

Clinicopathological characteristics of anti-centromere antibody- and/or anti-SSA antibody-positive Sjögren's syndrome

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Conflict of interest: None

Objectives: We aimed to examine the clinicopathological characteristics of anti-centromere antibody (ACA)-positive Sjögren's syndrome (SS). Methods: We evaluated 13 patients with ACA-positive and SSA-positive SS (ACA+SSA+ group), 67 patients with ACA-negative and SSA-positive SS (ACA−SSA+ group), and 24 patients with ACA-positive and SSA-negative SS (ACA+SSA− group). We performed minor labial salivary gland biopsy, evaluated focus scores, and compared clinicopathological data of these 3 groups. Serum levels of many cytokines were also estimated using multiplex assays. Results: The 2 ACA-positive groups had a higher positive rate for Raynaud's phenomenon. No patient developed new skin sclerosis during the follow-up. Saxon's test results in the ACA+SSA+ group was lower than that in the ACA−SSA+ group. The 2 SSA-positive groups had lymphocytopenia and high serum IgG levels. The focus scores and fibrosis of the biopsy specimens did not differ significantly. Two ACA+SSA+ patients had pulmonary hypertension. Serum IL-12 was high in the ACA+SSA+ group; IFN-γ was high in the 2 SSA-positive groups. Conclusions: Clinicopathological data and serum cyto-

kine profile in the 3 groups differed. Thus, measuring ACA is an important component in the management of SS.

ICW3-13

Intestinal microbiota plays a critical role in the production of antinuclear antibodies in lymphopenia-induced autoimmunity

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Conflict of interest: None

[Objectives] Antinuclear autoantibodies (ANA) were observed in systemic autoimmune diseases but the mechanism of their production is unclear. Past studies showed lymphopenic transfer model mice, in which $CD4^+CD25^-$cells were transferred into athymic nude BALB/c mice, produced ANA and various organ-specific autoimmune diseases. We evaluate the production of autoantibodies in this model, in terms of lymphopenia-induced homeostatic proliferation (LIP), follicular helper T (T_{FH}) cells and the role of gut microbiota. [Methods] $CD4^+$T cells from wild-type BALB/c mice were adoptively transferred into BALB/c nude mice. Gut microbiota were depleted by orally administering broad-spectrum *antibiotics*. [Result] Transfer of $CD4^+CD25^-$cells resulted in the production of various patterns of ANA and organ-specific antibodies. Germinal center formation and IL-21-producing PD-1^+T_{FH} cells generated via LIP of transferred $CD4^+CD25^-$cells were observed. Depletion of gut microbiota resulted in the inhibition of LIP and LIP-induced T_{FH} differentiation, and the significant reduction of systemic and organ-specific antibodies. [Conclusion] The novel insight that intestinal microbiota plays a critical role in ANA production, would help to understand the immunopathogenesis of systemic autoimmune diseases.

ICW3-14

Clinical analysis of patients with IgG4-related disease complicated with perivascular lesions

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Conflict of interest: None

[Objective] To clarify the clinical features of IgG4-related disease (IgG4-RD) complicated with perivascular lesions (PLs). **[Methods]** We examined the clinical features such as 1) clinical background, 2) serum examinations, 3) location of PLs, 4) other organ involvements, 5) response to treatment in 7 patients with IgG4-RD who had PLs followed up at the University of Tsukuba Hospital from April 2010 to October 2013, retrospectively. **[Results]** 1) Six males and one female, and mean age was 64.8±6.8 yrs. 2) The serum IgG4 levels were higher than 135 mg/dl in all 7 patients (mean was 933±527 mg/dl). CRP levels were elevated in only 2 out of 7 patients (mean was 1.41±3.56 mg/dl). 3) PLs were located in thoracic aorta (n=2), pulmonary artery (n=1), coronary artery (n=1), abdominal aorta (n=6), celiac artery (n=1), SMA (n=1), renal artery (n=2), IMA (n=4) and iliac artery (n=3). 4) Other organ involvements were identified in 6 of 7 patients. 5) All 7 patients were treated with prednisolone (0.6 mg/kg/d), and PLs rapidly improved in all 7 patients as well as other organ involvements. **[Conclusion]** This study revealed that PLs in IgG4-RD had wide variety of distributions and elevation of CRP was mild or not detected. Corticosteroid was effective for PLs in IgG4-RD as well as other involvements.

ICW3-15

The effect of tocilizumab on preventing relapses of adult-onset Still's disease; a retrospective, single center study

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Conflict of interest: None

[Objectives] To investigate the effectiveness of tocilizumab (TCZ), an anti-interleukin-6 receptor monoclonal antibody, on preventing relapses of adult-onset Still's disease (AOSD). [Methods] Clinical data of 40 patients under regular follow up at our institute in June 2013, including 10 patients who used TCZ, were analyzed retrospectively. Relapse free rate was analyzed by Kaplan-Meier method. [Results] Median (interquartile range, IQR) age of disease onset was 39 (29-52) years old. Median (IQR) duration of disease in June 2013 was 86 (41-193) month. A total of 87 relapses were documented. Thirteen patients had not experienced any relapse. Ten patients with refractory or relapsing disease received 8 mg/kg TCZ every 2 to 4 week. After 6 months of TCZ treatment, median levels of C-reactive protein and ferritin were significantly decreased from 6.3 to 0.01 mg/dl and from 938 to 53 ng/ml, respectively. Eleven relapses were observed before using TCZ, and no relapse was observed after TCZ. Relapse free rate of the 10 patients after using TCZ was significantly better in the comparison with all the 40 patients at baseline (100% and 79% at 6 month, p=0.02). [Conclusion] TCZ might be effective not only on improving activity of AOSD but also on preventing relapses.

ICW4-1

MicroRNA-30a promotes B cell hyperactivity in patient with SLE by direct interaction with LYN

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Objectives. To investigate the reason why the level of LYN is significantly decreased in B cell from a majority of patients with systemic lupus erythematosus (SLE) and to determine the role of microRNA-30a (miR-30a) in B cell hyperactivity of patients with SLE. **Methods.** Luciferase reporter gene assays were performed to identify the interaction between miR-30a and three prime untranslated region (3'UTR) of LYN. The level of miR-30a and LYN messenger RNA was tested by real-time qPCR. The protein level of LYN was determined by Western blotting. **Results.** We demonstrated that miR-30a could specifically bind the 3'UTR of LYN. The level of miR-30a was significantly higher in B cell from SLE patients than health donor and negatively associated with the level of LYN. Overexpression of miR-30a could promote the proliferation of B cell lines and the production of IgG antibodies. **Conclusion.** We herein reveal that the elevated miR-30a is responsible for the reduction of LYN in B cell from the patients of SLE and consequently plays an important role in B cell hyperactivity.

ICW4-2

Elevated circulating cell-free DNA is associated with active lupus nephritis and may mainly derive from NETosis in systemic lupus erythematosus

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[Objectives] Abnormal formation and insufficient clearance of neutrophil extracellular traps (NETs) has been involved in lupus nephritis (LN). This study answers whether elevated cfDNA could be attributed to residual NETs and related to LN in SLE. [Methods] Fifty four SLE patients and 43 healthy controls were included in the study. cfDNA concentration was measured with Picogreen Kit, low-density granulocytes (LDGs) percentage was tested by flow cytometer and DNase I activity was measured by radial enzyme-diffusion method. [Results] SLE group exhibited a significantly elevated cfDNA, and among SLE group, LN patients exhibited a significantly higher cfDNA, and among LN patients, patients with active LN exhibited the highest cfDNA. In SLE group, cfDNA positively correlated with quantitative 24-hour urinary protein, LDGs and neutrophils, and reversely correlated with albumin and endogenous creatinine clearance rate. Compared to control group, SLE group exhibit-

ed a significantly increased LDGs and a significantly decreased DNase I activity. [Conclusion] Elevated cfDNA is associated with active LN and may mainly derive from NETosis by neutrophils as well as LDGs in SLE. cfDNA could potentially aid in the prediction of LN risk in SLE patients.

ICW4-3

Immunopathological Roles of the Novel Anti-inflammatory Cytokine Interleukin-35 in Patients with Systemic Lupus Erythematosus

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[Objectives] The project will study the immunomodulatory role of the novel anti-inflammatory cytokine IL-35 in systemic lupus erythematous (SLE). [Methods] Plasma concentrations of IL-35 and soluble gp130 were measured using ELISA. Expression of IL-35 receptor subunits IL-12Rβ2 and gp130 on the $CD4^+$ helper (Th) cells and $CD19^+$ B cells, and the number of $CD4^+CD25^{hi}CD127^-$ Treg cells were quantitated by flow cytometry. The ex vivo effect of IL-35 on the lymphocytes produced cytokines were tested by luminex multiplex assay. [Results] Plasma IL-35 levels were significantly higher in active SLE patients than healthy controls (HC). The %Treg cells in active and inactive SLE patients were both significantly lower than HC (all $p<0.05$). Moreover, the expression of gp130 on Th cells of inactive and active SLE patients was significantly lower than HC. Meanwhile, the %Treg cells were inversely correlated with SLE disease activity index/SLEDAI but positively correlated with the expression of gp130 on Th cells in all of the patients and controls. [Conclusion] The above results may imply the potential immunological roles of IL-35 receptor. Results of this cross-sectional clinical study may also elucidate the crucial immunoregulatory roles of IL-35 in SLE and shed light for the novel therapeutic modality of SLE.

ICW4-4

Phenotype and function of alternatively activated dendritic cells derived from patients with systemic lupus erythematosus

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Conflict of interest: None

[Objectives] We aimed to generate alternatively activated DCs (aaDCs) by treating monocytes from SLE patients with 1,25 dihydroxyvitamin D (3), dexamethasone (Dex) and lipopolysaccharide (LPS) and examined their in vitro immunoregulatory properties. [Methods] Monocyte derived DCs (MDDCs) were derived from SLE patients and normal controls and were treated with VitD3/Dex/LPS and VitD3 and LPS alone as controls. Maturation status, cytokine production of MDDCs and MDDC-T co-culture was performed to examine effectson allogeneic T cells proliferation, differentiation and cytokine production. [Results] Lupus aaDCs had semi-mature phenotype that remained stable despite challenge by CD40L, CpG DNA, inactive and active SLE serum. They exhibited tolerogenic function with suppressed allogeneic T cell activation and proliferation comparable to normal aaDCs and was superior than VitD3 treated MDDCs. They polarised naïve T cells into IL-10 producing T effector cells which can suppress third-party T cells and attenuated production of IFN-γ and IL-17 by memory T cells. They expressed cytokine profile of $IL\text{-}12^{lo}IL\text{-}10^{hi.}$ [Conclusion] VitD3/Dex/LPS represented a superior method in the induction of aaDCs from lupus MDDCs with comparable tolerogenicity to aaDCs derived from healthy subjects.

ICW4-5

Bendamustine increases interleukin-10 secretion from B cells via p38 MAP kinase activation

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Conflict of interest: Yes

[Objectives] To investigate the effects of bendamustine on B cell functions, and to explore a possible clinical application of the drug to autoimmune diseases. [Methods] A human B cell line, Ramos, was cultured with bendamustine for 4 days. The proliferation of the cells was analyzed by XTT assay. The secretions of IgM and interleukin-10 (IL-10) by the cells were measured by ELISA. The cells were collected for FACS analysis and RT-PCR. [Results] The proliferation of Ramos cells was significantly inhibited by 25-100 μM of bendamustine in a dose-dependent manner. Concordantly, IgM secretion from Ramos cells was significantly inhibited at these concentrations by up to 70%. Interestingly, the production and secretion of IL-10 were dramatically increased by 25-100 μM of bendamustine. Moreover, bendamustine enhanced the activation of p38 MAP kinase and inhibition of the kinase led to abrogation of bendamustine-induced IL-10 production. Sp1 was identified as the downstream transcription factor invovlved in the activation of p38 MAP kinase by bendamutine. [Conclusion] P38 MAP kinase-Sp1 pathway plays a crucial role in IL-10 production from B cells by bendamustine. Our study proposes a novel therapeutic option for autoimmune diseases through the upregulation of IL-10.

ICW4-6

Impaired balance of B cell - T cell - dendritic cell axis in the pathogenesis of systemic lupus erythematosus

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Conflict of interest: None

[Objectives] To investigate the interactive activation between B cells and surrounding immunocompetent cells including T cell and dendritic cell (DC) in the pathogenesis of systemic lupus erythematosus (SLE). **[Method]** Circulating B cell, T cell and DC subsets were defined by multicolor flow cytometry in the peripheral blood of 34 SLE patients. **[Results]** The number of effector B cells and plasmablast has increased, whereas IgM memory B cells decreased, in SLE compared to healthy donor (HD). Likewise, the proportion of effector memory T cells and effector T cells increased in SLE. The frequency of myeloid DCs decreased in SLE and that of plasmacytoid DCs was not different with HD. A new population of DCs that express neither CD11c nor CD123 has characteristically detected in SLE. The proportion of IgM memory B cells negatively correlated with the BILAG. The new DCs subset showed positive correlation with both the population of plasmablast and the serum level of IgG and anti-dsDNA antibody. **[Conclusion]** The effector subsets of B and T cells are increased in SLE patients with an active disease. The specific population of DCs which correlates with increased plasmablast and antibody production may contribute the pathogenesis of SLE in cooperation with B cell activation.

ICW4-7

The significance of urinary podocyte number and urinary podocalyxin level in SLE

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Conflict of interest: None

[Objectives] To clarify the significance of urinary podocyte-related biomarkers in SLE. [Methods] Numbers of urine podocytes (U-Pod) were determined by counting podocalyxin (PCX)-positive cells in urine sediments. Urine levels of PCX (U-PCX) were measured by ELISA, normalized to urine creatinine levels. Eighty three SLE patients with or without kidney diseases (KD) were enrolled. [Results] U-Pod and U-PCX of KD (+) group were significantly higher than those of KD (-) group in SLE (U-Pod KD (+): 7.9±24.9 cells/mL vs KD (-): 0.2±0.6 cells/mL, $P<0.0001$, U-PCX KD (+): 362.2±298.8 μg/gCr vs KD (-): 128.9±113.5 μg/gCr, $P=0.0012$). Among 36 patients with biopsy-proven lupus nephritis, U-Pod of patients with Class IV lesion was significantly

higher than that of patients without (20.0±38.6 vs 0.7±0.6 cells/mL, P=0.0025). U-PCX of patients with Class V lesion tended to be higher than that of patients without (549.1±344.5 vs 347.8±274.0 cells/mL, P=0.058). ROC analysis showed that U-Pod>0.9 cells/mL predicted pure and mixed Class IV (sensitivity 81.0%, specificity 71.4%, P=0.004), and that U-Pod<1.25 cells/mL and U-PCX>686.0 μg/gCr predicted pure Class V (sensitivity 60.0%, specificity 96.7%). [Conclusion] U-Pod and U-PCX are high in lupus nephritis, and histological class might be predictable with U-Pod and U-PCX.

ICW4-8

The role of autoantigen TRIM21 in pathogenesis of systemic lupus erythematosus

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Conflict of interest: None

[Objectives] The increased expression of type I interferon (IFN)-inducible genes, called "IFN signature", has been suggested to have important roles in pathogenesis of systemic lupus erythematosus (SLE). Here, we investigated the pathological role of TRIM21, an autoantigen also called Ro52 or SSA1, in SLE. [Methods] We collected peripheral blood mononuclear cells (PBMC) from 20 patients with SLE and 24 healthy controls (HC). The mRNA expression levels of TRIM21, type I IFN-inducible genes and type I IFNs were analyzed by quantitative RT-PCR. We also investigated the protein levels of TRIM21 and IRF family genes by Western blotting. [Results] The mRNA levels of TRIM21 and other type I IFN-inducible genes were higher in PBMC from patients with SLE as compared to HC. TRIM21 mRNA level correlated positively with other type I IFN-inducible genes. Although the mRNA levels of type I IFNs showed negative correlations with TRIM21 mRNA level in HC, these correlations were not observed in SLE. After treating with MG-132, the protein levels of IRFs were increased in PBMC from HC, but not in the PBMC from patients with SLE. [Conclusion] These results suggest that the malfunction of TRIM21 as an E3 ubiquitin ligase for IRF family may lead to the increased expression of type I IFNs in SLE.

ICW4-9

CaMK4 promotes T_H17-driven autoimmunity though Akt/mTOR and CREM-α

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Conflict of interest: None

[Objectives] To determine the molecular mechanisms whereby calcium/calmodulin-dependent protein kinase IV (CaMK4) controls the generation of T_H17 cells. [Methods] The expression of CaMK4 was examined under T_H1, T_H2, T_H17 or T_{reg} conditions. We induced EAE in B6 mice or B6 *Camk4*$^{-/-}$ mice and evaluated the disease activity. MRL/*lpr* mice were treated with KN-93, an antagonist of CaMK4, and examined IL-17 producing T cells in *in vitro* and *in vivo*. Furthermore, we analyzed an epigenetic remodeling and signaling pathways related to CaMK4 induced T_H17 cells. To determine the relevance of our findings to human SLE, we analyzed the effect of CaMK4 inhibition on T_H17 cells function in T cells from patients. [Results] CaMK4 is solely expressed under T_H17 condition. EAE and MRL/*lpr* lupus-like disease are ameliorated by genetic or pharmacological inhibition of CaMK4 along with a decrease in the frequency of IL-17-producing T cells. The effects of CaMK4 on T_H17 cell generation are mediated through the mTOR pathway and CREM-α which controls the epigenetic remodeling of *Il17*. Importantly, silencing of CaMK4 in T cells from patients with SLE decreases the expression of IL-17A. [Conclusion] Our results suggest that CaMK4 inhibition may be a promising therapeutic agent for T_H17-driven autoimmune diseases.

ICW4-10

The effectiveness of tacrolimus for minor flares of SLE

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Conflict of interest: None

[Objectives] We assess the effectiveness of tacrolimus (TAC) for minor flares of SLE. [Methods] The minor flare was defined as an increase in SLEDAI, which remained between 3 to 11. We recruited 15 patients who treated with add-on medication with TAC for the minor flares (TAC group). As a control, sex, age, and dose of glucocorticoids (GCs) and SLEDAI at flare matched 15 patients administered increased dose of GCs for minor flare were also recruited (GC group). All patients were maintained remission for 3 months before the flares with GCs (≦10mg/day) and/or immunosuppressants except calcineurin inhibitors. [Results] The clinical characteristics of baseline were comparable between the two groups. After 12 months, SLEDAI was improved to the level before the flares in 73% in TAC group and 67% in GC group. There was no significant difference in SLEDAI at 12 months between the two groups. Two patients in both groups developed flares. TAC discontinued in only 1 patient because of fatigue. The normalization rate for anti-ds-DNA antibody levels was higher in TAC group than GC group (60% vs 0 %, p=0.028). [Conclusion] Our study suggested that the effectiveness of TAC for the treatment of SLE with minor flares was not inferior to GC without increasing frequency of adverse effects

ICW4-11

Randomized Controlled Trial of Low-Dose Intravenous Cyclophosphamide versus Oral Mycophenolate Mofetil in Treatment of Lupus Nephritis

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Objectives To compare the efficacy and safety of oral mycophenolate mofetil (MMF) with fixed, low-dose intravenous cyclophosphamide (CYC) in patients with lupus nephritis. **Methods** This was a prospective, randomized study including patients with Class III/IV/V lupus nephritis. The patients were randomized to either CYC (6 fortnightly pulses of 500 mg) or MMF (1.5-3gm/day) for 24 weeks. All patients received oral steroids. The primary end point was pre-specified decline in proteinuria and serum creatinine. Secondary end points included complete remission, disease activity (assessed by SLEDAI) and adverse events. **Results** Of the 94 patients screened, 53 were randomized. At 24 weeks, both groups had similar response rates. In intention-to-treat analysis, 19 of 26 patients (73.1%) receiving CYC and 19 of 27 patients receiving MMF (70.4%) met primary end point (95% CI, 0.34 - 3.78%; p=0.83). Complete remission was achieved in 13 of the 26 patients (50.0%) and 13 of the 27 patients (48.1%), respectively (p=0.89). Gastro-intestinal symptoms and infections were significantly more in the MMF group. Four patients (1 in CYC group and 3 in MMF group) died during the study period. **Conclusion** MMF had similar efficacy but more adverse events than low dose intravenous CYC in Indian lupus nephritis patients.

ICW4-12

Treatment of refractory SLE with combination of tacrolimus and mizoribine

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Conflict of interest: Yes

[Objectives] We have focused on multitarget therapy with combination of prednisone, tacrolimus and mizoribine as induction or additional therapy for refractory SLE. The aim of this study is to evaluate efficacy and safety of multitarget therapy for SLE. [Methods] Twenty six patients treated with multitarget therapy in our department since April 2009 were involved. They were divided into two groups; (A) 10 patients who were initially treated with this therapy as induction, and (B) 16 patients who were additionally treated with this therapy due to difficulty in reducing prednisone dose. We evaluated efficacy and safety of this therapy respectively. [Results] (A) Five of 10 patients had lupus nephritis. Complete nephritis remission rate at 6 months was 80%. Five patients not suffered from nephritis had cytopenia, skin rash, arthritis, and hypocomplementemia. All of these patients improved their symptoms or blood examination data. There were 3 severe adverse events. (B) Fourteen of 16 patients showed improvement of clinical findings, decrease of the autoantibodies, and elevation of complements. We can reduce the dose of prednisone without flare in 13 patients. There was no severe adverse event. [Conclusion] Multitarget therapy is very effective for refractory SLE.

ICW4-13

Ephrin-B2 regulates lung and skin fibrosis *in vivo* by promoting myofibroblast differentiation

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Conflict of interest: None

Objetives: The goal of this study is to investigate the role of ephrin-B2 in the development of skin and lung fibrosis in vivo. **Methods:** Mice were injected subcutaneously with recombinant ephrin-B2/Fc (100μg/Kg) daily for two weeks and assessed for the development of skin fibrosis. Fibroblast-specific ephrin-B2 knockout (KO) mice were generated and subjected to the bleomycin-induced skin and lung fibrosis model. Fibrosis was assessed by histology, hydroxyproline levels, q-PCR and western blot. Ephrin-B2 levels were determined by ELISA and immunohistochemistry (IHC). **Results:** Ephrin-B2 treatment induced myofibroblast differentiation *in vitro*, as indicated by increased expression of α-SMA and collagen type I. Subcutaneous injection of ephrin-B2/Fc induced skin fibrosis in mice as showed by increased hydroxyproline content and α-SMA-expressing myofibroblasts. Fibroblast-specific ephrin-B2 KO mice were significantly protected from bleomycin-induced lung and skin fibrosis, as indicated by reduced hydroxyproline and TGF-β levels. Upregulation of ephrin-B2 levels in fibroblasts and skin sections from SSc patients was showed by q-PCR and IHC. **Conclusion:** Our study identifies ephrin-B2 as a novel mediator of fibrosis and highlights this ligand as a new therapeutic strategy in SSc.

ICW4-14

Elevated 8-isoprostane in scleroderma: implications of its role in inhibiting vascular endothelial growth factor-induced angiogenesis

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[Objectives] Scleroderma (SSc) is a complex disease characterized by inflammation, vasculopathy, and disposition of collagen. Increase in vascular endothelial growth factor (VEGF) in SSc has been observed; however, angiogenesis does not occur normally. Activation of the thromboxane A2 receptor (TXAR)-mediated ROCK pathway by 8-isoprostane (8-IP) inhibits VEGF-induced endothelial cell (EC) migration. We will examine its role in SSc. [Methods] Dermal ECs were isolated from healthy subjects or patients with diffuse SSc. Angiogenesis was assessed by chemotaxis. [Results] SSc patients had significantly higher 8-IP in plasma and EC conditioned media (CM). SSc EC CM decreased VEGF-induced tube formation in healthy ECs while vitamin E restored it. 8-IP inhibited VEGF-induced healthy EC migration, and the inhibition of TXAR or ROCK restored it. In SSc ECs, the impaired response towards VEGF was restored by TXAR or ROCK inhibitors. Basal and 8-IP-induced ROCK activity was significantly higher in SSc ECs compared to normal ECs. [Conclusion] This study provides a potential link between oxidative stress and impaired angiogenesis in SSc, and shows that 8-IP is not just a by-product as a result of oxidative stress, rather it plays a significant role in impaired angiogenesis that characterizes SSc.

ICW4-15

Effects of extracorporeal shock wave therapy (ESWT) to the digital ulcers of Scleroderma (SSc): a pilot study

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Conflict of interest: None

[Objectives] **SSc** patients often display Raynaud syndrome with digital skin ulcers. As these ulcers don't depend on autoimmune or abnormal coagulation, immunosuppressive and anticoagulants are ineffective. ESWT have been induced for lithotripsy and its low energy application has yielded evidence for myocardial ischemia. The rationale is new angiogenesis induced by VEGF produced at arteries. We tried to introduce ESWT to digital ulcers of SSc. [Methods] We enrolled 9 SSc patients with new digital ulcers. All 9 patients had been treated with conventional therapies. One ESWT sitting consisted of 20 areas in both hands and 15 in both feet, totaling 7000 impulses. Treatments were done weekly for 9 weeks. We counted the number of skin ulcers, and checked skin elasticity as well as patients' pain and function index. [Results] Numbers of skin ulcers were reduced from 5.4 per person to 1.1 by 9 weeks. 10/18 large ulcers (>5mm) disappeared and average size was diminished from 10.8 to 3.7mm. RodnannTSS, HAQ, EQ5D and PainVision™ scores were improved. Fingers displayed a temparature rise. All 9 patients completed the therapy without any side effects. [Conclusion] ESWT may be a fast, efficacious and safe treatment that can be used as a type of therapy for indolent digital ulcers caused by SSc.

ICW5-1

Active Rheumatoid Arthritis Is An Independent Risk Factor Of Chronic Kidney Disease

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Conflict of interest: None

[Objectives] To determine whether active RA is an independent risk factor for CKD. [Methods] This prospective study included 134 RA patients and 1156 non-RA individuals. When patients showed eGFR less than 60 ml/min/1.73m^2 or positive for urinary protein test, they were judged as having CKD. [Results] Annual decline of eGFR and annual incidence of CKD were greater in RA group compared with control (-5.81±11.75 vs. 0.71±8.51, P = 0.000) (15.7 % vs. 4.6 %, P = 0.000). Logistic regression analysis showed RA is an independent risk factor of incident of CKD (P = 0.005, relative risk = 2.968, 95%CI. =1.393 to 6.327). Among RA patients, significant correlation was found between DAS28CRP at baseline and annual decline of eGFR (R = -0.238, P = 0.006). Active group had greater annual decline of eGFR compared to remission group (-8.9 ± 11.2 % vs. -3.5 % ± 11.7, P = 0.003). Multiple regression analysis showed that high DAS28 CRP is correlated with annual decline of eGFR in the patients with RA (B = -2.026, 95%CI. -3.909 to -0.142, P = 0.035). [Conclusion] RA is an independent risk factors of

CKD incident. RA activity is correlated with annual decline of eGFR in patients with RA, suggesting that RA activity, presumably systemic inflammation, could contribute to development of CKD.

ICW5-2

Pentraxin-3 (PTX3) in Patient with Rheumatoid Arthritis (RA): High disease activity or Infection

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Conflict of interest: None

Infection is a critical complication in management of patient with rheumatoid arthritis (RA). When you examine a patient with high level of serum C-reactive protein (CRP), it isn't easy to distinguish worthing of RA and complicated with infections, in some time. If we have a biomaker which can distinguish the two easily, it is very helpful in daily clinical site. PTX3 is a novel biomaker which was reported in usefulness in some disease. [Objectives] To evaluate the diagnosability of PTX3 in RA patients with high level of CRP. [Methods] 21 RA patients with infections (infection RA: iRA), 20 with high disease activity of RA (flare RA: fRA), 23 healthy controls (HC) were enrolled in this study. We measured PTX3, CRP and procalcitonin (PCT) before and after the treatments (iRA and fRA), at any time (HC). [Results] In iRA, average levels of PTX3 significantly reduced pre- and post-treatment. In pretreatment iRA, PTX and PCT have correlation. In pretreatment, iRA's PTX3 level was higher than that of fRA, but both of level were higher than that of HC. In post treatment PTX3, there wasn't significant distinction in iRA and fRA, but both level were higher than that of HC. [Conclusion] PTX3 is a useful biomaker which can distinguish worthing of RA and complicated with infections.

ICW5-3

Effectiveness and obstacles of the treat-to-target (T2T) strategy in Japan - data from The Epidemiological Study for T2T

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Conflict of interest: None

[Objectives] To elucidate effectiveness and obstacles of the T2T strategy in Japan. [Methods] We assessed clinical outcomes, implementation and impediments of the T2T strategy in rheumatoid arthritis patients with moderate to high disease activity. [Results] Of 197 cases (female 77%, mean age 61 y/o, mean disease duration 59 months), SDAI remission at week 12, 24, and 48 were achieved in 21%, 38%, and 49%, and low disease activity (LDA) in 47%, 43%, and 38%, respectively. HAQ remission rates were 56% and 60% at week 12 and 24. Adherence rates to T2T (remission achieved and maintained, remission predicted as achievable, treatment adjusted, LDA permitted) were 84% for week 0-24 and 88% for week 24-48. Among 77 cases whose treatment was not adjusted even with non-remission at week 12, the most common reason was physicians' prediction that remission would be achievable (45 cases). Of the 45 cases, 21 achieved remission at week 24. Reasons of non-adherence to T2T were difficulty in treatment intensification due to adverse events or comorbidities, lack of patients' consents, or no other appropriate treatment options, etc. [Conclusion] High SDAI and HAQ remission rates were achieved by implementing the T2T strategy in real clinical settings. Factors impeding the strategy were revealed.

ICW5-4

What is the utility of routine ANA testing in predicting development of biological DMARD-induced lupus/vasculitis in patients with rheumatoid arthritis?

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Conflict of interest: None

Objective: Anti-TNF therapy is often associated with newly developed autoimmune diseases. We determine the clinical significance of ANA in patients with rheumatoid arthritis (RA) receiving TNF inhibitor (TNFi). Methods: Patients with first TNFi use since 2005 were identified in University of Leeds and Yokohama city university. Serial autoantibody profiles, treatments, and adverse events were evaluated. Results: In Leeds, 454 patients were identified. Infliximab was associated with higher ANA seroconversion rates (31.2%) compared with etanercept (11.8%) and adalimumab (16.1%) ($p<0.001$). Median therapy duration was 10.9 months. Positive anti-dsDNA was noted in 6 patients (median 2.0 years). One patient developed lupus. An association between seroconversion and secondary non-response to TNFi was observed. In Yokohama, 90 patients were identified. ANA seroconversion rates were 40.8%, 20.6% and 14.3% in infliximab etanercept and adalimumab, respectively. Two patients developed lupus. Three of 4 patients having infusion reaction to infliximab showed ANA seroconversion. Lupus patients were successfully managed with rituximab and abatacept. Conclusion: ANA seroconversion was associated with anti-TNF-induced lupus in only a minority, secondary non-response to the agent, and drug allergy.

ICW5-5

Effects of biologic agents on inhibition of large joint-destruction in patients with rheumatoid arthritis and the risk factors of progress in joint-destruction

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Conflict of interest: None

[Objectives] The goal for treatment of rheumatoid arthritis is to inhibit and arrest joint-destruction. Many clinical trials tell us that biologic agents inhibit small joint-destruction, however, there have been a few reports demonstrating inhibitory effects on large joint-destruction. [Methods] Sixty-three patients receiving the latest biologic agent for a year or more are included in this study. The mean age at initiating the latest biologic agent was 60.5 year-old, and a total of 222 joints including shoulder, elbow, hip, knee, and ankle joints were evaluated whether there was progress in joint-destruction comparing the radiographs before and after treatment. [Results] DAS28/ESR was significantly improved from 4.18 to 2.58 after treatment ($p<0.01$). Progress in joint-destruction was found in 14 patients (22%) and 18 joints (8.1%), and there was significantly higher rate of progress in joint-destruction in Larsen grade III/IV than I/II joints ($p<0.01$). Multiple regression analyses showed that age at initiating biologic agents was a risk factor for progress in joint-destruction (odds ratio = 1.137). [Conclusion] These results showed that progress in joint destruction occurs in approximately 10% of large joints even if disease activities are well controlled using biologic agents.

ICW5-6

Residual synovial inflammation determined by comprehensive ultrasound assessment predicts relapse after discontinuation of biological treatment in patients with rheumatoid arthritis in clinical remission

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Conflict of interest: Yes

[Objective] To determine whether the comprehensive ultrasonographic assessment of synovial inflammation predicts relapse after discontinuation of biological treatment in patients with RA in clinical remission. [Methods] RA patients in clinical remission (DAS28<2.6) receiving biological treatment who agreed to discontinue the biological treatment were recruited. Patients underwent a comprehensive ultrasound scan on 134 synovial sites in 40 joints and were prospectively followed up for 6 months. [Results] Forty-two patients were enrolled. Using the optimal cut-off values determined by ROC analysis, relapse rates were significantly higher in patients whose total ultrasound scores at discontinuation were high than in those whose scores were low (P<0.001 for both total gray-scale (GS) and power Doppler (PD) scores), whereas the difference between high and low DAS28 was not statistically significant (P=0.158) (log-rank test). PPV and NPV were 80.0% and 73.3% for the total GS score and 88.9% and 74.2% for the total PD score, respectively. [Conclusion] In RA patients in clinical remission receiving biological treatment, residual synovial inflammation determined by comprehensive ultrasound assessment predicts relapse within a short term after discontinuation of the biological treatment.

ICW5-7

What factors lead to achieve early remission in rheumatoid arthritis patients with TNF inhibitors?

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Conflict of interest: None

[Objectives] To evaluate predictors for early remission in rheumatoid arthritis (RA) patients with TNF inhibitors and its impact on the drug persistency [Methods] A total 249 RA patients with etanercept or adalimumab were included in this analysis from the retrospective biologics registry. Early remission of RA patients was defined as a disease activity score 28 less than 2.6 at 3 months after initiation of TNF inhibitors. The prevalence of early remission was estimated and its predictors were identified using multivariate logistic regression analysis. We also performed Kaplan Meier curve and log rank test to evaluate its impact on the drug persistency. [Results] Thirty one patients (12.4%) achieved early remission in RA patients with TNF inhibitors. In multivariate analysis, male (OR 4.39, CI 1.66-11.63), negative rheumatoid factor (RF) (OR 2.80, CI 1.08-7.25) and the number of previous use of non-biologic DMARDs ≤3 (OR 3.85, CI 1.45-10.0) were identified as predictors for early remission. There was no difference of persistency of TNF inhibitors between the patients with and without early remission (log rank test p=0.72). [Conclusion] Male, negative RF and less use of previous non-biologic DMARDs were the predictors for early remission in RA patients with TNF inhibitors.

ICW5-8

Comparison of the efficacy and safety of Tocilizumab and Abatacept using propensity score matching method at 52 weeks. ~ The Tsurumai Biologics Communication registry ~

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Conflict of interest: None

[Objectives] These days, there are many reports of studies to compare biologics directly. The comparison between biologics directly will become more important in future. Prospective study is ideal, but difficult in clinical practice. Therefore, we have the propensity score matching method, which is a highly detailed retrospective analytical technique using the data which accumulated until now. [Methods] We investigated 381 RA patients who administrated TCZ or ABT in TBCR from April 2008 to September 2012. We compared the two groups using conventional adjusted logistic regression, as well as matching subjects across age, RA duration, biologic and MTX history, DAS28ESR, stage, class, and MMP-3 using a propensity score to adjust the patient background. [Results] In total, 170 patients (TCZ 85 patients, ABT 85 patients) were enrolled. The average of TCZ patient age, RA duration, rate of using biologics, CDAI was 61.9 years, 12.1 years, 47%, 23.2. That of ABT was 61.8 years, 11.3 years, 55%, 24.4 respectively. The low disease activity and remission rate of CDAI was 61%, 16% in the TCZ group and 41%, 11% in the ABT group at week 52. The rate of adverse events of the TCZ group was 5.9%, and that of the ABT group was 2.4%. [Conclusion] TCZ was more effective than ABT, and ABT was safer than TCZ.

ICW5-9

Interleukin-6 blockade reduces circulating N-terminal pro-brain natriuretic peptide levels in patients with active rheumatoid arthritis

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Conflict of interest: None

[Objectives] Individuals with rheumatoid arthritis (RA) have a 1.5–2.0 fold higher risk of developing congestive heart failure than the general population. Small increases in NT-proBNP level are predictive of left ventricular dysfunction. Data on the effects of IL6 blocking agents on NT-proBNP levels in active RA patients (pts) are limited, but may be informative. [Methods] Sixty consecutive RA pts (mean age, 57 ± 10 years) with active disease without a clinical diagnosis of cardiovascular disease were enrolled. The RA pts received anti-IL6 antagonist tocilizumab (TCZ) once a month after 24 wk. NT-proBNP levels were measured at baseline and at 24 wk. We examined the association of NT-proBNP with RA disease activity and severity of outcomes. [Results] NT-proBNP levels decreased significantly after 24 wk of TCZ treatment (median NT-proBNP level, 142.0 pg/mL vs. 97.5 pg/mL, p = 0.004). Changes in NT-proBNP levels were associated with changes in the DAS28 (r = 0.27, p = 0.03). On multivariable analysis, changes in DAS28 were independently associated with changes in NT-proBNP levels. [Conclusion] These results show that TCZ decreases NT-proBNP levels by approximately 32% in patients with RA without cardiac symptoms. This suggests no treatment-induced deterioration in cardiac function.

ICW5-10

Experimentation about serum cytokines and subsets of peripheral blood mononuclear cells in rheumatoid arthritis patients treated with abatacept

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Conflict of interest: Yes

OBJECTIVE: To examine the mechanism of abatacept (ABT) for RA patients by serum cytokines and subsets of peripheral blood mononu-

clear cells (PBMC) and their activation markers. **METHODS:** 9 serum pro-inflammatory cytokines and PBMC subsets of T, B, NK cells and monocytes including activation markers were quantified using high sensitive ELISA system and flow cytometry at a baseline, Week 2, 12 and 24 of the treatment with ABT in 51 RA patients who had not been treated with any biologics. The relations between the cytokines, cell surface markers and clinical data were analyzed. **RESULTS:** The mean age was 65.8 years, with the mean disease duration of 8.6 years. Mean DAS28-ESR was 5.3 at a baseline. The numbers of HLA-DR+CD4, OX40+CD4, HLA-DR+Th1, HLA-DR+Th2, HLA-DR+Th17, regulatory T cells (Treg) and HLA-DR+Treg were significantly decreased at Week 24. The ratio of surface expression of CD69 in monocytes also decreased. Changes of the ratios of HLA-DR expression in CD14+CD16+ monocytes were statistically correlated with those of DAS28-ESR and serum IL-6 levels. **CONCLUSIONS:** The activation of CD4+T cells including Treg totally decreased in bio-naive RA patients treated with ABT and especially the activation of non-classical monocytes and IL-6 were related to the effectiveness of ABT.

ICW5-11

Prognostic factors and therapeutic response prediction by the treatment with Abatacept in patients with rheumatoid arthritis. The ALTAIR next study

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Conflict of interest: None

[Objectives] To determine the prognostic factors affecting clinical outcomes by the treatment with Abatacept (ABT) in RA patients. [Methods] 108 patients with rheumatoid arthritis were treated with abatacept for 52 weeks in routine clinical practice. [Results] At Week 52, 25% of patients achieved clinical remission (SDAI<3.3), while functional remission (HAQ≦0.5) and Structural remission (ΔmTSS<0.5) were achieved in 31% and 63% of patients respectively. 15% of patients achieved comprehensive disease remission (CDR), which was defined as SDAI≤3.3, HAQ≤0.5, ΔmTSS ≤0.5, while 20% of patients achieved comprehensive disease control (CDC), which was defined as SDAI≤11.0, HAQ≤0.5, ΔmTSS ≤0.5. RF was the independent prognostic factor for SDAI at 52 weeks (cutoff value; RF >125IU/ml at baseline). The prognostic factors predicting functional and structural remission were HAQ and CRP (HAQ≦1.0 and CRP≦1.4mg/dl), whereas age was the predictive of CDC achievement (cutoff value; age <48) by logistic regression analysis. Improvement of HAQ at 2weeks was the only independent variable for SDAI at 52 weeks (cutoff value; ΔHAQ <-0.125). [Conclusion] ABT enables personalized treatment according to the patient's specific disease state and early improvement of HAQ can predict the efficacy of ABT.

ICW5-12

Retrospective analysis of safety and efficacy of the treatment with biologic agents in elderly patients with rheumatoid arthritis

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Conflict of interest: None

Objective: Regarding the treatment of elderly RA patients, no guideline exists for the use of biologic agents. This study aimed to clarify the safety efficacy of the treatment with biologic agents in elderly RA patients. **Methods**: We retrospectively assessed hospital records of RA patients over the age of 70 years from January 2006 to August 2013. Patients were classified into groups of treatment of biologic agents (n=58, observation period 3.7y) or non-biologic agents (n=220, observation period 3.9y). The incidence of serious infections requiring hospitalization was examined. In addition, risk factors of serious infections in elderly patients were analyzed. **Results**: Rates of MTX use (82.7% vs 77.7%), PSL use (44.8% vs 40.4%) and pulmonary complication (39.6% vs 27.7%) were not significantly different between biologic agents group and non-biologic agents group. Furthermore, the incidence of serious infections was not significantly different between two groups (20.7% vs 18.6%). Serious infections were significantly associated with PSL use (OR 6.1; CI 95%, 3.1-12.1, p=0.0001). **Conclusion**: Our study indicates that biologic agents can be used safely in elderly RA patients, but PSL use is an important risk factor for serious infections regardless of use of biologic agents.

ICW5-13

Hepatitis B virus (HBV)-DNA monitoring in occult HBV carrier patients with rheumatoid arthritis during methotrexate and/or biologics therapies

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Conflict of interest: None

[Objectives] To estimate a frequency of hepatitis B virus (HBV) reactivation in RA patients during methotrexate (MTX) and/or biologics therapies. [Methods] Of our RA database, 503 patients had been examined for serum HBs- Ag and HBs-/HBc-antibodies. Infected patients were examined for serum HBV-DNA, and the DNA (+)/Ag (-) subjects (occult carrier) were monitored for the DNA during RA therapies. [Results] A total 109 (21.7 %) infected patients were identified in 503 RA patients. Of these, 8 patients were HB-Ag positive, and 1 (1.7 %) occult carriers were found in the 60 patients examined for serum HBV-DNA. The 8 carriers (the number of cases) had received, MTX (2), biologics (3), sulfasalazine (4), prednisolone (6), bucillamine (2) and tacrolimus (1). In 3 carriers, HBV-DNA was elevated during RA therapies, and the additional treatment by nucleoside analogs decreased the HBV-DNA without development of hepatitis. In the HBV-infected patients including occult carriers, no one developed hepatitis during MTX (a total observation 386 person years), biologics (135 person years), or other therapies. [Conclusion] In the HBV-infected non-carriers, reactivation risk by MTX or biologics therapy may be limited, and 3 of 8 carriers showed the reactivation before antivirus treatments.

ICW5-14

Correction of valgus hindfoot contributes to clear reduction of ankle joint pain; in rheumatoid arthritis patients

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Conflict of interest: None

[Objectives] We often see painful ankle joint destruction concomitant painful valgus hindfoot in RA cases. For such cases, valgus hindfoot was firstly corrected and fused, and then ankle joint pain has been observed. [Methods] Two RA women were underwent correction and fusion surgery in subtalar and talo-navicular joint, and calcaneal osteotomy. They had been using wheel-chair because of severe pain in ankle joint and hindfoot despite of TCZ biologics therapy. After surgery, patients kept non weight bearing with BK casting for 2 months, and then partial weight bearing was started. [Results] Of course, both patient complains no pain in hindfoot, (case1: 14 months, case2: 5months after surgery), furthermore, dramatic pain reduction in ankle joint was also observed (VAS; case1: 25mm, case2: 10mm), and they can walk without any support. In addition, From the X-ray picture, loading axis of whole lower extremities passed more nearly to the center of ankle joint (case1: 15mm preoperative→6.5mm postoperative, case2: 21mm preoperative→7mm postoperative). [Conclusion] Correction of valgus hindfoot causes the centralization of weight bearing line in ankle joint, so it has effect not only for hindfoot pain, but also ankle pain reduction, suggesting the possible preservation of ankle joint.

ICW5-15

Quantitative analysis of nailfold capillary morphology in patients with fibromyalgia

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[Objectives] The aim of this study was to determine the Nailfold capillaroscopy (NFC) pattern in fibromyalgia (FM) with clinical features. [Methods] 67 FM patients and 30 age and sex-matched healthy controls were included for this study. Nailfold capillary patterns were analyzed using computerized NFC. Capillary dimension was determined by calculating the number of pixels. [Results] FM patients had lower capillary number but higher deletion score than health controls. Both apical limb width and capillary width were also significantly decreased in FM patients, indicating that FM patients have the abnormality of decrease in digital capillary diameter as well as capillary density. Interestingly, there was no difference in the capillary dimension on Adobe Photoshop between the two groups, which suggests that length or tortuosity of capillaries in FM patients is increased to compensate diminished microcirculation. Physical function by FIQ showed a weak negative correlation with capillary dimension ($r = -0.248$, $p = 0.048$). [Conclusion] FM patients had an altered capillary density and diameter in the digits. Diminished microcirculation on NFC may explain FM symptoms such as peripheral coldness, and might cause the hormonal and biochemical abnormalities in FM pathogenesis.

ICW6-1

Type 1 angiographic arterial lesion with coronary artery stenosis in Takayasu's Arteritis: two case reports

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Conflict of interest: None

[Objective] Takayasu arteritis (TA) is a chronic inflammatory disease of large vessel disease. TA affects the aorta, its major primary branches and also ostial of coronary arteries. It mainly affects young women. The angiographic findings of TA were classified into six types according to the International Conference on TA 1994. Type 1 lesion which involving the aortic arch vessels is common among patients in Japan, United States and Italy. [Method and Results] We describe two interesting cases of TA who had Type 1 angiographic arterial lesion with coronary artery involvement (one had ostial left main stem disease who finally had coronary artery bypass grafting done after in-stent restenosis and the other had chronic total occlusion of right coronary artery with poor ejection fraction). The latter patient also had Type IV arterial lesion. Both of them had in-stent restenosis after percutaneous transluminal angiographic intervention for aortic arch vessels and renal arteries respectively. They were successfully treated with glucocorticoid and immunosuppressant therapy (methotrexate and or cyclophosphamide) with no active disease activity as demonstrated on ^{18}F-FDG PET-CT scans. [Conclusion] In summary, coronary artery involvement is not uncommonly affected in young women with TA.

ICW6-2

NETs-ANCA vicious cycle in MPO-ANCA-associated vasculitis

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Conflict of interest: None

[Objectives] MPO-ANCA-associated vasculitis (MPO-AAV) is closely related to neutrophil extracellular traps (NETs). The aim of this study is to elucidate the enhanced formation and disordered regulation of NETs in MPO-AAV. [Methods] Patients enrolled in this study included 38 MPO-AAV and 23 SLE patients. NETs induction rate was evaluated by reaction of patient-IgG with healthy neutrophils primed by TNF-α. ANCA affinity was determined by the competitive inhibitory ELISA method. DNase I and NETs degradation abilities were evaluated by ELISA and the incubation of patient serum with formed NETs, respectively. [Results] MPO-AAV patient-IgG induced NETs. The induction rate was 16.6±9.7% and significantly higher compared to those in SLE patients and healthy controls. Moreover, the NETs induction rate was correlated with BVAS and ANCA affinity. While, DNase I, the important regulator of NETs in vivo, was generally low in MPO-AAV patients and many patients showed impaired degradation of NETs. Furthermore, the presence of anti-NETs antibodies, which could interfere with the degradation of NETs, was demonstrated in some MPO-AAV sera. [Conclusion] These findings suggested that NETs-ANCA vicious cycle could be involved in the pathogenesis of MPO-AAV.

ICW6-4

Characteristics of Japanese ANCA-associated Vasculitis Patients Classified as Granulomatosis with Polyangiitis by the European Medicines Agency Algorithm

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Conflict of interest: None

[Objectives] ANCA-associated vasculitis (AAV) is a disease with significant differences among different ethnic groups. Reports on characteristics of Japanese GPA patients are limited, and this study was undertaken to determine characteristics of Japanese AAV patients classified as granulomatosis with polyangiitis (GPA) by the European Medicines Agency (EMA) algorithm. [Methods] This was a retrospective chart study of GPA patients who had attended our departments between 2007 and 2012. [Results] Twenty-four GPA patients had attended our departments during the study period. Fourteen (58.3%) were positive for C-ANCA, and eight (33.3%) were positive for P-ANCA. P-ANCA positive GPA patients and C-ANCA positive GPA patients differed in the organs involved at diagnosis with P-ANCA positive patients having nose and sinus involvement less frequently compared to C-ANCA positive patients. Interstitial lung infiltrates were more common among P-ANCA positive patients compared to C-ANCA positive patients. [Conclusion] Japanese AAV patients who are diagnosed as GPA by the EMA algorithm includes a significant number of P-ANCA positive patients, and characteristics of those patients may be different from the classical picture of GPA.

ICW6-5

B cell abnormality and efficacy of rituximab therapy in ANCA associated vasculitis

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Conflict of interest: None

[Background] B cell depletion by rituximab is effective treatment for ANCA associated vasculitis (AAV). However, the selection criteria for RTX remains unclear. **[Methods]** Circulating B cell subsets were defined by flow cytometry in 8 AAV patients (3 GPA, 2 MPA, and 2 EGPA). Based on the analysis, the patients were considered suitable to receive immunosuppressive drugs or RTX. **[Results]** There were 4 male and 4 female patients analyzed, whose mean age was 62.9 years, and mean duration of disease was 22.9 months. All patients had organ involvements including upper and lower respiratory tract or nephropathy, and were treated with high dose steroids. The proportion of effector memory or class-switched memory B cells was increased in 4 patients, thereby treated with RTX (375mg/m2 once per week for four times) and all achieved

in remission. Four patients without B cell abnormality received immunosuppressants (2 IVCY and 2 azathioprine): 3 patients achieved remission, but one died from alveolar hemorrhage. **[Conclusion]** The results suggested that RTX therapy is effective in AAV patients with abnormal B cell differentiation to effector memory B cells. The evaluation of B cell phenotype may serve to predict to the response to RTX therapy in AAV.

ICW6-6

Clinical usefulness of mycophenolate mofetil in patients with ANCA associated vasculitis

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Conflict of interest: None

[Objectives] The concomitant use of cyclophosphamide (CY) for remission induction and azathioprine (AZA) for the maintenance are recommended as a standard therapy for ANCA associated vasculitis (AAV). However these concomitant drug are sometimes difficult to continue if treatment failure or adverse effect. [Methods] We evaluated the clinical usefulness in 14 patients with AAV treated with mycophenolate mofetil (MMF). [Results] Three patients with granulomatosis with polyangiitis and 9 patients with microscopic polyangiitis were included; their average age was 65 years. Although 3 of 4 patients with refractory disease achieved remission, only 1 patient could maintain remission. The mean dosage of glucocorticoid (GC) in 10 patient with relapsing disease under previous treatment were 5.5 mg/day and their concomitant drug before MMF were mizoribine (N=6), AZA (N=3), CY (N=1). All cases achieved second remission and 80% (8 /10) maintain remission for 1 year. Only 1 patient experienced second relapse and only 1 patient discontinued because of adverse effect. The mean dosages of GC were increased up to 13.5 mg/day at relapse but could be decreased to 5.9 mg/day after 1 year. [Conclusion] MMF may be useful as the second line concomitant drug for remission maintenance.

ICW6-7

The change of peripheral blood neutrophil count before and after IVIg therapy for EGPA

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Conflict of interest: None

[Objectives] Intravenous immunoglobulin therapy (IVIg) is known to be effective for eosinophilic granulomatosis with polyangitiis (EGPA) with refractory neuropathy or cardiopathy. But its mechanism is not yet clarified. [Methods] The changes of laboratory data including peripheral blood neutrophil count before and after IVIg in EGPA patients who visited our hospital between 2006 and 2013 were examined. The changes of peripheral blood eosinophil count, and serum IgG and IgE levels were also examined. The data before and after IVIg were defined those observed within 2 days before, and those within 3 days after, respectively. [Results] 5 EGPA patients with refractory peripheral neuropathy (3 males and 2 females, aged 67.2±4.4) had 17 IVIg courses, totally. In all of the17 courses, IgG level showed increase, and neutrophil count showed decrease from before and after IVIg ($p<0.01$). A negative correlation was observed between IgG level and neutrophile count ($r=-0.6$, $p<0.01$). Neither eosinophil count nor IgE level showed no statistically significant difference between before and after IVIg. [Conclusion] The peripheral blood neutrophil count decreased significantly from before to after IVIg, and showed negative correlation with serum IgG level, during the course.

ICW6-8

Study on the safety and efficacy of infliximab, an anti-TNF-αantibody, in 21 patients with refractory intestinal Behcet's disease

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Conflict of interest: None

[Objectives] Intestinal Behcet's disease (BD) is an intractable condition of BD which can affects mortality and morbidity. In the present study, safety and efficacy of 3-years-treatment with an anti-TNF-α antibody Infliximab (IFX) on refractory intestinal BD were estimated. [Methods] IFX was administered to 21 intestinal BD patients. The healing rate of intestinal ulceration on colonoscopy was used as the primary efficacy endpoint. The secondary endpoint used was the ameliorating effect based on the "Disease Activity Index for Intestinal Behçet's disease" (DAIBD), and the dose of corticosteroid (CS) tapered. [Results] The retention rate was 85.7 %. No severe adverse effects were observed during observation period. The healing rate of intestinal ulceration on colonoscopy was 66.7% and average DAIBD score decreased significantly from 73.3 to 21.4 (1 year), 11.1 (2 year), 11.7 (3 year). The dose of concomitant CS was reduced significantly from 14.2 mg/day to 2.5 (1 year), 1.5 (2 years), 1.3 mg/dl (3 year). [Conclusion] IFX treatment is highly effective in the treatment of intestinal BDin cases of refractory intestinal BD, and that it demonstrates excellent tolerability. IFX therapy has been shown to be effective treatment strategies for intestinal BD.

ICW6-9

Clinical study of Mizoribine pulse therapy for Polymyalgia Rheumatica patients resistant to steroid monotherapy

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Conflict of interest: None

Background: Polymyalgia Rheumatica (PMR) patients are good response to low-dose glucocorticoids, but in reality, some cases are steroid resistant, and relapsing. There are some case reports that Biological agents or strong immune-suppressants are effective for PMR patients, but it's not ideal for elderly patients. Objectives: To assess the efficacy of mizoribine (MZR) pulse therapy for polymyalgia rheumatic (PMR) patients resistant to steroid monotherapy. methods: Seven PMR cases were analysed in this study. Six cases were female, and their average age was 72.8 years old. Average creatinine (Cr) level was 0.602mg/dl and estimated Glomerular Filtration Rate (eGFR) was 78.8ml/min. We performed MZR pulse therapy every other day and three days a week, and estimated the activity of PMR before and after the therapy. We also measured the blood concentration of MZR. We also adjusted to the dose of the MZR to the blood peak level of MZR equal to 3-4μg/ml. Results: After MZR pulse therapy, five PMR patients were improved and reduced dose of PSL less than 5mg/day. No side effect was found. Conclusions: For its safety and efficacy, the addition of MZR pulse therapy monitoring the blood concentration might be a good option for PMR patients resistant to steroid monotherapy.

ICW6-10

Clinical features and results of patients with Polymyalgia Rheumatica

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Conflict of interest: None

[Objectives] To clarify clinical features and results of patients with Polymyalgia Rheumatica (PMR). [Methods] Sixteen PMR patients (6 males and 10 females) were recruited; mean age was 74 (50-90) years old and mean follow up was 29 (6-67) months. We evaluated pain locations, initial value of ESR and serum MMP-3, the duration between the onset and steroids initiation, initial dose and the rate of relapse/recurrence. We

also evaluated the magnetic resonance imaging (MRI) findings of the shoulder joint for 5 patients. [Results] The pain locations were the shoulder in 9 patients, the neck in 6 and the lumber and buttock in 4, whereas 3 patients felt pain in the regions besides the shoulder or neck. The mean initial ESR and MMP-3 values were 80 (40-128) mm and 287 (33-1430) ng/ml. The mean duration to steroids initiation was 64 (5-365) days and mean initial dose was 10.3 (7.5-20) mg. The relapse/recurrence rate was 31% (5 cases); the duration to steroid initiation of this group was longer than that of non-relapse/recurrence group. Effusion in subacromial bursa was observed in all patients underwent shoulder MRI. [Conclusion] Imaging analysis with ultrasound or MRI could be a reliable indicator for detecting synovitis in PMR. Early intervention may decrease relapse/recurrence rate.

ICW6-11

Cytomegalovirus Infection in Rheumatic Diseases: Trends in Incidence and Mortality in a 10-year period

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Conflict of interest: None

[Objectives] To investigate the factors affecting incidence and mortality of cytomegalovirus (CMV) infection in rheumatic diseases. **[Methods]** We measured the CMV pp65 antigen (C7-HRP) in 655 patients with rheumatic diseases suspected of CMV infection in our hospital from January 2003 to September 2013. We compared the clinical characteristics between two groups of CMV infection and non-infection to identify the risk factors for incidence. Moreover, we analyzed the patients who died for detecting the poor prognostic factors. **[Results]** The 96 patients had the positive for C7-HRP and 70 patients were diagnosed with CMV infection. The estimated number of the C7-HRP positive cells in determining CMV infection was 6 out of 50000 WBCs. The responsible factors for CMV infection were the daily doses of steroid and steroid pulse therapy in the last one year. The 18 patients resulted in dead despite antiviral therapies. The mortality was higher in patients with intestinal pneumonia, hypoalbuminemia, lymphocytopenia, and CMV pneumonia statistically. **[Conclusion]** We should watch out CMV infection in using the high-dose steroid in rheumatic diseases. Interstitial pneumonia, hypoalbuminemia, lymphocytopenia, and CMV pneumonia are significant risk factors for poor outcomes.

ICW6-12

Effectiveness of trimethoprim-sulfamethoxazole for prevention of *Pneumocystis jirovecii* pneumonia in patients receiving immunosuppressive therapy for rheumatic diseases

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Conflict of interest: Yes

[Objectives] To identify effectiveness of trimethoprim-sulfamethoxazole (TMP-SMX) for prophylaxis of *Pneumocystis jirovecii* pneumonia (PCP) in patients with rheumatic diseases given immunosuppressive therapy [Methods] We prospectively observed 418 in-patients with rheumatic diseases who started prednisolone (PSL) ≥0.5mg/kg/day. Patients who started TMP-SMX at baseline (N=277, prophylaxis group) and patients without TMP-SMX throughout observation period of 6 months (N=141, non-prophylaxis group) were compared. [Results] Patients in the prophylaxis group had higher rates of pulmonary comorbidities (43.3% vs. 26.2%, $p<0.01$) and interstitial pneumonia (30.7% vs. 17.7%, $p=0.04$), but had a lower incidence rate of PCP (1.4% vs. 6.4%, $p=0.01$) than those in the non-prophylaxis group. Cox hazard regression analysis indicated that prevention with TMP-SMX lowered risk for development of PCP (HR 0.19, 95%CI 0.06-0.65), after adjusting for covariates at baseline. Of 112 patients who discontinued TMP-SMX (40.4%), four patients developed PCP after the discontinuation. [Conclusion] TMP-SMX was effective for the prevention of PCP in patients with rheumatic diseases who started PSL ≥0.5mg/kg/day. Studies questing for better usages of TMP-SMX with improved drug retention rates are warranted.

ICW6-13

Clinical study of Pneumocystis pneumonia (PCP) during rheumatoid arthritis (RA) treatment - Biological treatment (Bio) and MTX treatment-

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Conflict of interest: None

[Objectives] We reveal the onset factor that developed PCP. [Methods] I was examined 25 patients that developed PCP during RA at our department. Bio-PCP group was 13 patients and non-Bio-PCP group was 12 patients. I was studied retrospectively for Bio-PCP group and 128 patients not developed PCP to be administered more than six months on adalimumab (Bio group). Also, I was studied retrospectively 10 patients of MTX treatment that developed PCP (MTX-PCP group) and 138 patients not developed PCP for MTX (MTX group). [Results] 12 of 13 patients developed PCP within 24 weeks Bio started. In addition, Bio-PCP group was higher rate in lung disease, diabetes, and steroid combination as compared to the Bio group. However, We were no significant difference between gender, et al. On the other hand, MTX-PCP group has developed in the 281 week average. MTX-PCP group were older, coexistence lung disease, and combined rate of steroid was higher as compared to the MTX group. But, We were no significant difference between weight, et al. [Conclusion] If elderly, coexistence of lung disease, long disease duration, steroid combination have the potential to increase the risk of developing PCP in MTX. Making a prophylaxis may be effective at risk even six months on Bio because of PCP that developed on Bio are almost within 24 weeks.

ICW6-14

Understanding the pathology of the arthropathy in chronic infantile neurological cutaneous and articular syndrome (CINCA) by using induced pluripotent stem cells (iPSCs) technology

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Conflict of interest: None

【Objectives】 CINCA syndrome is caused by gain-of-function of NLRP3 mutation. The pathology of CINCA syndrome is explained by activation of protein complex producing IL-1β, NLRP3 inflammasome, supported by clinical observation that anti-IL-1 therapy is effective on systemic inflammation. However, one of its characteristic features, epiphyseal overgrowth is resistant to anti-IL-1 therapy, which raises a question that mechanisms independent of NLRP3 inflammasome play a role in abnormal chondrocyte overgrowth.【Methods】 We established disease-specific iPSCs from 2 male CINCA patients who had mutations of NLRP3 as somatic mosaicism and studied the effect of mutant NLRP3 on chondrocytes which were differentiated from iPSCs.【Results】 CINCA-derived iPSCs produced larger chondrocyte mass due to glycosaminoglycan overproduction that correlated with increased expression of chondrocyte master-regulator SOX9. In addition, *in vivo* transplantation of immature cartilaginous pellets from CINCA-derived iPSCs into immunodeficient mice showed dysregulated ossification that recapitulated disorganized ossification in CINCA patients.【Conclusion】 We succeeded in recapitulating the arthropathy in CINCA patients. The iPSCs technology uncovered the chondrocyte pathology of human disease, CINCA syndrome.

ICW6-15

MEFV and TNFRSF1A gene mutations in patients with inflammatory myopathy with abundant macrophages

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Conflict of interest: None

[Objectives] Inflammatory myopathy with abundant macrophages (IMAM) is characterized by diffuse infiltration of macrophages in fascia. We analysed MEFV and TNFRSF1A mutations in patients with IMAM. [Methods] Nine patients with IMAM were enrolled. Clinical characteristics and MEFV and TNFRSF1A were analysed. [Results] The patients with IMAM had myalgia, muscle weakness, arthralgia, fever and erythema. The thickening of fascia was observed in STIR images from MRI. In biopsied speciemens, a number of CD68+ macrophages were found apparently in the fascia. In genetic analysis, seven of nine patients had MEFV variants (P369S-R408Q, E148Q-L110P, G304R, R202R and E148Q) and one patient had TNFRSF1A mutation (C43R). [Conclusion] These results suggest that MEFV gene polymorphisms and TNRRSF1A mutations are susceptibility and modifier gene in IMAM.

Poster Session

P1-001

Medication adoherence to treatment in patients of with Rheumatoid Arthritis is associated with disease activity

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Conflict of interest: None

[Objectives] Medication adoherence is a important problem in patients with rheumatoid arthritis (RA). Consistent predictors of medication adoherence in japanese patients of RA are not determined. We use a 8 item questionnaire of drug attitude inventory (DAI), and we aim to determine whether DAI has a temporal association with RA disease activity. [Methods] We measured 8 item questionnaire, DAS28, and CDAI in 529 RA patients (male 134, female 396, mean age 63.1) from October to December in 2011. Using the score of DAI, we divide them into good compliance group (group A) and low compliance group (group B), and evaluated the association with sex, age, disease duration, DMARDs and corticosteroid use, Biologic DMARDs use, DAS28, and CDAI. [Results] DAS28 and CDAI were significantly lower, respectively, in the group A than those in the group B (2.79 vs 3.02 P=0.02, 6.08 vs 7.58 P=0.001). Biologic DMARDs user were respectively higher score of DAI than the others. the other parameters were not significant variables in two groups. [Conclusion] This result displays that medication adoherence has a great influence of RA disease activity and that DAI questionnaire may be a useful tool for the evaluation of medication adoherence in RA patients.

P1-002

Characteristics of the patients who visit rheumatoid arthritis clinic with joint symptoms and consideration of RA classification criteria

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Conflict of interest: None

[Objectives] With the spread of general awareness of rheumatoid arthritis, patients who visit rheumatoid arthritis clinic with joint symptoms are increasing. Here, we reveal the characteristics of these patients and consider relation with RA classification criteria. [Methods] 112 patients who visited our clinic with joint pain and/or swelling from April to September 2013 were included. Patients who started DMARDs and/or biologics were defined as RA. We examined the classification ability of 2010 RA classification criteria. [Results] 23 of new patients were women of 50-54 years and only 5 defined as RA. 37 patients of all started treatment. Sensitivity of 2010 classification criteria was 75.7%, specificity 92.0%, positive predictive value 82.3%, and negative predictive value 88.5%. 9 patients started treatment with classification score under 6. They were all RF and ACPA negative but synovitis was found in MRI. Three of them showed elevated CRP and MMP-3. [Conclusion] Proportion of women in early 50s was large in new patients but ratio leading to the diagnosis of RA was small. Symptoms from other causes such as menopause and OA could be considered. CRP, MMP-3 and MRI findings are useful for diagnosis in patients who do not meet classification criteria.

P1-003

A therapeutic strategy targeting low disease activity improved functional outcome of patients with elderly-onset rheumatoid arthritis: two-year results of the CRANE cohort

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Conflict of interest: Yes

[Objectives] To evaluate a two-year-functional outcome of treat-to-target (T2T) strategy and to identify predictors of the outcome in elderly-onset rheumatoid arthritis (EORA). **[Methods]** Data from 101 methotrexate (MTX)-naïve EORA patients from a prospective cohort (CRANE) were analyzed. Treatment was adjusted every three months targeting low disease activity (LDA). Treatment was initiated with non-biologic disease-modifying antirheumatic drugs, followed by biologics. The primary outcome was the Health Assessment Questionnaire-Disability Index (HAQ-DI) at week 104. **[Results]** By week 52, 30.6% of the patients were given biologics. T2T strategy was implemented in 72% of the 101 patients. HAQ-DI ≦0.5 and LDA were achieved in 60.4% and 47.5% of the patients at week 52 and in 62.4% and 64.4% at week 104. Multivariate logistic regression analysis showed that age and HAQ-DI at baseline predicted poor physical function at week 104. Patients with the poor functional predictors (i.e., ≧75 years of age or ≧1.0 of HAQ-DI) who achieved LDA at week 52 had significantly lower HAQ-DI score (0.53±0.62 or 0.67±0.66) at week 104 than patients who did not achieve LDA (1.23±0.97 or 1.26±0.74). **[Conclusion]** Sustained LDA achieved with T2T strategy in EORA led to good functional outcome at two years.

P1-004

Current Status and Future Tasks of "Shizuoka Rheumatoid Arthritis Network (SRN)"

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Conflict of interest: None

[Objectives] Shizuoka Rheumatoid Arthritis Network (SRN) has established in 2007 in order to educate patients and co-medicals and to improve the quality of RA treatment. We have investigated how the clinical activities have changed before and after the SRN starts. [Methods] We questioned doctors in SRN. [Results] Sixteen centers in SRN have answered the questionnaire. Six centers have used the instructions for T2T in daily examination, 14 use disease activity indexes, 11 use functional indexes, 3 use radiological indexes in daily examination using some concepts. Four centers increased the dose of Methotrexate for patients, 5 increased the number of patients treated with Biologics after joining SRN, and all of them often take lectures of SRN interestingly. Eight centers frequently utilize lectures of SRN for education of their co-medicals and communicated the information of patients with other members. [Discussion] It is generalized that we evaluate disease activity or function with some indexes. However we haven't established to use some radiological indexes and to share T2T concept with patients, so our tasks are to promote the information. This network also has very important role to educate not only doctors but also co-medicals and RA patients.

P1-005

Low BMI could be associated with poor control of disease activity in rheumatoid arthritis patient

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Conflict of interest: None

[Objectives] To investigate the influences of low BMI on disease activity using data of NinJa (National Database of Rheumatic Diseases by iR-net in Japan) in 2011 and 2012. [Methods] A total of 1,660 RA patients in NinJa2011, whose disease duration was within 3 years, were included. Of these patients, (1) 985 who did not achieve clinical remission (CDAI>2.8), and (2) 447 who acheived clinical remission (CDAI≦2.8) were extracted. Both of the population (1) and (2) were categorized by BMI to the following groups: underweight (<18.5 kg/m2), normal or overweight (≧18.5 kg/m2). CDAI of NinJa2011 and of NinJa2012 were compared between the two groups, respectively. [Results] In both of the population (1) and (2), CDAI, disease duration, and age were not significantly different between the groups of BMI<18.5 and BMI≧18.5 at baseline (NinJa2011). One year later (NinJa2012), in the population (1), CDAI in the BMI<18.5 group was significantly higher than CDAI in the BMI≧18.5 group (9.89 vs. 7.53, p<0.01), while in the population (2), CDAI did not significantly differ between the two groups (3.00 vs. 2.85, p=0.76). [Conclusion] Low BMI in RA patients who had not achieved clinical remission, appears to result in a poor control of disease activity in the future.

P1-006

How can pharmacoeconomic evaluations play a role on the clinical practice guideline in Japan?

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Conflict of interest: Yes

[Objectives] To assess the feasibility of implementing pharmacoeconomic (PE) concepts on the clinical practice guidelines (CPG) of RA. [Methods] As part of the project of MHLW funded study group (PI: Nobuyuki Miyasaka) towards the development CPGs 2014, status of pharmacoeconomic concepts in CPGs developed by ACR and EULAR were reviewed. Health insurance coverage decisions, made by NICE in the UK, PBAC in Australia, CADTH in Canada, in which PE data were already required, are also reviewed. [Results] For CPG, both by ACR (2008) and by EULAR (2010) took PE concept into account, while few evidences were considered by ACR. EULAR separately conducted systematic review of PE researches and summarized the results into six recommendations, including the use of anti-TNF biologics for DMARDs-resistant patients, while uncertainties were remained quite large. For coverage decisions, they set stricter condition for use of biologics compared to ACR/EULAR did. Biologics could only be used if patients had failed at least two DMARDs. Lack of long term clinical evidence and different cost data prevented us from extrapolating foreign evidences into Japan. [Conclusion] PE aspects should be implemented into CPG in future, after sufficient domestic evidence would have been developed.

P1-007

Elderly rheumatoid arthritis patients who surpassed the life expectancy (1.5 year follw up)

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Conflict of interest: None

[Objectives] 85.90 -year-old female, male was 79.44 years average life expectancy of the Japanese Ministry of Health, Labour and Welfare in 2012 was announced. It is said that short few years than the average person life of patients with rheumatoid arthritis (RA) is not RA, but the life is becoming long surely advances in treatment. Be encountered in patients to care life expectancy often time, among the elderly, squeeze to patients beyond the average lifespan, and keep track. [Methods] From a patient was referred to our hospital Rheumatology center to the end of June from April 2012, women 85 years of age or older, as for patients 79 years of age or older, men followed the hammer after about one year. [Results] Became the target result of 60 women, 84 men people. In female patients, 2 cases died, 8 cases of fracture, 8 cases infection requiring hospitalization, respectively, 4 cases, 3 cases, 8 cases in male patients during the course. [Conclusion] That women are more long-lived in RA patients, and that the risk of fracture is high is guess. In addition, it was considered biological products and high capacity MTX also, and can be selected if you choose the case.

P1-008

Identification of IL-33 receptor-expressing myeloid progenitor cells in mouse bone marrow

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Conflict of interest: None

Interleukin-33 (IL-33) is a member of the IL-1 cytokine family, which includes IL-1 and IL-18. IL-33 plays critical roles in the allergic inflammation by inducing the production of Th2 cytokines. In addition, IL-33 is also involved in the pathogenesis of chronic inflammatory diseases, such as rheumatoid arthritis and inflammatory bowel diseases, as a proinflammatory cytokine. Recently, it was reported that a fraction of $CD34^+$ hematopoietic progenitor cells express IL-33 receptor (ST2 and IL-1RAcP). However, the precise characterization of these progenitor cells still remains unclear. To identify and purify the IL-33 receptor-expressing $CD34^+$ hematopoietic progenitors, we evaluated the expression level of ST2 in mouse bone marrow cells comprehensively. As previously reported, mature eosinophils, basophils and mast cells expressed ST2. In addition to these mature myeloid cells, the committed progenitor cells to these 3 lineages, eosinophil progenitors (EoP), basophil progenitors (BaP) and mast cell progenitors (MCP), also expressed ST2 clearly. When stimulated with IL-33, EoP, BaP and MCP produced not only IL-4, 5, 9, 13, but also IL-6 and TNF-α, suggesting that IL-33 may exert its roles in chronic inflammatory diseases as well as in the allergic inflammation.

P1-009

Detection of IFN-γ+IL-17+ cells in salivary glands from patients with Sjogren's syndrome and Miklicz's disease

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Conflict of interest: None

Objective: Recent studies suggested that Th17 cells. However, the role of IL-17 in Sjogren's syndrome or Mikulicz's disease remained to be elucidated. Patients and Methods: Salivary glands were taken from 15 Sjogren's patients and one Miklicz's patient. IFNγ-IL-17+ cells were detected by immuno-histochemistory staining. Results: IFN-γ+IL-17+ cells were detected in salivary glands from both Sjogren's disease patients and Mikulicz's disease patient. Descussion: IFN-γ+IL-17+cell in salivary glands from patients in this study are speculated to be Th1/Th17. Thus, Th1/Th17 may have an important role in the pathogenesis of Sjogren's syndrome and Miklicz's disease. Conclusion: IFN-γ+IL-17+cells were detected in salivary glands of Sjogren syndrome and Miklicz's disease.

P1-010

The serum cytokine/chemokine profiles are useful for differential diagnosis of rheumatoid arthritis, including anti-CCP-negative patients

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Conflict of interest: None

[Objectives] The regulation of systemic pro-inflammatory cytokines play important roles in the pathogenesis of rheumatoid arthritis (RA). This study was designed to evaluate the profiles of serum cytokines and chemokines and use them for discriminating anti-CCP antibody (ACPA)-negative RA from non-RA (NRA) patients. [Methods] By using a chemiluminescence immunoassay, twenty-eight of serum cytokines and chemokines, including IL-6, TNF-α, IL-17A and CXCL13, were measured in RA, NRA (including sero-negative spondyloarthropathy) patients, and sex-matched healthy controls (HC). Results were analyzed by Mann-Whitney U-test. Discriminant analysis was performed using multiple logistic regression analysis. [Results] Our study identified the cytokines and chemokines that were up-regulated in RA patients as compared with in HC. Multiple logistic regression analysis revealed that the combinations of three to five of the cytokines and chemokines can clearly discriminate ACPA-negative RA from NRA, as well as RA from HC. [Conclusion] Our study using a sensitive chemi-luminescence immunoassay led to the identification of the cytokines and chemokines elevated specifically in RA patients. Several of them were proved to be useful in the differential diagnosis of ACPA-negative RA from NRA.

P1-011

Serum cytokine concentrations in the rheumatoid arthritis

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Conflict of interest: None

[Objectives] The purpose of this study is to investigate the serum concentrations in the patient of rheumatoid arthritis. [Methods] Seventy one patients who were prescribed anti-RA drugs (PSL, MTX, and DMARDs) and fifty nine patients who were treated with biologics (IL-6 inhibitor; 26 Pt, TNF-αinhibitor; 26, co-stimulation modulator; 7) were enrolled in this study. The blood analysis was performed to see the several inflammation markers such as IL-6, TNF-α, adiponectin, pentosidine, and homocysteine. [Results] Compare to non-biologics group, co-stimulation modulator showed less IL-6 and TNF-α level. IL-6 inhibitor showed elevated IL-6 level and no change for TNF-α. TNF-αinhibitor showed elevated level of TNF-α. [Conclusion] There are difference among the biologics in the serum inflammatory cytokine level. This might be utilized as "tailor made" treatment for RA in the each patients based on their cytokine profile.

P1-012

Abatacept differentially regulates serum cytokine profiles in patients with rheumatoid arthritis

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Conflict of interest: None

[Objectives] The aim of this study was to investigate the impact of abatacept administration on serum cytokine levels in patients with RA. [Methods] 20 patients with RA who were treated with abatacept between January 2011 and October 2013 at our hospital. Sera were collected prior to treatment and again 24 weeks after starting abatacept therapy. Disease activity and clinical improvement were assessed using the disease activity score (DAS28), Clinical Disease Activity Index (CDAI), Simplified Disease Activity Index (SDAI). Levels of serum cytokine, including TNFα, IL-6, IL-17F, CCL3, CXCL8, CXCL10, CX3CL1, macrophage migration inhibitory factor (MIF) and vascular endothelial growth factor (VEGF), monocytes chemoattractant protein-1 (MCP-1) were measured with enzyme-linked immunosorbent assays. [Results] Significant reductions in TNFα, IL-6, CX3CL1, MIF, VEGF and MCP-1 were observed after 24 weeks of abatacept administration. [Conclusion] Our results suggest that the TNFα, IL-6, CX3CL1, MIF, VEGF and MCP-1 levels in patients with active RA may be sensitive to abatacept. Abatacept may differentially regulate serum cytokine profiles, resulting in the amelioration of RA disease activity.

P1-013

The expression of alphaEbeta7 (CD103) is induced through TGF-β signaling pathways in human peripheral CD8 T cells

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Conflict of interest: None

[Objectives] It has been reported that the expression of αEβ7 (CD103) is abnormally enhanced in T cells infiltrating in lachrymal glands (LG) of patients of Sjögren's syndrome (SS) and CD103 may play an important role in the damage of LG. In this study, we investigated possible involvement of the expression of PHA/TGF-β-induced CD103 in peripheral T cells. [Methods] PBMCs were isolated from peripheral blood samples of healthy individuals, and stimulated in vitro with PHA in the presence or absence of TGF-β. The expression of CD103 in PBMCs was analyzed by FACS and quantitative PCR (qPCR). The amounts of cytokines in the culture supernatants were measured by ELISA. The expression of TGF-β receptors was analyzed by western blotting (WB). [Results] FACS and qPCR analysis showed that the expression of CD103 was induced in CD8+ T cells upon stimulation with PHA and TGF-β further enhanced the expression of CD103 in the cells. Moreover, WB revealed that PHA induced the expression of TGF-β receptors in PBMCs. Production of IL-6, TNF-α and IFN-γ by PBMCs was remarkably enhanced upon stimulation with PHA. ($p<0.05$) [Conclusion] Our results indicate that PHA induced-TGF-β receptors and cytokines are involved in the overproduction of CD103 in CD8+ T cells through TGF-β signaling pathways.

P1-014

Fractalkine directly binds to Integrins αvβ3 and α4β1 and the integrin-binding defective mutant of fractalkine is an antagonist of CX3CR1

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Conflict of interest: None

Objectives: Fractalkine (FKN, CX3CL1) is a chemokine which plays a role in leukocyte trafficking. In a current model, FKN mediates leukocyte recruitment through binding to CX3CR1 and the direct binding to integrins is not involved in this process. However, We discovered that the chemokine domain of FKN (FKN-CD) directly interacts with integrins $\alpha_4\beta_1$ and $\alpha_v\beta_3$. Thus, we examined the role of integrins in FKN signaling. Methods: We generated an integrin-binding defective FKN-CD mutant (K36E/R37E), and studied the effect of FKN-CD and/or K36E/R37E on integrin activation, ternary complex formation (CX3CR1, FKN-CD, and integrin), and thioglycollate-induced peritonitis in mice. Results: K36E/R37E was defective in integrin activation and ternary complex formation, whereas this mutation had no effect on CX3CR1 binding. Notably, excess K36E/R37E suppressed integrin activation induced by wild-type FKN-CD and effectively suppressed leukocyte trafficking in vivo. Conclusion: These results suggest that FKN-CD binding to integrins and the resulting ternary complex formation is required for FKN signaling. Also, these findings suggest that K36E/R37E acts as a dominant-negative CX3CR1 antagonist and that FKN-CD/integrin interaction is a novel therapeutic target in inflammatory diseases.

P1-015

The inflammation amplifier is involved in various human inflammatory diseases including rheumatoid arthritis (RA)

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Conflict of interest: None

[Objectives] The inflammation amplifier, a chemokine inducer in non-immune cells, is activated by NFkB and STAT3 stimulation. The amplifier was seen to be involved in the development of inflammatory disease models including a rheumatoid arthritis (RA) in F759 mice. We extended these to studies to determine if the amplifier is also involved in various human diseases. [Methods] Genes of positive regulators and targets for amplifier activation, as identified by a lentivirus library carrying shRNAs and DNA microarray, were compared with disease-associated genes in GWAS databases. Epiregulin-ErbB1 pathway was investigated as a model pathway for these genes. [Results] Among the over 1000 genes related to the amplifier, 202 showed 492 indications of association with various human diseases like RA. We further confirmed a role of the Epiregulin-ErbB1 axis in activation of the amplifier in human diseases as well as mouse models. [Conclusion] We show that the inflammation amplifier is indeed associated with many human diseases including RA and identified genes that may make for potential therapeutic and diagnostic targets of the diseases.

P1-016

Possible negative feedback mechanisms by the CD26 costimulatory pathway: induction of preferential IL-10 production by crosslinking of CD26

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Conflict of interest: None

[Objectives] T cell costimulatory molecule CD26 is up-regulated following T cell activation, and the increased number of $CD26^+$ T cells has been detected in patients with diverse autoimmune diseases such as RA in both peripheral blood and inflamed tissues. The immune system is equipped with an intrinsic negative feedback mechanism that limits ongoing T cell activation. Our objective is to elucidate the negative feedback pathway for the excessive CD26-mediated signals. [Methods] Human $CD4^+$ T cells purified from PBMCs were incubated with plate-bound anti-CD3 mAb and anti-CD26 mAb or anti-CD28 mAb. After activation, profile of cytokine production, expression of inhibitory molecules and the signal transduction pathway were examined. [Results] Production of IL-10 and expression of LAG3 were preferentially induced following CD26-mediated costimulation in an Ab dose-dependent manner. In addition, these $CD4^+$ T cells evidently suppressed the proliferation of effector T cells and production of IL-2 and IFN-γ in an IL-10 dependent manner. This induction of IL-10 production may be associated with the enhancement of Egr2 and IL-21 expression following CD26 costimulation. [Conclusion] Our data show that preferential IL-10 production is induced to control the excessive CD26-mediated activation.

P1-017

Not only biologics but also DMARDs achieve repair of damaged joint, and it happens not only at small joints but also at large joints in rheumatoid arthritis

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Conflict of interest: None

[Objectives] To study on repair of damaged joints in rheumatoid arthritis (RA). [Methods] Eighteen RA patients who had repair of damaged joints were investigated. [Results] Sex; male 6 and female 12. Age; 54.1±11.6 y. Disease duration; 9.8±7.3 y. Period from start of treatment to the time when repair of damaged joints was observed; 2.4±1.5 y. Administrated drugs; Combination biologics (Bio) and DMARDs in 13 cases {the cases that the repair of damaged joint were observed and all cases of each Bio and DMARD administrated in combination: Infliximab 5 cases (4%) of 125 cases, MTX6~15mg/w. Etanercept 4 (2.8%) of 125, MTX 6mg 1case, SASP 1, SASP+bucilamine 1 and SASP+D-Pc 1. Tocilizumab 3 (6.5%) of 46, MTX 2 cases, Leflunomide 1. Abatacept 1 (5.3%) of 19, tacrolimus 1 case}. DMARD alone in 5 cases {MTX 3 caes, MTX+bucilamine 1 and tacrolimus 1}. Sites that the repair of dam-

aged joint were observed; hand 6cases, PIP 3, MCP 1, carpale 2, shoulder 1, elbow 1, MTP 5, tarsal 1, foot 1 and knee 1. Type of the repair of damaged joint; restore of bone destruction/erosion in 16 cases, restore of joint space narrowing in 12 and restore of porosis in 9. [Conclusion] Not only biologics but also DMARDs achieve repair of damaged joint, and it happens not only at small joints but also at large joints in RA.

P1-018

Destruction and Restoration of Large Joints in RA Patients Treated by Biological Disease Modifiers (BIO) (ARASHI Change Score)

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Conflict of interest: None

[Objectives] ARASHI score was used to evaluate progression and improvement of large joints in RA patients treated with BIO. [Methods] ARASHI score consists of ARASHI Status Score (ASS), one time measurement of 10 large joints at shoulders, elbows, hips, knees, and ankles, and ARASHI Change Score (ACS) measures at two time points. 73 RA patients with available images and clinical information were treated with BIO. [Results] Mean baseline ASS was 9.6 (0 - 42) and there were 31 patients with destruction at large joints consisting of progressive 15 patients (ACS > 0) and improving 16 patients (ACS < 0). While baseline DAS/ESR was higher in patients with ACS < 0, no difference in disease activity was found at last observed point. Patients with ACS < 0 showed higher improvements in DAS/ESR, SJC, CRP, and mHAQ. [Conclusion] While most of image evaluations were performed at small joints of hands and foot, image evaluation for large joints is not sufficient. Our study showed that improvement in disease activity may accompany restoration of joints. Therefore ACS is an effective method to evaluate small changes in large joints.

P1-019

The evaluation by using Larsen grade in Xray about the differnece between the restoration and maintenance of destructive joints responded to either TNF-α blockers or non-TNF-α blockers applied for patients in RA

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Conflict of interest: None

[Objectives] We examined the restoration and maintenance of the destructive joints responded to either TNF-α blockers or non-TNF-α blockers applied for patients in RA. [Methods] The multiple small and/or large joints were evaluated by Larsden grade in Xray. TNF-α blockers were used in 20 patients, and non-TNF-α blockers were used in 12 patients. The average observation period was 29.5 months after Bio therapy was introduced for these patients. [Results] In total, the progression of joint destruction was observed in only 19% (6 patients), and erosive or destructive change was seen in 1.33 joints per a patient. On the other hand, the restoration of joint destruction was observed in 81% (26 patients), and restored change was seen in 1.23 joints per a patient. TNF-α blockers seemed to be slightly more effective than non-TNF-α blockers. [Conclusion] Bio therapy effectively inhibited the disease activity of RA for long time. Furthemore, the ratio of the restoration and maintenance of joints was more than 80%, and more than one joint per a patient were restored from the destruction and erosion by RA.

P1-020

Evaluation of longitudinal changes of knee X-ray for RA patients treated by biologics for 5 years and more in our hospital

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Conflict of interest: None

[Objectives] There is a few reports about inhibition effect of joint destrucion by biologics in the middle term and also a few about X-ray evaluation of large joints. We evaluated longitudinal changes of knee X-ray for RA patients treated by biologics for 5 years and more in our hospital. [Methods] 16 knees (10 patients) were selected among 26 patients treated by the same biologics for 5 years and more. The mean age was 63.9±8.3 years, the mean disease duration was 2.2±1.1 years and the mean treated term was 7.6±1.0 years. 1. bone erosion, 2. joint space narrowing, 3. osteophyte, 4. ARASHI score (knees of 10 large joints) were evaluated. [Results] Bone erosion in 2 knees of 3 was dissapeared. 11 knees have no change in joint space narrowing. 8 knees have osteophyte formation. The mean ARASHI status score changed 0.75 to 1.1, and change score was 0.44. [Conclusion] The above 2 in Larsen classification is common in Kellgren-Lawrence classification. It is not necessarily appropriate for evaluation in RA, because Larsen grade is down according to OA change. ARASHI score in 2012 is more appropriate, including the above 1-3. As a result of this report, it was difficult for evaluation in RA in 5 knees because of their OA change, and inhibition effect of joint destruction were showed in 11 knees (69%) in the middle term.

P1-021

Association of hand MRI findings with plasma cytokines in patients with newly diagnosed rheumatoid arthritis

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Conflict of interest: None

[Objectives] To evaluate relationships between MRI and clinical, laboratory, radiographic findings and plasma cytokines in newly diagnosed rheumatoid arthritis (RA) [Methods] Forty-two newly diagnosed, untreated RA patients in our cohort (SAKURA study) were included. MRI of dominant wrist/metacarpophalangeal joints were scored for synovitis (RAMRIS) and we evaluated the presence of bone oedema and bone erosion. Relationships between MRI findings and clinical, laboratory, radiographic findings and plasma cytokines were assessed. [Results] Twenty-nine percent patients were female, the median age was 62 years, the median disease duration was 3 months, and the mean DAS28-ESR was 4.86. The mean synovitis score was 6.76 and bone oedema and erosion were found in 57% and 50% respectively. Significant correlations were observed between synovitis score and CRP, ESR, MMP-3, plasma IL-6 and IL-8 ($p<0.05$) but not DAS28 and modified Total Sharp Score. MMP-3 ($p=0.01$) and synovitis score ($p<0.001$) were significantly higher in patients with bone oedema compared with those without. [Conclusion] The RAMRIS synovitis score at the diagnosis of RA was significantly associated with plasma IL-6, IL-8, CRP, ESR and MMP-3.

P1-022

Maximum intensity projection with magnetic resonance imaging for evaluating synovitis of the rheumatoid hand

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Conflict of interest: None

[Objectives] Magnetic resonance imaging (MRI) with maximum intensity projection (MIP) is used to evaluate the hand in rheumatoid arthritis (RA). MIP yields clear visualization of synovitis over the entirety of the bilateral hands with a single image. In this study, we assessed synovitis with MIP images and power Doppler (PD) findings to examine the clinical usefulness of MIP images for RA in the hand. [Methods] Thirty RA patients were assessed with both contrast-enhanced MRI for bilateral hands and ultrasonography for bilateral wrist and metacarpophalangeal (MCP) joints. Articular synovitis was scored in MIP images, and the scores were compared with those for PD. [Results] The agreement on synovitis between MIP and conventional MRI images was excellent. A statistically significant correlation between the scores of MIP and PD images was found. Furthermore, the agreement between MIP images and positive on PD images was 0.73 (κ=0.44) for the wrist and 0.80 (κ=0.35) for MCP joints. [Conclusion] MIP images may predict further joint damage, since they allow semi-quantitative estimation of the degree of thickening of the synovial membrane.

P1-023

Comparison of MRI findings in patients of RA: infliximab vs tocilizumab

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Conflict of interest: Yes

[Objective] We compared therapeutic efficacies of TCZ with infliximab (IFX) by using low-field-MRI. [Methods] Twenty one patients treated by TCZ and 20 patients treated by IFX were followed up by MRI, and were enrolled in this study. SDAI and MRI images of both hands were examined at baseline and 24 weeks. The effect of biologics on joints in RA patients were examined by compact MRI score. [Results] 1) In both groups, SDAI was significantly improved at 24 weeks (TCZ: 21.73±9.56→8.22±6.98, IFX: 22.12±10.12→7.18±6.55). 2) MRI findings of synovitis were improved significantly in both groups at 24 weeks (TCZ: 19.43±9.72→15.94±7.46, IFX: 16.67±7.29→11.83±6.89). 3) MRI findings of bone marrow edema (BME) was significantly improve only in IFX group but not in TCZ group, although there was no difference in delta BME score between 2 groups (TCZ vs. TNF: -2.86±7.58 vs. -8.19±10.95). 4) In TCZ group, there is no difference in improvement of MRI findings between biologics naïve or TNF failure. [Conclusions] The MRI findings of synovitis was no difference between in TCZ and IFX groups. However, BME was not significantly improved in TCZ group, suggesting BME might be left in RA patients treated by TCZ even if clinical evaluation was improved.

P1-024

Etanercept or tocilizumab? The choice of a second biologic for RA treatment from the MRI perspective

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Conflict of interest: None

[Objectives] The purpose of this study was to determine which of etanercept (ETN) or tocilizumab (TCZ) is more effective in improving MRI findings when switching from infliximab (IFX) in RA patients. [Patients] 14 RA cases with insufficient efficacy of IFX; the E group (i.e., switched to ETN, 7 cases; mean age 56.7 years; mean duration of ETN use, 24.6 months); the T group (i.e., switched to TCZ; 7 cases; mean age, 59.1 years; mean duration of TCZ use, 21.1 months). [Methods] MR images were obtained prior to IFX use, before switching to the second biologic, and after using the second biologic. RAMRIS scoring was performed for bone erosion, bone edema, and synovitis. [Results] In the E group, the mean MRI score (erosion-edema-synovitis) before IFX use was 25.3-19.3-10.6. The mean MRI score before the switch to ETN was 24.4-19.7-10.9, and the mean score after switching was 20.6-13.3-5.0. In contrast, in the T group, the mean MRI score before IFX use was 16.9-16.9-7.3. The mean MRI score before switching to TCZ was 20.6-20.0-8.1, and the mean score after switching was 18.7-10.9-5.6. [Conclusion] When used as a second biologic, ETN significantly improved synovitis. There was a trend for TCZ to improve bone edema and synovitis.

P1-025

Comparison of MRI findings in patient with RA : abatacept vs infliximab

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Conflict of interest: Yes

[Objectives] The aim of this study was to evaluate the efficacy of abatacept (ABT) and infliximab (IFX) by using low field extremity magnetic resonance imaging (cMRI) in patients with rheumatoid arthritis (RA). [Methods] Thirty five RA patients treated with ABT or IFX were included. The clinical response to the therapy was evaluated by Simplified Disease Activity Index (SDAI). Hand images were taken by 0.3Tesla cMRI. Two examinations were performed before and 24 weeks after the treatment. [Results] 1) SDAI were significantly decreased after administration of biological agents (ABT: 19.00±10.98 to 6.24±5.06 P<0.001, IFX: 22.06±10.64 to 8.49±7.68 P<0.001). 2) There were significant improvements in synovitis score (ABT: 12.22±9.28 to 7.16±5.03 P=0.006, IFX: 17.37±7.41 to 12.12±7.21 P=0.001) and bone marrow edema score (ABT: 5.90±9.58 to 2.22±4.05 P=0.018, IFX: 8.43±9.65 to 2.73±2.93 P=0.011) after the treatment. 3) Between ABT and IFX, degree of score changes (delta value) in synovitis and bone marrow edema were not significantly. 4) No significant change was found in erosion score. [Conclusion] ABT and IFX improve synovitis and bone marrow edema in RA patients, suggests the same effect on MRI findings in RA patient.

P1-026

Reliability of classification for osteonecrosis of the femoral head

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Conflict of interest: Yes

[Objectives] The aim was to clarify the reliability of the Japanese Ministry of Health, Labor and Welfare (JMHLW) type classification for osteonecrosis of the femoral head. [Methods] We performed inter-observer and intra-observer trials using sets of 40 MRIs, 20 of which were produced by a 0.5T superconductive unit and the other 20 produced by a 1.5T unit in patients with non-collapsed and asymptomatic osteonecrosis of the femoral head (JMWLH stage 1 or 2). JMHLW type classification (A, B, C1, or C2) was determined from T1-weighted coronal images at the center of the femoral head. Six orthopaedic surgeons independently assessed all 40 images twice with an interval of four to five weeks between sessions. [Results] Regarding inter-observer reliability, %agreement was 85% and weighted kappa was 0.709 for 0.5T versus %agreement of 82% and weighted kappa of 0.724 for 1.5T. Regarding intra-observer reliability, %agreement was 82% and weighted kappa was 0.780 for 0.5T versus %agreement of 80% and weighted kappa of 0.800 for 1.5T. Inter-observer and intra-observer reliabilities did not significantly differ between 0.5T and 1.5T. [Conclusion] JMHLW type classification provided high inter-observer and intra-observer reliabilities.

P1-027

The efficacy of Iguratimod to RA patients for short-term results

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Conflict of interest: None

[Objectives] To evaluate Iguratimod (IGU) to RA patients. [Methods]

From November 2012, twelve cases treated with IGU were evaluated by recording DAS28 (4/ESR). The average amount of IGU was 32.5mg. [Results] DAS28 was 4.04 and decreased to 1.90 at 24 weeks, CRP was also reduced from 2.56 to 0.33. [Conclusion] The therapy of IGU was effective for short-term results.

P1-028

The efficacy and safety of iguratimod in eight patients with rheumatoid arthritis

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Conflict of interest: None

[Objectives] To investigate the efficacy and safety of iguratimod in patients with rheumatoid arthritis (RA) who had inadequate response to conventional therapy. [Methods] Three men and 5 female patients with RA who visited Department of Systemic immunological diseases Tokyo Metropolitan Komagome Hospital between January 1, 2013 and July 31, 2013 were enrolled. Patients' age, clinical features, previous treatment were reviewed. Changes in DAS28-CRP at 4 months and 6 months were evaluated. [Results] Mean age at initiation of iguratimod was 67.2 years and mean disease duration was 12 years. Three patients used MTX. Two patients had history of malignancy, one had cryptogenic organizing pneumonia and one had inefficacy of infliximab in 5 patients who did not use MTX. Daily dose of iguratimod was 50 mg in 6 patients and 25 mg in 2 patients. The score of DAS28-CRP changed from 4.30 ± 0.84 (N=7) at baseline to 3.32 ± 1.8 (N=5) at 4 months and 3.42 ± 1.7 (N=5) at 6 months. One patient ceased iguratimod for incidental finding of colon cancer. Other 7 patients continued iguratimod safely. [Conclusion] Iguratimod may be useful and safely for patients with RA who could not use MTX.

P1-029

Usefullness of Tcrolimus in the treatment of Rheumatoid arthritis (RA)

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Fuji Toranomon Orthopedics Hospital

Conflict of interest: None

We report 3 cases of Rheumatoidoarthritis (RA) that achieved good response with Tacrolimus based on EULAR criteria.

P1-030

Tofacitinib improves arterial stiffness with methotrexate-resistant active rheumatoid arthritis

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Conflict of interest: None

[Objectives] To examine the effect of Tofa plus methotrexate (MTX) on arterial stiffness in MTX resistant RA patients in a cohort study design. Methods) 3 RA patients with moderate to severe active disease despite MTX treatment (disease activity score: DAS28>3.2) were received Tofa plus MTX. Arterial stiffness was assessed with cardio-ankle vascular index (CAVI) and augmentation index corrected for a heart rate of 75 beats per minute (AIx@75) at baseline and 24 weeks follow-up. Clinical data were collected at regular visits. CAVI is very similar to pulse wave velocity (PWV),. Results) Treatment with Tofa (10.68 ± 1.77 and 9.48± 1.28%; p = 0.26), attenuated the CAVI significantly from baseline to 24 weeks follow up. Treatment with Tofa (36.7 ± 8.6, 32.2 ± 3.6 %; p = 0.14) attenuated the Aix@75 significantly from baseline to 24 weeks follow up. Conclusions) These findings suggest that combination therapy, Tofa with MTX not only reduced RA disease activity but also limited vascular damage in patients with MTX resistant active RA. But this study is very small, we need further more large study.

P1-031

Analysis of recent MTX therapy in rheumatoid arthritis

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Conflict of interest: None

[Objectives] To investigate the state of MTX therapy in RA, after 3years the approval of dose up to16mg/ week. [Methods] The backgound, disease activity, continuity, monotherapy or combination of other drugs were evaluated. [Results] The number of patients, treated with MTX was 78. (Mean age: 64years). Mean disease duration: 11years. RA stage I:22, II:22, III:30, IV:3. Disease activity of DAS28-CRP (remission5, low49, moderate23, high0). Mean CRP value: 0.17mg/dl. Mean dosage of MTX: 7.2mg/week. Mean continuity periods of MTX: 4.2years. Steroids and biological agents were used 40% and 19%, respectively. 10mg/w:10, 8mg/w:37, 6mg/w:23, 4mg/w:6 cases. Two of over 12mg/w cases were stopped because of ineffectiveness and side effect. The ratio of monotherapy with MTX was 65% in 6mg-group, however, 19% in 8mg-group and 0% in 10mg-group. A lot of patients were treated with combination therpy using other DMARDS or biologic agents. The survival rate of MTX monotherapy were 54% at 3 years. In recent 5 years, one case of malignant lymphoma was occurred, but other severe adverse events were not observed. [Conclusion] Sufficient control of RA disease activity and safety was observed by combination therapy under 10mg/w of MTX and mainly DMARDS, without dose up to over 12mg/w.

P1-032

Remission rate in early active rheumatoid arthritis at one year in routine clinical practice in a community teaching hospital in Japan

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Conflict of interest: None

[objectives] Remission has become a realistic goal in patients with early RA. However how many patients can achieve remission in routine practice is not well known. [Methods] The patients with early active RA who visited Department of Rheumatology, Kameda Medical Center from Jan 2009 to Jan 2012 were included. Inclusion criteria for eligible patients were age 18 years or older, disease duration less than 2 years and DAS28-ESR ≥3.2 at first visit. We investigated medical records retrospectively. We divided into two groups as a boundary in Feb 2011 that is MTX dose increased approval and studied remission rate at one year. [Results] Among 103 patients who were included, 91 could be followed at one year. Baseline characteristics of patients include mean age 60.1 years, female 70%, disease duration 28.6 weeks, mean DAS28-ESR 4.77 and radiographic erosion 21%. The rates of remission defined by DAS28-ESR at one year were 47% and 65% (P=0.085). When compared baseline characteristics, we could not find any significant factor. [Conclusion] In routine practice, we compared the DAS28-ESR remission rate after one year of early active RA patients of MTX dose increased approval before and after. It was on the increase in post-approval, but it was no factor with significant difference.

P1-033

Prevention of development of rheumatoid arthritis (RA) in patients with undifferentiated arthritis (UA) by very early therapeutic intervention of methotrexate (MTX)

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Conflict of interest: None

[Objectives] Previously we reported that the patients with early-onset UA (EUA) showing high-titer of ACPA (>15U/ml) developed RA within a year at high-rate (>80%). To examine whether early therapeutic intervention of MTX could prevent development of RA in the patients with EUA showing high-titer of ACPA. [Methods] The total number of 48 patients with UA showing high-titer of ACPA and fulfilling 1994 JCR criteria for early RA but not 1987 ACR criteria for RA who have never treated with any DMARDs. One group was treated with MTX concomitant with PSL (<10mg/day) and/or NSAID (MTX+, n=29). The other was treated without MTX (MTX-, n=19). Primary endpoint was development of RA defined by fulfilling 1987 ACR criteria for RA within a year. A bone-progression was assessed by Heijdi-modified Sharp scores (H-S score). [Results] 17.2% of patients in the MTX+ developed RA compared with 78.9% of patients in the MTX- ($p < 0.001$). Although the mean interval changes from the baseline of H-S score per year showed no significant differences ($p = 0.092$), the number of patients without obvious radiographical progression was relatively more in MTX+ (76.9%) compared to in MTX- (50%). [Conclusion] Very early therapeutic intervention of MTX might prevent development of RA in some populations of EUA.

P1-034

Bezafibrate for methotrexate-induced acute liver toxicity in patients with rheumatoid arthritis (The 2nd report)

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Conflict of interest: None

[Backgraound] We reported the efficacy of bezafibrate on methotrexate (MTX)-induced acute liver injury in patients with rheumatoid arthritis (RA) in 2013. [Objectives] We enrolled more patients to ascertain the impact of bezafibrate. [Methods] Twenty-one RA patients on MTX who developed acute liver toxicity were enrolled in the study. The baseline clinical characteristics of the patients were scrutinized for details regarding the values of serum aspirate aminotransferase (AST), alanine aminotransferase (ALT) and weekly MTX dose, Disease Activity Score in 28 joints using the erythrocyte sedimentation rate (DAS28-ESR). All patients were given 400 mg of bezafibrate after the onset of liver injury and were observed for 6 months. AST and ALT values and DAS28-ESR score at week 24 were compared to those at enrollement. [Results] At the time of inclusion, mean weekly MTX dose was 10.0±2.5 mg. Mean AST and ALT values were 67.4±24.9 IU/L and 85.7±49.3 IU/L, respectively. 68.0 % of patients achieved normalization of both AST and ALT values and 80.0 % of them showed improvement in DAS28-ESR score at week 24. Only one patient withdrew bezafibrate due to pancytopenia. [Conclusion] Bezafibrate ameliorates MTX-induced liver toxicity without exerting negative impact on disease activity.

P1-035

Clinical and pathological characteristics of MTX-related lymphoproliferative disorder in patients with rheumatoid arthritis

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Conflict of interest: None

[Objectives] To elucidate the clinical and pathological features of methotrexate-related lymphoproliferative disorder (MTX-LPD) in patients with rheumatoid arthritis (RA). **[Methods]** Medical records of 12 RA patients who were diagnosed as MTX-LPD were retrospectively examined regarding clinical and pathological findings, treatment and outcome. **[Results]** Of 12 patients, 2 were male and 10 were female. Mean age at onset of MTX-LPD was 59.3. Mean dosage of MTX was 8.2mg/week and mean period of MTX therapy was 5.3 years. Mean interval between onset of RA and MTX-LPD was 13.3 years. 10 patients had lymph node swellings, one had pharyngeal ulcer and one had uterus ulcer. Pathological diagnoses were DLBCL in 7 patients and T-cell lymphoma, Hodgkin's lymphoma, lymphomatoid granulomatosis in one patient each. 8 cases improved within 1 to 4 weeks only with discontinuation of MTX. LPD was refractory in 3 cases and they needed to undergo chemotherapy. After discontinuation of MTX, arthritis was improved with a small amount of steroid in 6 cases and tocilizumab (TCZ) or iguratimod was added due to worsening of articular symptoms in 3 cases. **[Conclusion]** These results suggest that TCZ or iguratimod is possible first choice for the therapy of refractory RA after MTX discontinuation due to MTX-LPD.

P1-036

Evaluation of 24w-administration of iguratimod to subjects with rheumatoid arthritis

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Conflict of interest: Yes

[Purpose] The effects of iguratimod were evaluated in the 24-w treatment of RA patients whom current oral DMARDs and biologecs didn't demonstrate sufficient efficacy. [Subjects] 16 RA patients and over 24 w-administration of iguratimod were recruited in our clinic and the effects of iguratimod were evaluated. Mean age was 48±11 y.o. MTX was administrated to 13 subjects in mean dosage of 12.2 mg/week. [Results] The disease activity was significantly improved form 3.1±1.0 to 2.1±1.1 in DAS28-CRP, from 17.8±11.8 to 8.9±10.0 in CDAI and from 18.5±11.8 to 9.5±10.3 in SDAI ($p<0.05$). Remission rates were 63%, 31% and 31%, respectively. According to EULAR response criteria based on DAS28-CRP, "good response", "moderate response" and "no response" were 38%, 18% and 44%, respectively. Patients in "good response" or "no response" showed no differences in MTX administration, MTX dosages and initial DAS28-CRP values. [Conclusion] The effects of iguratimod were evaluated in the 24-w treatment of RA patients whose mean DAS28-CRP was 3.1. Statistical significant improvements in disease activity were observed. There was a trend that patients were classified into iguratimod-sensitive or -resistant and the novel biomarker may be required for the selection of iguratimod-sensitive group.

P1-037

Comparison of serum matrix metalloproteinase-3 levels in rheumatoid arthritis after treatment with adalimumab or abatacept for 24 weeks

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Conflict of interest: None

[Objectives] To investigate the impact of the trend of MMP-3 and CRP during the treatment Adalimumab (ADA) and Abatacept (ABT) in RA patients. [Methods] Among 411 patients with active RA (DAS28-CRP≥2.7) who were recruited in TBC registry, 210 patients were received ADA and 201 patients were received ABT therapy. We analyzed 112 patients who had DAS28-CRP remission (DAS28-CRP<2.3) at 24 weeks, consisting of 73 patients in ADA group and 39 patients in ABT group respectively. We compared the change in serum MMP-3 and CRP

levels between the two groups. [Results] The change in serum MMP-3 levels at 4, 12, and 24 weeks was greater in the ADA group than in the ABT group. The % change in serum MMP-3 levels at 12, and 24 weeks was significantly greater in the ADA group than in the ABT group. The % change in serum CRP levels at 4 weeks was significantly greater in the ADA group than in the ABT group. However, there was no difference in the % change in CRP levels at 12, and 24 weeks between the two groups. [Conclusion] ADA showed improvements in serum MMP-3 levels from an early stage in 24 weeks in a comparison with ABT. ADA can suppress synovitis and therefore the progression of joint destruction by strongly inhibiting MMP-3 when it is administered from an early stage.

P1-038

Study on the efficacy of Golimumab at this institution; group comparison based on pateints' background

Masamitsu Natsumeda[1], Koji Takasugi[1], Misuzu Yamashita[1], Kayo Ezawa[1], Kazuhiko Ezawa[1], Yoshihisa Nasu[2], Wataru Yamamoto[3], Keiichiro Nishida[4]
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Conflict of interest: None

[Objectives] Evidence based on GO-AFTER study in overseas was established. Treatment outcome of golimumab with or without previous treatment of TNF-α inhibitor was analyzed. [Methods] 19 patients who were receiving golimumab in post-marketing study were assigned with or without previous treatment of biological antibody drugs. Also, patients switched to golimumab after previous treatment of biological antibody drugs were assigned with or without TNF-α inhibitor. The clinical efficacy and continuation rate were analyzed. [Results] The assessment was used as observed. In 50% patients switched to golimumab with previous treatment of biological antibody drugs, the remission was showed. In patients switched to golimumab with or without previous treatment of TNF-α inhibitor, the remission of 66.6% patients without previous treatment of TNF-α inhibitor and 50% patients with that of TNF-α inhibitor were showed. [Conclusion] Similar to GO-AFTER study, our study showed the good efficacy in patients who had previously received TNF-α inhibitors. These findings indicated golimumab could be 2nd or 3rd line TNF-αinhibitor for patients with rheumatoid arthritis who have had inadequate responses to DMARDs or other TNF-α inhibitors.

P1-039

Examination of the case that the extension of adalimumab (ADA) dosage period was possible after disease activity decreased

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Conflict of interest: None

[Objectives] We have 14 cases which were not recurred disease activity even after taking gradual decrease in PSL usage and next extended interdose interval in ADA case. We examined the progress of these cases. [Methods] One male, female 13. Introduction average age 63.4 (27-91) year. A mean disease period was 7.8 (0.2-30) year. Stage 1:1 2:5 3:3 4:5. Class 1:6 2:8 3:0 4:0. PSL dose 1.1mg/ day, MTX dose 7.1 mg/ week at ADA started. The disease activity evaluation reached in DAS28-ESR and SDAI. [Results] 5 cases had PSL at ADA start time and needed it by cancellation after gradual decrease in an average of 5.1 (0.9-10.5) month. It took in an average of 11.9 (4.2-23.8) month to extend ADA interdose interval without flare up the disease activity from two weeks to four weeks and was an average of 17.2 (2.8-38.8) month afterwards from extension to follow-up point. The mean disease activity at each point was at introduction 4.24, 15.04, at PSL free time 2.3, 4.29, at the time of extension 2.1, 1.68, at one month later extension of period 1.96, 1.78, at follow-up point 1.95, 1.15. [Conclusion]We thinks we could extend the periods of injection ADA because ADA is antiTNF α antibody preparation. It is the medical matter that the extension is welcomed economically during a period.

P1-040

Altered cytokine net work profile in human rheumatoid arthrits through TNF-alfa inhibition

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Conflict of interest: None

[Objectives] Decision of the change of the TNF inhibitor is not yet clear. Therefore, we analysed various cytokine under the treatment and examined retrospective. [Materials] 19 patients (man 14, woman 5, average age 45.4) follow-up more than 12 months under TNF α inhibition. Three switched from IFX to TCZ, ADM, and ABA, while one did IFX/ETN to TCZ. [Methods] The serum levels were measured at the same time, by the Bio-Rad company beads-array method: IL-1β, IL-6, IL-10, IL-15, IL-17, IFN - γ. Particularly, repeated it for the next 12 months about the IL-17 high. [Results] 1) Il-1β and IL-15 were almost controlled. 2) In the effect insufficiency, increase in IL-6 and IL-10 was seen commonly. 3) In the change to TCZ, an IL-6 super high was seen. 4) In an effective and effect insufficiency, an IL-17 high was seen, but the dominant change was not reproduced afterwards. [Conclusion] 1) The evaluation of the anti-inflammatory cytokine cascade is effective for the continuation propriety of the TNF inhibitor. 2) In the effect insufficiency, an IL-6 increase not a little existed, and the switch to antiIL-6R antibody was suitable. 3) In an effective and effect insufficiency switch, IL-17 high price existed, but it seemed that further examination was necessary for participation in condition of a patient.

P1-041

Usefulness of Infliximab Dose Escalation in Patients with Insufficient Infliximab Efficacy, Particularly Those with Secondary Failure

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Conflict of interest: None

[Objective] We examined the significance of infliximab (IFX) dose escalation in the treatment of rheumatoid arthritis (RA). [Methods] We assessed changes in DAS28-ESR values and CRP, RF, and MMP3 levels in 126 RA patients who were treated with IFX between July 2004 and April 2013. [Results] The treatment could be continued for at least a year in 120 patients. The IFX dose was increased to ≥6 mg/kg in 37 patients in whom primary therapy was ineffective. The 37 patients were divided into the following groups: continued administration (n=20) and discontinued administration (n =17) groups. DAS28-ESR values and CRP, RF, and MMP3 levels improved significantly in the early period after dose escalation in the continued administration group compared with those in the discontinued administration group. Furthermore, in the group that could continue the therapy with 3mg/kg of IFX as well as ≥6 mg/kg while maintaining low disease activity, RF were significantly lower after 3 months than before IFX administration. [Conclusion] Patients who showed a marked improvement after the introduction of IFX could continue the treatment at an elevated dose of ≥6 mg/kg effectively, even if secondary failure occurred. Furthermore, it is suggested that RF is a useful predictor of treatment outcome.

P1-042

Therapeutic result of golimumab in rheumatoid arthritis

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Conflict of interest: None

[Objectives] We surveyed retrospectively on the therapeutic results of Golimumab (GLM)-treated patients for 52 weeks or more. [Methods] The subjects were 49 RA cases (8 M, 41 F, mean age: 59.7, mean duration of disease: 12.4 years) treated with GLM from September 2011. GLM was administered to 27 cases at 50 mg and 22 cases at 100 mg. The concomitant MTX usage rate was 91.8% (mean 6.9mg). Bio-naive cases were 21 (including 2 in clinical trial) and bio-switchover cases 28. Clinical results were assessed by DAS28 (CRP). [Results] The cases with low disease activity and remission (DAS28 (CRP) < 2.7) were 36.7% (37.0% in the 50 mg and 36.4% in the 100 mg) at Week 52, indicating an improvement of 12.2% (19.2% in the 50 mg and 13.6% in the 100 mg) as compared with the pretreatment level. Improvement to 28.6% was noted in the naive group and to 42.9% even in the group that shifted to other drug. However, the dose was increased to 100 mg in 10cases after the start at 50 mg due to the insufficient effect within 52 weeks. The continuation rate was 77.6%. The discontinuation cases were as follows: ADR, 2; insufficient effect, 7; move-out, 2. [Conclusion] It is considered desirable to start from 100 mg in the switchover cases.

P1-043

The effect of adalimumab administration on QOL improvement in the treatment of rheumatoid arthritis

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Conflict of interest: None

[Objectives] We used adalimumab (ADA) as a 1st choice biological agent (BIO) for the treatment of rheumatoid arthritis, and its effect on QOL improvement was investigated. [Methods] The 54 patients who were treated with ADA over 1 year continuously were entried in this study. The time course of disease activity score and mHAQ was investigated. [Results] In the administration pre- average 5.42~6 month, The average of DAS28-ESR (4) was 5.42 before the treatment, and was decreased to 3.06 by 6 months. Low disease activity in the mean value was maintained for 48 months. The 45 patients treated with ADA were naïve patients to BIO, and DAS28 improvement rate and continuation rate of ADA exceeded those of infliximab (68 patients), and were equivalent to that of golimumab (15 patients). Average mHAQ was improved from 1.1 to 0.6 after one year treatment, and in cases with joint destruction especially the knee joint destruction, the improvement of leg function such as activity and progress was bad. [Conclusion] Since self-administration is possibly and administration interval is relatively long, usefulness of ADA is high. It seemed to be indispensable to achieve the functional remission (HAQ 0.5 or less) to start the treatment in the time when the joint destruction was not observed.

P1-044

Biologics to rheumatoid arthritis in Miyazaki Prefecture (3rd report)

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Conflict of interest: None

[Objectives] We have analyzed the medical practice with biologics to rheumatoid arthritis in Miyazaki Prefecture in 2010 (1st report), 2011 (2nd report) and 2012 (3rd report) using questionnaires. [Methods] Twenty-three medical facilities participated to this study and the information from 792 patients receiving biologics was available. [Results] The numbers of patients with biologics were 505 (IFX 30.9%, ETN 48.7%, ADA 11.1%, TCZ 9.3%) until 2010, 183 (IFX 29.4%, ETN 36.6%, ADA 13.1%, TCZ 18.0%, ABT 1.1%, GLM 1.1%) in 2011, and 104 (IFX 18.3%, ETN 24.0%, ADA 24.0%, TCZ 23.1%, ABT 6.7%, GLM 3.8%) in 2012. Methotrexate (MTX) usage rate together with biologics was 65% (median dosage: 8mg/w) until 2011, which increased to 79% (median dosage: 10mg/w) in 2012. The clinical data were available in 380 patients. The disease duration before using biologics was 101 months before 2010 and was 68 months after 2011. Clinical response rate using SDAI was 38% before 2010 and was 44% after 2011. [Conclusion] These data suggested the variety of biologics used, MTX usage and its dosage, and clinical response rate increased year by year in the general medical practice of patients with RA.

P1-045

Bio-free rate of Glimumab for RA patients

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Conflict of interest: None

[Objectives] We performed 8 cases of mono therapy (Go-Mono study) of Golimumab (GLM) and 4 cases of combination of MTX (Go-Forth study). Total 12 cases (female 9 and male 3 cases) were evaluated about bio-free rate of GLM after therapeutic trial. [Methods] The average age was 55.6 years, disease duration was 5 years and ACPA positive rate was 84% at start of therapeutic trial. Trial duration was 2.5 years and GLM of all cases was stopped after therapeutic trial. We divided maintained Bio-free group and Bio restart group and compared DAS28-ESR. Survival rate of maintained Bio-free was calculated by Kaplan-Meier method. [Results] The average follow up was 2.4 years. Bio restart group were 6 cases, and GLM were 5 cases and Abatacept was a case. DAS28-ESR of Bio restart group was 4.56 in RA flare. On the other hand, DAS28-ESR of maintained Bio-free group was 2.91. It was significantly lower than that of Bio restart group. Survival rate of maintained Bio-free was 66.7% (one year) and 58.3% (two years) using end point of restart biologics. [Conclusion] After 2.4 years ended therapeutic trial, maintained Bio-free was 50%. Survival rate of maintained Bio-free was 66.7% (one year) and 58.3% (two years). This rate was similar to that of other biologics (Infliximab and Adalimumab) reported.

P1-046

Effectiveness and sustention of adalimumab (ADA) treatment in Rheumatoid Arthritis (RA) at Chikugo-area 2 years clinical trial

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CHARM (Chikugo Adalimumab Research Members)

Conflict of interest: None

Objective: Two-years clinical data of ADA treatment in RA was investigated in Chikugo-area. Methods: 175 patients who passed follow-up period of 2 years since first ADA treatment were enrolled for analysis on treatment efficacy (DAS/CRP) and drug survival rate. The patients were divided in groups based on 1) concomitant MTX use, 2) disease duration 3) disease stages, and 4) date of first ADA treatment for comparative analysis of ADA drug survival rate. Reasons for ADA withdraw such as adverse events and no or reduced efficacy were analyzed by LOCF method. Result: Mean DAS/CRP reduced from 4.1 to 2.5 after 2 years treatment of ADA and survival rate was 78.8%. Group of patients with MTX showed significantly lower DAS/CRP and higher ADA drug survival rate than the group of patients without MTX. There were no significant differences in ADA drug survival rate by means of disease duration, stages, and date of first ADA treatment. Comparative analysis of patients background based on reasons for ADA withdraw found that DAS/CRP at first ADA treatment is significantly higher in patients with no or reduced efficacy and cut-off was DAS/CRP ≤ 4.3. Conclusion: It indicates that patients with concomitant MTX and DAS/CRP ≤4.3 are factors for continuing ADA treatment.

P1-047

The efficacy and continuity of Golimumab treatment with rheumatoid arthritis for 52 weeks from TBC Registry

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Conflict of interest: None

[Objectives] To evaluate the efficacy, safety and continuity of Golimumab (GLM) treatment for 52 weeks by using Tsurumai Biologics Communication Registry (TBCR). [Methods] 87 patients with RA were started with GLM treatment and registrated into TBCR. Concerning 51 patients have completed GLM treatment for 52 weeks, we assessed disease activity with use of DAS28-ESR and SDAI, retention rate of drug continuity with Kaplan-Meier method. [Results] In characteristics of 51 patients, the mean age and disease duration were 62.0 y.o. and 12.1 years. 39 (76.4%) patients were treated with MTX. 23 (45.1%) patients have been treated with other biologics. Disease activities in patients with GLM treatment were decreased significantly at 4 weeks, and improved to 3.52 on DAS28-ESR (4.74 at baseline) and 10.1 on SDAI (20.9 at baseline) at 52 weeks. 51.8% of patients were achieved clinical remission or low disease activity on DAS28-ESR. The continuation rates of GLM in BioNaïve and BioSwitch patients at 52 weeks were 89.3% and 80.3%. Nine patients stopped GLM treatment because 5 cases were inadequate response, 2 cases occurred adverse events and two were other reason. [Conclusion] These results suggested that GLM therapy was excellent profile in efficacy and safety, and well tolerated for RA patients.

P1-048

Ten Years of Biopharmaceuticals-Treatment Outcome in Patients with Rheumatoid Arthritis (RA) in the First and Second Periods-

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Conflict of interest: Yes

[Objective] The outcome of treatment in patients with RA with infliximab (IFX) as the 1st biopharmaceutical was compared between the 1st (Sep 2004–Aug 2008) and 2nd (Jan–Nov 2012) period. [Methods] Efficacy and safety at Week 54 of treatment were compared between the 200 patients in the 1st period (age 63.3±16.6, disease duration 3.5±5.23, CRP 2.6±2.8 mg/dL, DAS28-CRP 5.1±5.2) and the 46 patients in the 2nd period (age 57.0±13.7, disease duration 4.9±5.7, CRP 1.9±2.0 mg/dL, DAS28-CRP 4.7±0.9). [Results] The DAS28-CRP scores improved to 2.2 and 2.0 in the 1st and 2nd period (LOCF), respectively. The ratios of patients in the 1st and 2nd periods were as follows: continued on IFX treatment, 70.5% and 52.2%; withdrawn IFX, 4.5% and 10.9%; discontinued as nonresponders, 10% and 6.5%; and of hospital transfer, 4.5% and 8.7%; respectively. The DAS28-CRP scores at IFX-withdrawal after deep remission for ≥6 months were 1.2 and 1.4 in the 1st and 2nd period, respectively. In the 2nd period, the poor responders who discontinued the treatment as nonresponders were 6.5% and who increased the dose were on treatment through Week 54 (8.7%). [Discussion] Early diagnosis, early treatment and tight control with IFX may enable remission and withdrawal of IFX. The data at Week 78 will also be presented.

P1-049

Efficacies of Golimumab 100mg on patients with BIO switch from TBCR data

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Conflict of interest: None

Objectives: We investigated efficacies of Golimumab (GLM) 100mg as initial dose on rheumatoid arthritis (RA) patients with Biologics (BIO) switch using Tsurumai Biologics Communication Registry (TBCR). **Methods:** In 51 RA patients who were completed with GLM treatment during 52 weeks from 87 patients registered to GLM treatment in TBCR, we evaluated efficacies of 100mg as initial GLM dose on 28 patients with BIO switch. **Result:** In 10 patients treated with GLM 100mg as initial dose, anti-TNF drugs or other biologics as previous biologics were treated to 6 and 4 patients respectively. The reasons for withdrawn were 9 patients with insufficient efficacy and a patient with other. DAS28-ESR was decreased significantly (p=0.022) from 4.8±1.9 at baseline to 3.8±1.7 at 16 weeks. These efficacies of GLM 100mg were not affected by MTX combination or prior biologics exposure. **Conclusions:** These results suggested that GLM 100mg as initial dose on RA patients with BIO switch was useful. However, it is necessary to consider its adaptation, because these were some patients who were showed limited efficacy during treatments comparing with GO-AFTER.

P1-050

Clinical evaluation of low dose etanercept therapy (25mg/2week vs. 25mg/week) in rheumatoid arthritis at 1 year follow-up

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Conflict of interest: None

[Objectives] To investigate the clinical evaluation of low dose ETN therapy in RA at 1 year [Methods] RA patients who were started either 25mg/2w (28pts) or 25mg/w (22pts) ETN therapy were evaluated at 1 year. The mean ages, disease duration, DAS28-CRP (25mg/2w: 25mg/w) were 57.4: 60.6 years, 9.3: 10.1 years, 4.03: 4.16, respectively. Persistency, DAS28-CRP and EULAR response criteria were evaluated. The dose was allowed to reduce to 25mg/3w or increase to 25mg/w. Endpoint was set as discontinuance or increase to 50mg/w. LOCF method was used for evaluation. [Results] Increase to 25mg/w in 25mg/2w group was observed in 43%. Although persistency of both groups under the dose of 25mg/w were not significant (86%: 64%), persistency under the dose of 25mg/2w was significantly high in 25mg/2w group (43% vs. 18%). DAS28-CRP, Disease activity (R/ L/ M/ H) and Good + Moderate responses of both groups were not significant (2.90: 2.62, 39/ 4/ 39/ 18%: 45/ 14/ 32/ 9% and 68%: 73%). [Conclusion] There was no significant difference between 25mg/2w and 25mg/w therapy at 1 year. However, the persistency under the dose of 25mg/2w was significantly high in 25mg/2w group. Because only few cases were tried to reduce the dose, there is a possibility that some cases in 25mg/w were able to control by 25mg/2w.

P1-051

Instructional issues and their countermeasures of self-injection when choosing a device of etanercept injection

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Conflict of interest: None

[Objectives] We examine their countermeasures of self-injection

when changing a device of etanercept (ETN) injection from a syringe to a pen-type formulation. [Methods] We examined 27 RA patients who previously conducted self-injection with a syringe formulation of ETN but changed the formulation to a pen-type. The nurses in charge instructed and recorded at the time of the device change and then conducted the retrospective study based on the recorded contents after confirming the self-injection status a month later. [Results] After a month, 19 patients (28-78 y/o) successfully acquired the instructional procedure although 7 patients (44-80 y/o) failed to do so. After 1-2 months, 12 patients (63.2%) returned to a syringe formulation due to their request. The reasons why they had a difficulty to use a pen-type were... "Can not press a injection button well because a syringe is sunk into abdominal skin", "Desire to have an injection in abdominal region due to a strong pain in femoral region", and "Can not press an injection button because it is too tight to press". [Conclusion] A fear reduction and easy-usage of self-injection could be important to improve QOL of RA patients, but it also needs a device selection with consideration of patient's physical characteristics.

P1-052

Survey of awareness on RA remedy in patients treated with biologics

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Conflict of interest: None

[Objectives] To investigate awareness of rheumatoid arthritis (RA) remedy in patients treated with biologics (Bio). [Methods] RA patients treated with Bio at our department was surveyed using questionnaire. [Results] Distribution rate of questionnaire was 75.2% (218 of 290) and collection rate was 98.6% (215 of 218). Age of responders was 61.2±14.0 y and disease duration was 12.0±10.0 y. Information source of Bio therapy; doctor 84.7%, other medical staff 4.7%. Better communication while Bio therapy; with doctor 43.3%, with nurse 44.2%. Knowledge of RA treatment: 1) T2T; comprehensible 5.1%, knowing to some extent 20.5%. 2) disease activity indices; comprehensible 2.3%, knowing to a certain degree 15.3%. 3) remission as goal; comprehensible 20.9%, knowing to some extent 31.2%. Cost and benefit of Bio; expensive but outcome is compensative 66.0%. Estimation of Bio therapy; very beneficial 52.6%, beneficial to some extent 29.8%. Stopping Bio after remission; continue Bio because of risk of exacerbation 66%, stop Bio if possible 8.8%, difficult to decide at present 32.1%. Recommend Bio to others; yes 87%. [Conclusion] Estimation of Bio therapy by RA patients is good. More education of RA remedy for patients is needed. Accumulation of evidence and providing information on Bio free is expected.

P1-053

The evaluation of the pain and satisfaction of the subcutaneous injection of biologics for rheumatoid patients

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Conflict of interest: None

[Objectives] To investigate the pain and satisfaction of the subcutaneous injection of biologics for RA patients. [Methods] The questionnaires were conducted in 42 RA patients. Twenty patients were treated with etanercept (ETN), 10 patients were treated with adalimumab (ADA), 12 patients were treated with golimumab (GLM). The main contents of the questionnaires were the degrees of pain of the injection of drug, the place where the patients wanted to be injected, and the satisfaction rate with 5 levels (1~5) for each biologics. The degrees of pain were evaluated with visual analog scales (VAS). DAS28-CRP was used for evaluation of the disease activity. [Results] The pain during the injection of ADA was significantly stronger based on VAS than that of ETN and GLM. No correlations were observed between pain of the injection and satisfaction rate, and between DAS28 and satisfaction rate. More than 80% of patients were satisfied with each biologics. [Conclusion] In this study the pain of the injection of ADA was significantly stronger based on VAS than ETN and GLM. One of the reasons of the stronger pain of the injection of ADA may be the lower pH of the liquid of drug which is reported by the company.

P1-054

Comparative drug retention rates of biological treatment options after etanercept failure in rheumatoid arthritis

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Conflict of interest: None

[Objectives] Optimal treatment for rheumatoid arthritis (RA) after etanercept (ETN) failure remains uncertain. We investigated retrospectively to compare the continuation of biological agents (BIO) after ETN failure. [Methods] Among RA patients who were registered in the TBC Registry (TBCR) of the Nagoya University, this study focused on comparison of the continuation among tocilizumab (TOC), abatacept (ABT) and golimumab (GOL) after ETN failure in patients for whom follow-up observation was possible for 52 weeks or more. [Results] 104 cases after ETN failure were available for analysis, 49 with TOC, 49 with ABT, and six with GOL, and 52-week adherence was respectively 83.7%, 71.4%, and 83.3%. In 83 cases of inadequate response to ETN, there were significant highly retention rates with TOC and GOL. On the other hand, in 16 cases of adverse events for ETN, the retention rate with ABT was relative high. [Conclusion] Selection of BIO after ETN failure was influenced with reasons of the discontinuation of ETN. When there was inadequate response to ETN, TOC and GOL were selected. On the other hand, ABT was selected in many cases to adverse events for ETN. Although it was not a randomized prospective study, we could confirm trends of BIO selection after ETN failure.

P1-055

Histological changes of synovium after biologics treatment for rheumatoid arthritis (RA)

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Conflict of interest: None

[Objectives] We examined histological changes of synovium before and after biologics treatment for rheumatoid arthritis (RA). **[Methods]** The paraffin embedded synovium were obtained from 20 RA patients. Each patient took biologics after DMARDs treatment. We examined histological and immunohistochemical changes of synovium before and after treatment by DMARDs or biologics, respectively. **[Results]** The inflammatory score such as the number of synovial lining cells, blood vessels and inflammatory cells decreased more massive after treatment by biologics than DMARDs. In addition, the number of positive cells of MMP-3, TNF α, TNFR-I, TNFR-II, CD68 and CD34 decreased more massive after treatment by biologics than DMARDs, too. Especially, the effect of the biologics was massive in non-responder of DMARDs. **[Discussion]** By using histochemical examination, the results suggest that biologics have stronger anti-inflammatory effects especially in non-responder of DMARDs. **[Summary]** Histologically, biologics suppress the synovial inflammation even in refractory RA.

P1-056

The short-term efficacy of -certolizumab pegol in rheumatoid arthritis patients with prior failure of biological therapy

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Conflict of interest: None

[Objectives] To examine the efficacy of 3-month administration of certolizmab pegol (CZP) in patients with active rheumatoid arthritis (RA), who had one or more kinds previous biologics use. [Methods] In this 3-month, multicenter, retrospective study, 21 RA patients previously failing >1 biologics were included in this analysis. CRP, ESR, MMP-3, DAS28-ESR and HAQ were determined at baseline (before use of CZP) and after use of CZP (3 months). [Results] Ten of the patients achieved a good or moderate response, wheres 6 patients showed no response. Four patients had to stop CZP by 3 months from baseline due to adverse effect, such as bacterial pneumonia or allergy. [Conclusion] This small case series suggest that CZP might offer a good biological swiching option for the treatment of RA with failure of biological therapy.

P1-057

Efficacy of Infliximab and steroid reduction in patients with rheumatoid arthritis

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Conflict of interest: None

[Objectives] Efficacy of Infliximab and steroid reduction in patients with rheumatoid arthritis were studied. [Methods] 100 rheumatoid patients have been treated with Infliximab and methotrexate for average of 42 months. [Results] Remmision rate was 48% and steroid reduction was achieved in 84% patients. [Conclusion] Infliximab was usefull for achievment of remmition and steroid reduction.

P1-058

Intensive therapy of infliximab in patients with rheumatoid arthritis

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Conflict of interest: Yes

[Objectives] To analyze efficacy and safety of infliximab (IFX)-intensive therapy in RA patients who had not responded to conventional IFX therapy. [Patients] Six males and 23 females, with a mean age of 58.0 years and mean disease duration of 8.12 ± 11.0 years, were studied. MTX dose: 7.4 ± 1.5 mg/w, DAS28-ESR4: 5.60 ± 1.08. High disease activity: 19, moderate disease activity;10 [Results] 1) Short interval therapy; 5, High dose IFX therapy; 9, Combination; 15. 2) EULAR Good response (GR); 11, Moderate response (MR); 7, No response (NR); 11. 3) Nine NR cases in IFX-therapy were changed to adalimumab (ADA), etanercept (ETN) or tocilizumab (TCZ). Both ETN and TCZ led to GR or MR, while ADA was ineffective. Three patients administered ADA were changed to TCZ (2) and abatacept (1). TCZ showed MR. 4) Antibody to IFX was detected in some NR patients. 5) Adverse events: Cerebral infarction; 1, Herpes zoster; 2, pneumonia; 1, Bacterial infection of pulmonary cyst; 1 [Conclusion] It is suggested that intensive IFX therapy could be a useful strategy for conventional IFX-resistant RA.

P1-059

Two cases with sarcoidosis developing during anti-TNF therapy in patients with rheumatoid arthritis (RA)

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Conflict of interest: None

Case1 (57F): Adalimumab (ADA) was administered for treatment for RA. After 13 months, bilateral hilar lymphadenopathy (BHL) was found. The diagnosis of sarcoidosis was made and BHL diminished after ADA was withdrawn. Abatacept (ABT) was initiated and switched to tocilizumab (TCZ). In these 30 months, arthritis has been controlled without recurrence of sarcoidosis. **Case2 (65F):** Methotrexate (MTX) and etanercept (ETN) were administered for treatment for RA. After 15 months, she was affected pyelonephritis. On MRI imaging, mediastinal lymphadenopathy and several nodules in kidney and right thigh were detected. After withdrawal of ETN, these findings diminished and no further investigation was not done. ETN was restarted later. After 51 months of ETN treatment, BHL and pulmonary nodules were appeared on chest X-ray. PET-CT demonstrated multi-disseminated hot spots in her brain, mediastinum, lungs, intra-abdominal lymphadenopathy and right thigh. The diagnosis of sarcoidosis was made histologically by lung biopsy. Those findings have been under careful follow-up after ETN was withdrawn. **Clinical significance:** During anti-TNF treatment for RA, sarcoidosis can develop due to cytokine unbalance for granuloma formation. Rheumatologist should aware of this rare paradoxical phenomenon.

P1-060

Gender difference of clinical efficacy, activity of the daily life, quality of life and depression scale in rheumatoid arthritis treated by biologic therapy

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Conflict of interest: Yes

Objectives. To elucidate between gender difference and biologic agents in terms of their efficacy and their effects on the ADL, QoL and depression in RA patients. Methods. One hundred sixty-one patients (139 females, 22 males) were assessed prior to treatment and 30 weeks after initiating the biologic therapy. The SDAI score, the ADL (mHAQ), the QOL (SF36) and the depression scale (HAM-D) were administered to the patients. All dates were analyzed by mean of the repeated measure ANOVA. Results. After 30 weeks of administration, the SDAI scores changed from 22.1 ± 11.9 to 8.9 ± 7.8 (females) and from 27.9 ± 11.7 to 12.7 ± 8.6 (males), the mHAQ scores changed from 0.46 ± 0.50 to 0.32 ± 0.45 (females) and from 0.57 ± 0.49 to 0.43 ± 0.63 (males), HAM-D scores changed from 6.2 ± 4.8 to 3.8 ± 4.1 (females) and from5.6 ± 3.9 to 4.8 ± 3.9 (male), respectively. Although the SDAI and general health and mental health of SF-36 were significant difference between female and male, the other categories were not significant improvement. Conclusion. In this study, limited categories of the QOL and SDAI were significant difference between female and male by biologic agent treatment in RA. No other categories were significant improvement as common in males as in females.

P1-061

Infliximab treatment to the rheumatoid arthritis for ten years in our hospital

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Conflict of interest: Yes

[Objectives] After beginning of clinical application of infliximab to rheumatoid arthritis, ten years passed. In 39 patients with more than 2 years treatment of infliximab (240 patients year), course of treatment and effectiveness and prognosis were examined. [Results] In 19 patients with continuous treatment of inliximab for 24 to 120 months (an average of 68.6 months), all patient's disease activities improved, and remission was attained by 11 patients and the low disease activity and better was attained by 14 patients. The improvement of mHAQ was obtained in all patients. Nine patients required the switch from infliximab among 39 patients. The stopping of infliximab was tried to 11 patients among 39 patients. Bio free was attained in eight patients. The patients who can not stop infliximab treatment have a long disease duration, and possibility of

bio free are not associate with the disease activity, a serological activity and duration of inliximab treatment. Among 43 examples which introduced infliximab, one patient died by pneumonia. [Conclusion] By the treatment by infliximab over a long period of time, the more than half patients could maintain the improvement, and 1/5 patients could attain bio free, and the validity over a long period of time was shown.

P1-062

The efficacy and retention rate of biologics in our hospital; 2014 edition

Junichi Fujisawa[1], Naoki Kondo[2], Masaaki Nakano[3], Takeshi Kuroda[3], Shuichi Murakami[3], Yoko Wada[3], Takeshi Nakatsue[3], Hiroe Sato[3], Katsumitsu Arai[4], Takahiro Netsu[5], Naoto Endo[2]
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Conflict of interest: None

[Objectives] To examine the efficacy and retention rate of biologics in our hospital. [Methods] 425 patients who started to treat biologics between May, 2001 and August, 2013, were included in this study. The average age was 55.7. The average follow-up period was about 2.5-year. They were subdivided as follows; Infliximab (IFX); 56, Etanercept (ETN); 68, ETN+Methotrexate (MTX); 129, Tocilizumab (TCZ); 94, Adalimumab (ADA); 47, Abatacept (ABA); 17 and Golimumab; 11, and DAS28 (3)-CRP values on introduction and 6 months after were compared to examine their efficacies. In addition, Kaplan-Meier survival rates were plotted to determine retention rate for each group. [Results] DAS28 (3)-CRP value on introduction was 4.35 in IFX, 3.94 in ETN, 3.91 in ETN+MTX, 4.04 in TCZ, 3.08 in ADA, 3.48 in ABA and 3.52 in GLM group, respectively. Then 6 months after, each value was 2.79, 2.63, 2.33, 2.33, 2.25, 2.26 and 2.49. The retention rate 1 year after was 72.8% in IFX, 81.4 % in ETN, 82.4% in ETN+MTX, 80.3% in TCZ, 65.2% in ADA, 71.2% in ABA and 52.6% in GLM group, respectively. The retention rate 2 years was 60.6, 75.0, 76.4, 74.6, 56.0 and 70.6, respectively (exclude GLM). [Conclusion] These findings suggest that each group showed almost the same efficacy in DAS28 (3)-CRP.

P1-063

Investigation of radiographic remission in biologic-free patients with rheumatoid arthritis after discontinuation of infliximab

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Conflict of interest: None

Objectives: We investigated the potential of radiographic remission in biologic-free patients (maintained with clinical remission) with rheumatoid arthritis (RA) after discontinuation of infliximab (IFX). Methods: Eleven patients (including the discontinuation in the adverse event (AE)) with RA were investigated by clinical evaluation (DAS28CRP, SDAI) and radiographic evaluation (mTSS ≦ 0.5). Results: Baseline characteristics of patients were followings, 7 patients with discontinuation after clinical remission, 4 patients with discontinuation after AE, mean age was 53 years, mean duration of disease was 4.3 years, mean administration of IFX was 1.3 years, mean of MTX dosage was 8.1mg/week, and mean of DAS28 and SDAI before discontinuation of IFX were 1.32 and 1.48. Duration of observation was 1~5 years (average 2.8 years). After one year later stopping IFX, mean of DAS28 and SDAI were 1.47 and 2.37. At the last observation, DAS28 and SDAI were 1.34 and 1.53, and the rate of DAS28 and SDAI remission rate were 100% and 81%. The rate of MTX combination decreased to 63.6% (average 11.6mg/week), but all patients were maintained with radiographic remission. Conclusion: It is suggested that deep clinical remission after discontinuation of IFX leads to radiographic remission.

P1-064

Clinical usefulness of adalimumab based on Bio treatment history, duration of RA, and dose of concomitant MTX ~ Remission induction and treatment continuation at 52 weeks in 124 patients ~

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Conflict of interest: None

[Objectives] Clinical usefulness and treatment continuation following 52 weeks of adalimumab (ADA) in rheumatoid arthritis (RA) patients were investigated. [Methods] Subjects were 124 analyzable patients introduced to ADA at the author's institution from May 2009 to October 2012. Mean age was 53 years, mean duration of illness 7.2 years. 35 patients had a duration of illness below 2 years (<2 group) and 89 at least 2 years (≥ 2 group), 85 were Bio Naive (N group), 39 were Switch (S group), 95 received MTX ≥10 mg/week (≥10 group) and 24 MTX<10 mg/week (<10 group). There was no significant difference in baseline disease activity. [Results] Overall DAS28 (CRP) remission rate showed clinical remission in 40% of patients from 4 weeks. Changes in DAS 28 (CRP) remission rates for the <2 and ≥2 groups were similar to those seen in the N and S groups, but differed from those in the ≥10 and < 10 mg groups. Overall HAQ remission rate at 52 weeks was 82%; treatment continuation rate was 72%. MTX concomitant treatment response rate was 90%. [Conclusion] Remission was induced early with ADA in about 40% of patients. ADA plus an adequate dose of MTX in early-stage RA and Bio Naïve patients is the best approach to maximally exploit the ADA potential.

P1-065

Clinical Usefulness of Adalimumab in High Disease Activity RA Patients ~Remission Induction Rate at 24 weeks in 49 Patients~

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Department of Internal Medicine and Rheumatology, Seirei Hamamatsu General Hospital, Hamamatsu, Japan

Conflict of interest: None

[Objectives] Clinical usefulness of 24-week adalimumab (ADA) treatment in high disease activity (HDA) RA patients (DAS28ESR>5.1) was investigated over time. [Methods] Subjects were 49 analyzable HAD RA patients that were introduced to ADA treatment at this institution from May 2009 to April 2013. Mean age was 59 years, mean duration of illness 7.8 years, rate of concomitant MTX use 92% (mean dose of 10.8 mg/week), and mean DAS28ESR (DAS) 6.1. Efficacy of ADA treatment after 24 weeks was comparatively investigated in each group, namely, the Bio Naïve (N group) and Switch (S group), duration of illness below 2 years (<2 group) and ≥ 2 years (≥ 2), MTX ≥10mg/week (≥10 group) and <10mg/week (<10 group). [Results] At 24 weeks, DAS remission rate in the overall patients was 37% with significantly high efficacy for the N and <2 groups, and a high tendency for the ≥10 group. At 24 weeks, HAQ remission rate for the overall patients was 77%, which was good. [Conclusion] Good responsivity was achieved with ADA even in HDA· RA patients. In particular, it was demonstrated that the potential of ADA can be exploited maximally producing better treatment efficacy when it is given concomitantly with an adequate dose of MTX to early onset and Bio Naïve patients.

P1-066

Six Year Experience of Rheumatoid Arthritis Circulatory Regional Collaboration-Pathway for treatment of RA

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Conflict of interest: Yes

[Objectives] Since September 2007, we have used the RACRC-Path: Rheumatoid Arthritis Circulatory Regional Collaboration-Pathway, and used electronic medical record reference system which can browse record

from collaboration hospitals. We report the six year summary. [Methods] For 46 hospitals and 78 patients, the RACRC-Path was applied as a tool of biologic and non-biologic DMARDs in convenience for patients and physicians. [Results] Collaborating hospitals are situated close to RA patients, after induction phase of biologics, they can take care of patients. Collaboration hospitals have used electronic medical record reference system to browse RA patients record from our Medical Record for 4 years. [Conclusion] Critical pathway and electrical connection can be useful for rheumatoid arthritis characteristics.

P1-067

Safety of shortened infliximab infusion times in rheumatoid arthritis and other rheumatic diseases

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Conflict of interest: None

[Objectives] Infliximab (IFX) is the only intravenous TNF-alpha antagonist. Accelerated IFX infusion were officially approved in May 2012 in Japan. In this study, we investigate the safety of shortened IFX infusion times in patients with rheumatoid arthritis (RA) or other rheumatic diseases. [Methods] The patients who completed IFX infusion without any infusion reaction (IR) at least 3 times and gave informed consent were allowed to shorten infusion times. [Results] 364 shorter IFX infusions in 50 patients (36 RA, 12 Behcet's disease, 1 psoriatic arthritis, 1 relapsing polychondritis) were observed in a total of 489 IFX infusions in 59 patients from May 2012 to October 2013. Although a RA patient experienced minor IR with erythema on the back and upper extremities, IFX infusion could be continued in the patient by using anti-allergy medication routinely. [Conclusion] Infusion time of IFX can be safety shortened in patients with other rheumatic diseases as well as rheumatoid arthritis.

P1-068

Clinical outcome of golimumab in patients with rheumatoid arthritis who discontinued prior biologics from TBC registry

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Conflict of interest: None

[Objectives] To assess GLM therapy in biologic switcher in rheumatoid arthritis [Methods] On our biologic study group (TBC), there were 31 cases which were enrolled to have been given GLM and switched from other biologics. Previous biologics treatment could have been discontinued for any reason. [Results] The mean of disease duration were 15.0 years and the proportion of MTX-treated patients was 52% (16/31). With regard to prior biologics, there were most patients switched from IFX (n=12). In entire switcher group, the mean of DAS-ESR was 4.54 at baseline and 3.81 at week 24, and there was significantly improvement. At week 24 as an endpoint, drug retention rate in whole switcher group was 84%. In patients switched from IFX (n=12) and ETN (n=8), there were not significantly improvement of DAS-ESR from baseline (3.54, 5.41, respectively) to week 24 (3.07, 5.01). In patients with low disease activity (DAS-ESR<3.2) at baseline, low disease activity was maintained until week 24. [Conclusion] GLM reduced disease activity of rheumatoid arthritis in patients who had previously received biologics and drug retention rate was good. That may be influenced by kind of prior biologics.

P1-069

The predictor analysis for good responder to dose escalation of infliximab (IFX) in the treatment of rheumatoid arthritis (RA)

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Conflict of interest: None

[Objectives] The retrospective study was conducted to predict the response toward the dose escalation of IFX in the treatment of RA. [Methods] The IFX dosage was increased in 15 bio-naïve RA patients (12 female, 54±12 yo) whose response was incomplete after the first 14 weeks of therapy (DAS28ESR>3.2). Based on the continuation of IFX therapy at the 104 week, patients were divided into continuous (C; N=7) or discontinuous group (D; N=8). [Results] The IFX dosage (mg/kg) was similar at the first infusion (C; 3.4, D; 2.9) as well as at the dose escalation (C; 5.1, D; 4.6). No significance of DAS28ESR value was observed at the start point (C; 6.1, D; 6.1), 14 weeks later (C; 4.5, D; 4.4), and the dose escalation date (C; 4.5, D; 4.9), but the value at 8 weeks after the increase was significantly higher in D group (C; 3.6, D; 5.0, p=0.036). The increase rate of DAS28ESR during this period was 0.86 (C) and -0.15 (D), and 87.5% of patients with >0.4 of the rate were supposed to see the long term efficacy of IFX. Time to dose escalation was also shorter in D group (C; 52, D; 22 weeks). [Conclusion] The DAS change rate is useful to predict the effect of increased IFX dosage. If the first response after the increase may be insufficient, the treatment strategy should be reconsidered quickly.

P1-070

Predictors for achieving sustained remission after discontinuing biologics

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Conflict of interest: None

[Objectives] To find predictors for achieving sustained remission after discontinuing biologics in RA patients. [Patients and methods] 181 patients who started biologic treatment at our hospital before October 2012 were enrolled: infliximab (IFX, n=54), etanercept (ETN, 41), adalimumab (ADA 26), tocilizumab (TCZ, 40), and abatacept (ABT, 26). Patients who have achieved either Boolean or SDAI remission for 1 year or more, extended administration intervals and then discontinued. Laboratory results were compared between patients who were able to stay without using biologics over 6 months (F group) and patients who failed to extend admission intervals (non F group). [Results] Biologics used in each group are as follows: F group (IFX; n=6, ETN; 0, ADA; 1, TCZ; 4, ABT; 1) and non-F group (IFX; n=2, ETN; 6, ADA; 2, TCZ; 14, ABT; 1). As of October 2013, the average bio-free duration for F group was 1.3 years (6mo-2.1yr). Significant differences were observed in RF normalization and IgM normalization between the groups. Among these agents, IFX had the highest rate of achieving bio-free remission. [Conclusions] Achieving deep remission for a certain period of time, RF normalization and IgM normalization were determined as predictors for accomplishing bio-free remission.

P1-071

Pain assessment for subcutaneous injection of biologics in the treatment of rheumatoid arthritis

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Conflict of interest: None

[Objectives] To evaluate the severity of subcutaneous (sc) injection-related pain in patients receiving biologics via these injections. [Methods] The visual analogue scale (VAS) scale was used to assess the impact of the sc injection-related pain. The VAS is a 10-cm horizontal line with pain descriptors. Etanercept (ETN), adalimumab (ADA), and golimumab (GOL) were the selectable drugs that the patients received at present and/or in the past, and sc of influenza vaccination (IV) was used as a control. [Results] A total of 149 rheumatoid arthritis (RA) patients participated in this study. The number of patients who provided VAS scores for IV, ETN, ADA, and GOL injections was 149, 78, 74, and 25, respectively. The VAS scores (mean, median, IQR) were as follows: IV, 31.9, 30, 16-45; ETN, 41.6, 41, 24.75-57; ADA, 55.7, 54.5, 35.5-80.25; and GOL, 29.5, 33, 13.5-40.5. Injections of GOL seemed to be the least painful. [Conclusion] Patient-orientated evaluations of pain caused by sc injections showed that injections of GOL caused less pain than those of the other biologics. Although evaluations of injection-associated pain differ with each patient, more comfortable sc injections are necessary to improve patient convenience and increase compliance with RA treatment.

P1-072

Investigation of serum matrix metalloproteinase 9 (MMP-9) levels in rheumatoid arthritis patients treated with infliximab: from the viewpoint of cardiovascular event risk

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Conflict of interest: None

[Objectives] Matrix metalloproteinase 9 (MMP-9) is a risk factor for cardiovascular events. We mesured the serum MMP-9 level (sMMP-9) in rheumatoid arthritis (RA) patients and analyzed the effects of an anti-TNF-α antibody, infliximab, on the sMMP-9. [Methods] The sMMP-9 were measured before and after treatment with infliximab (IFX; 3 mg/kg) in 18 RA patients. [Results] The average sMMP-9 was 203.1 ng/ml before treatment with IFX in RA patients (normal range: less than 43.8 ng/ml). In 12 patients whose sMMP-9 were measured at 2 weeks after treatment with IFX, sMMP-9 2 weeks after treatment was significantly lower than before treatment (161.7±25.2 ng/ml vs 238.5±25.7, P=0.043). However, there was no significant change in sMMP-9 between before and 2 years after treatment with IFX (180.2±19.5 ng/ml). The results suggest that cases with little sMMP-9 reduction are resistant to IFX treatment. There was no significant correlation between the changes in sMMP-9 and the changes in the RA disease activity indicators including sMMP-3. [Conclusion] The sMMP-9 were high in RA patients with active disease, and were reduced by IFX independently of the reduction in disease activity. Thus, IFX may reduce the risk of cardiovascular events directly in the early course of treatment.

P1-073

Efficacy and safety of Golimumab therapy in patients with rheumatoid arthritis in Juntendo University hospital

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Conflict of interest: None

【Objective】To evaluate the efficacy and safety of golimumab (GLM) therapy in patients with rheumatoid arthritis (RA).【Methods and Patients】56 patients were started to receive subcutaneous injections every 4 weeks of GLM since Oct. 2011. The remission rate of DAS28-CRP, persistence rate and progression of joint distraction by Genant-modified Sharp scoring were examined.【Results】Among all patients, 91% were female, the mean age was 52.1±13.6 years, disease duration was 8.5±7.3 years. 91% of all was treated with concomitant methotrexate (MTX). Bio naïve was treated with MTX mean dose 10.2mg/W, on the other hand bio-switch was treated with MTX 5.9mg/W. Persistence rate of bio-naïve was 82.4% at 52 weeks. The mean score of DAS28 at baseline, week 4,12 and 52 were 3.9±1.2, 2.7±1.0, 2.4±1.1, 2.1±0.8. 61.5% of Bio-naïve patients achieved DAS28-CRP remission at week 52, bio-switch patients achieved DAS28 remission at only 28.6%. Genant-modified Sharp scoring system delta score is 1.73±2.58. Plegmone and pneumonia were detected in two patients, respectively.【Conclusions】For patients with long duration RA, GLM therapy was continuously effective from the early weeks to 52 weeks. Bio-naïve had greater effect than bio-switch in DAS28-CRP remission rate and persistence rate.

P1-074

The long-term efficacy and safety of golimumab (GLM) in patients with rheumatoid arthritis (RA)

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Conflict of interest: None

[Objective] We assess the long-term efficacy and safety of GLM in active RA patients with no history of biologic use (naïve group) and with prior biologics therapy (switch group). [Methods] Seventeen RA patients with GLM therapy continuously for more than 3 months were enrolled. Their mean age was 66 years old and average disease duration was 14.4 years. Naïve and switch groups included 5 and 12 cases, respectively. We evaluated for clinical efficacy and safety of GLM from baseline to month 12. [Results] The disease activity parameters resulted in remarkable decreases after 12 months with GLM treatment. After 12 months, the CRP, DAS28CRP and MMP-3 values had significantly improved (to 0.4, 1.7 and 87, respectively). Also, after 6 to 12 months, remission rates (SDAI and Boolean) were increased from 31% to 38% and from 31% to 50%, respectively. There was no significant difference between patients with the naïve and switch groups in the clinical efficacy. And, the retention rate of GLM therapy was 92% (n=12) at month 10. Only one patient had discontinued treatment because of allergic dermatitis. [Conclusion] GLM therapy appears to be highly effective and well tolerated during clinical treatment of active RA. And, GLM was also very useful to patients with a history of biologics therapy.

P1-075

The combination effect of Golimumab (GLM) and MTX in the RA patients

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Conflict of interest: None

[Objectives] The combination effect of Golimumab (GLM) and MTX in the RA patients. [Methods] Background of 46 RA patients who introduce GLM were as follows; mean age 60.2 years, sex ratio (male/female) 7:39, mean disease duration 12.4 years, mean DAS28-CRP 3.99, mean SDAI 17.12 at before GLM administration. 84.5% patients were used MTX and mean dose was 7.95 mg/weeks. Mean PSL dose was 3.1 mg/day and 50% patient was used PSL. We analyzed the difference of effectiveness in MTX dose with GLM. [Results] DAS28-CRP and SDAI were rapidly improved to 2.67 and 7.86 respectively at 2 weeks after GLM introduction. Although a little improvement effect was recognized, the obvious effectiveness of GLM was not seen in cases without MTX. DAS28-CRP and SDAI were improved to 2.69 and 6.92 respectively at 2 weeks after GLM administration in low dose MTX (2-4 mg/week). No clear difference was recognized in the combination therapy of GLM and three MTX administration groups; less than 6 mg/w, less than 10 mg/w and more than 10 mg/w. [Conclusion] Possibility was indicated that combination therapy of GLM and MTX is independent from MTX dose. In order to evaluate the long-term effect and joint damage prevention effect in the non-dose-dependency of MTX, further study would be necessary in future.

P1-076

Therapeutic effects according to an infliximab (IFX) dose escalation protocol

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Conflict of interest: None

Objectives: After dose increase of IFX in RA was approved also in Japan in July 2009, there have been many reports on the efficacy & safety at high doses but only a few on the dose increase due to the disease activity. We report the therapeutic effects of IFX in the dose escalation protocol based on SDAI. Methods: In IFX induction & maintenance cases assessed by SDAI since April 2012, the dose in moderate or high SDAI cases increased to 6 mg/kg in the 3 mg/kg group and 10 mg/kg in the 6 mg/kg group. When the remission or LDA continued for 6 months after the increase, IFX decreased by 3 mg/kg and was withdrawn in the 3 mg/kg group. Results: 28 RA patients were treated for 52 weeks by this protocol. The mean SDAI at Week 52 decreased to 8.8, compared with 15.3 at registration. At Week 52, 25% had SDAI remission and 39.3% had LDA status. The continued IFX therapy rate after 52 weeks was 79.2%, except 4 withdrawn cases (ADRs: 3, switch to biotherapy: 1, changing hospital: 1). Joint echography was conducted in the SDAI remission cases and the imaging confirmed good finding in the remission-maintaining cases. Conclusion: Dose escalation of IFX according to this protocol is considered to improve the clinical efficacy and increase the continued therapy rate without increasing ADRs.

P1-077

The induction of low disease activity and drug-free remission by golimumab in patients with rheumatoid arthritis

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Conflict of interest: None

[Objectives] The aim of this study is to evaluate the efficacy of golimumab (GLM) for patients with rheumatoid arthritis (RA). [Methods] The 11 patients with biologics-naïve RA were enrolled in this study. Patients with methotrexate (MTX) and without MTX were 6 and 5 cases, respectively. Disease activity {(disease activity score (DAS28)-erythrocyte sedimentation rate (ESR), simple disease activity index (CDAI)} and HAQ-DI were assessed until 52 weeks after GLM administration. [Results] Disease duration and baseline disease activity (DAS28-ESR) were 13.8 years and 5.37, respectively. DAS28-ESR was decreased from 4.82 to 2.71 (GLM+MTX group) and 6.03 to 2.95 (GLM alone). Furthermore, SDAI was decreased from 26.43 to 8.60 (GLM+MTX group) and 32.22 to 11.18 (GLM alone). In addition, HAQ-DI was also significantly improved after GLM administration. After 112 weeks, 5 RA patients were discontinued of GLM, and maintained low disease activity and remission in patients with RA. [Conclusion] The present study suggests that GLM alone or in combination with MTX can induce good clinical improvements in patients with RA. Furthermore, GLM-free remission/low disease activity can be achieved in some patients.

P1-078

The efficacy and the continuation rates of the infliximab according to the increase in quantity method

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Conflict of interest: None

[Objectives] Because of approval dose escalation of Infliximab (IFX), the effect attenuation decreases. However, the quantity of escalation varies according to the judgment of each administrator in spite of the recommended method of escalation in actuality. We examined the efficacy according to the increase in quantity method. [Methods] 154 patients received IFX infusion were assigned. We divided them into 4 groups, 57 in non-increase in quantity group (maintained 3 mg/kg), 55 in full bottle increase group, 34 in one vial increase group and 8 in tight control group (6 mg/kg and 10 mg/kg) and compared the background, DAS28 and MMP-3. In addition, we examined to compare a persistency rate before and after the increase in quantity approval. [Results] In the tight control group, disease activity at introduction of IFX was higher than other groups and there were administered more MTX doses. The DAS28 improvement rate in tight control group was better from 4.83 to 1.70 than in other groups. The difference was not seen in MMP-3. The persistency rate was group 83.9% after the increase in quantity approval group and 69.1% before group, after introduction in one year. [Conclusion] We should perform tight control in following protocol for patients with the effect attenuation of IFX decreases.

P1-079

Clinical evaluation of golimumab in our department

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Conflict of interest: Yes

[Objectives] To investigate the efficacy and the adherence of golimumab in patients with rheumatoid arthritis in our department. [Patients] Four males and 18 females, with a mean age of 66.1 years and mean disease duration of 9.2 years, were studied. MTX and prednisolone were administered to 16 patients (mean 5.39mg/w) and 11 patients (mean 2.85mg/day), respectively. Ten patients were Bio-naïve. [Methods] Efficacy of golimumab was evaluated by DAS28-ESR4 at 0, 12, 24 and 52 weeks after injection of golimumab. [Results] 1) Sixteen patients (72.7%) continued receiving golimumab at week 52. Twelve of these 16 patients (75%) were concomitant with MTX and half of them were Bio-naïve. 2) The reasons for drop-out were as follows; cough and leukocytopenia, organizing pneumonia, persistent pain after injection and erythema, including 4 patients with inadequate response. 3) DAS28-ESR was significantly reduced at week 52 ($P<0.05$). EULAR response criteria: Good response; 5, Moderate response; 8, No response; 9. [Conclusion] Like other TNF blockers released earlier, it is suggested that the concomitant MTX is important to continue golimumab therapy.

P1-080

Selective factors for biologics in rheumatoid arthritis

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Conflict of interest: None

【Objectives】Currently, 7 biologics / 9 formulations have been approved for the treatment of rheumatoid arthritis (RA) in Japan. The decision to select a drug is becoming more complicated as we have more alternatives. Therefore, we conducted a survey in order to examine how the selection of biologics is being made.【Methods】We questioned 50 RA patients who were biologics naïve at our hospital.【Results】62% of patients preferred SC as route of administration. For the administration method (IV: 8wk, 4wk, SC: 2wk, 4wk), SC/4wk was the most preferred choice. The utmost priority for selecting the drug was the cost of treatment, followed by dosing interval. In addition, the necessity of treatment was higher when we compared the relative ratio among treatment costs and the necessity of treatment.【Conclusion】Many patients prefer SC as

it has a shorter duration of administration, however, this changes with the length of the dosing interval. The high cost of treatment is also an important selection factor, but this also alleviates as the patient fully understands the necessity of treatment. We must take into account the living conditions and different patient background for each formulation when choosing a biologic for the treatment of RA.

P1-081

An Analysis on Cases of Discontinuation of Biologics (Bio) due to Adverse Effects in Rheumatoid Arthritis (RA) Patients: A Retrospective Single-Center Study in Japan

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Conflict of interest: None

[Objectives] The objective of this analysis is to describe the adverse effects that resulted in the discontinuation of Bio for treating RA patients. [Methods] An observational, retrospective, single-center study was conducted on RA patients who discontinued Bio from April 2012 to October 2013. [Results] There were 10 cases (mean age 66.7 years, 7 females and 3 males) of discontinuation which included 7 cases of infection and 2 of malignancy. Cases of infection included septic arthritis (3), pneumocystis jirovecii pneumonia (2), and acute cholecystitis (1), whereas malignancy cases included colon cancer (1) and lung cancer (1). Arthrotomy and irrigation was performed for the all cases of septic arthritis. Discontinued Bio included 3 cases of tocilizumab, 3 of golimumab, 2 of abatacept, 1 of adalimumab and 1 of certolizumab. DAS28CRP was 4.7 before using Bio and became 2.8 at the point of discontinuation, showing that RA has significantly improved from moderate to low. [Conclusion] This study describes the adverse effects which resulted in the discontinuation of Bio for treating RA patients were mainly infection and malignancy. Thus, close monitoring regarding infection as well as malignancy is highly recommended.

P1-082

Influence of the reason for discontinuation of previous TNF antagonists on the retention of tocilizumab

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Conflict of interest: None

[Objectives] To investigate the relationship between the retention of tocilizumab (TCZ) and the reason for discontinuation of previous TNF antagonists in RA patients. [Methods] This study included 181 RA patients who were switched from TNF antagonists to TCZ therapy in Tsurumai Biologics Communication Registry (TBCR). The continuation rates and causes of discontinuation of TCZ were compared between two groups divided by the reason for discontinuation of previous TNF antagonists (group A: 142 patients with lack of efficacy, and group B: 25 patients with adverse events). [Results] The continuation rate after 2 years in group A (76.8%) was significantly higher compared with group B (56.0%). At the rate of discontinuation due to inefficacy, no significance was shown between the two groups (9.2% vs 4.0%). On the other hand, the rate of discontinuation due to adverse events in group A was significantly lower than group B (6.3% vs 36.0%). [Conclusion] RA patients who are switched from TNF antagonists due to lack of efficacy to TCZ have high rates of continuation.

P1-083

Significance of the serum MMP-3 in evaluation of disease activity of rheumatoid arthritis patients treated with Adalimumab and Tocilizumab

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Conflict of interest: None

[Objectives] Evaluation of the biomarker and the disease activity in rheumatoid arthritis (RA) is important. MMP-3 is considered to be a specific biomarker than CRP or ESR in synovitis. It has been also RF that not correlate with the disease activity in may biological agents. We studied the significance of MMP-3 in evaluation of disease activity in the RA treated with Adalimumab (ADA) and Tocilizumab (TCZ). [Methods] Thirty-four RA patients were treated with ADA (n=20) or TCZ (n=24) in the Kinki University Hospital. Patient's background, DAS28, SDAI, CDAI, CRP, ESR, RF, MMP-3, the number of tender and swollen joints, VAS, HAQ, and the ultrasonographic assessments before and 24 weeks after the were compared between the patients treated with ADA and TCZ. [Results] DAS28 improved significantly after 24-week treatment with both ADA and TCZ. MMP-3 levels reduced in the TCZ group, while they did not change in the ADA group. RF titers tended to reduce in the ADA group, while there was no significant difference in the TCZ group. [Conclusion] MMP-3 correlated with the disease activity in the TCZ, but not with the RF titers. These data suggest that it is important to carefully utilize biomarkers such as MMP-3 in the evaluation of disease activity during the treatment of each biological agents.

P1-084

Prospective study on the possibility of MTX cessation in RA patients who have remained remission with combination of MTX plus tocilizumab (TCZ) the second report

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Conflict of interest: None

[Objectives] To evaluate the possibility of MTX cessation in RA patients remained in remission with combination of MTX plus TCZ [Methods] 13 RA patients who have been in remission with combination of MTX plus TCZ were randomly assigned to the MTX cessation group and MTX continuation group and we evaluated the efficacy of these 2 treatment strategies prospectively at week 24. [Results] 6 were assigned to the MTX cessation group, and 7 were to the MTX continuation group. Patients' background characteristics at the randomization, the mean MTX dose was 7.1 and 6.5 mg/week, DAS28-ESR was 1.56 and 1.43 respectively. CDAI was 2.6 and 2.5 respectively. HAQ was 0.7 and 0.8 respectively. DAS28-ESR after 24 weeks was 2.35 in the MTX cessation group, and 1.68 in the MTX continuation group. Similarly, CDAI was 5.7 and 4.6. The number of the patients who were in remission was 6 in the MTX continuation group and 4 in the MTX cessation group. HAQ-DI scores of the 2 groups at week 24 were 0.7 and 0.8 respectively. s for the adverse event, 3 patients of in the MTX continuation group showed liver dysfunction, and one patient showed leukopenia, but no adverse events were seen in the MTX cessation group. [Conclusion] MTX cessastion may be possible and safer in patients in sustained remission with TCZ plus MTX treatement.

P1-085

Comprehensive efficacy evaluation in patients receiving tocilizumab therapy

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Conflict of interest: None

[Objectives] It is important to perform a comprehensive evaluation employing not only clinical and physical-functional assessments but also imaging when interpreting therapeutic responses to biological agents. We comprehensively evaluated tocilizumab (TCZ). [Subjects and Methods] This study included 20 patients receiving TCZ therapy without interruption for ³3 years among 47 treated with TCZ since November 2008 at our department. Mean age was 53 years and mean illness duration was 12.5 years. Assessment parameters included imaging evaluation by modified total Sharp score and joint ultrasonography, plus clinical and physical-functional evaluations. [Results] The DAS28-ESR showed low disease activity in 80% of patients on TCZ for at least 3 years. The proportion with structural remission (mTSS <0.5/year) at 1, 2, and 3 years of TCZ therapy was 75%, 80%, and 85%, respectively. The 3-year PD scores on joint ultrasonography were grade 0, 1, 2, and 3 in 12, 6, 2, and 0 patients, respectively. [Conclusion] TCZ treatment not only improved clinical and physical assessments but also suppressed structural deterioration. Joint ultrasonographic findings indicated suppression of disease activity.

P1-086

Extension of tocilizumab dose intervals based on serum IL-6 levels: the first report

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Conflict of interest: Yes

[Objectives] Patients with rheumatoid arthritis (RA) receiving tocilizumab (TCZ) may experience disease flare when receiving TCZ at longer intervals or discontinuing TCZ, but may control RA after restarting TCZ. Patients without flare have less active RA, normal MMP-3 levels and low IL-6 levels. We investigated whether TCZ may be given at longer intervals by monitoring IL-6 levels. [Methods] Patients with CDAI≦10 during TCZ Q4W started TCZ Q8W when serum IL-6 level was <35 pg/mL. When CDAI exceeded 10 at 2 consecutive time points, patients returned to Q4W. The primary endpoint was the percentage of patients on TCZ Q8W at week 48, the secondary endpoints were the HAQ and TSS scores. [Results] Six patients (3 men and 3 women, mean age 66.2 yrs) enrolled. The mean CDAI score was 22.5 (18-73) before TCZ, and 4.59 (1-9) before TCZ Q8W. Mean serum IL-6 was 26.7 pg/mL (15.0-34.9) before Q8W. After initiating Q8W, none had CDAI>10 at 2 consecutive time points. The mean CDAI at week 48 was 2.4 (0-12), and all patients continued Q8W for 48 weeks. Although 2 of the 6 patients had an increase in MMP-3, no patients had tender or swollen joints. [Conclusion] The results suggest that patients with less active RA and IL-6<35 pg/mL may receive TCZ Q8W to maintain low disease activity for 48 weeks.

P1-087

Transition of disease activity and persistency in tocilizumab (TCZ) therapy

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Conflict of interest: None

[Objectives] To describe early and long term efficacy of TCZ for RA patients in daily clinical practice. [Methods] Change of disease activity and drug survival were examined in 58 RA patients treated by TCZ. Changes of CDAI and SDAI were evaluated by LOCF method. Drug survival rate was calculated by Kaplan-Meier estimates. [Results] CDAI/SDAI were 25.2/27.1 at baseline. After 1, 2, 4, 8, 12, 24, 30, 36, 42, 48 months, CDAI/SDAI were 15.0/15.3, 12.7/12.7, 10.9/10.9, 9.6/9.6, 9.6/9.7, 9.3/9.8, 8.4/8.4, 8.4/8.6, 8.5/8.6, 8.1/8.1, 8.3/8.4, SDAI50/70/85 achievement rate were 34/16/2%, 52/19/3%, 64/22/5%, 79/40/5%, 79/36/14%, 78/47/14%, 81/57/17%, 81/53/16%, 79/53/16%, 81/59/22%, 81/53/21%, CDAI/SDAI remission rate were 7/7%, 5/5%, 7/7%, 7/10%, 12/17%, 10/17%, 16/21%, 12/17%, 16/21%, 19/28%, 17/22%, cumulative persistency rate were 93%, 93%, 91%, 89%, 87%, 85%, 80%, 69%, 69%, 69%, 62% respectively. SDAI50 achievement rate continued increasing until 8 months, and was maintained afterwards. SDAI70/85 achievement rate were going up until 24/42 months, CDAI/SDAI remission rate increased for 42 months. [Conclusion] In TCZ therapy, significant clinical effect was shown within 8 months, Persistency rate was good and remission rate went on rising for a long term.

P1-088

Efficacy of tocilizumab in rheumatoid arthritis patients with progressive bone lesions despite negative results for inflammatory reactions

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Conflict of interest: None

[Objectives] [Methods] Some rheumatoid arthritis (RA) patients have progressive bone lesions despite being persistently negative for C-reactive protein (CRP), an inflammatory reaction marker. Since interleukin-6 (IL-6) reportedly elevates CRP, IL-6 involvement in the RA pathophysiology of patients with persistently negative CRP may be unlikely. Herein, tocilizumab, a humanized anti-IL-6 receptor monoclonal antibody, was administered to three women and a man with RA and progressive bone lesions despite persistently negative CRP. Tocilizumab efficacy, their clinical courses and movement of cytokines (IL-6, TNF) were evaluated. [Results] Pre-treatment serum IL-6 levels were undetectable, 10, 17 and 12 pg/mL in one patient each. DAS28-ESR and CDAI results at 24 weeks after tocilizumab treatment showed a tendency for improvement in all four patients. Three followed up for 24 weeks had no further bone lesion progression. One patient can successfully remain in clinical remission without Tocilizumab treatment. [Conclusion] As tocilizumab was effective, IL-6 was assumed to play an important role in RA pathophysiology, even in patients with persistently negative CRP.

P1-089

Investigating the effectiveness of tocilizumab in patients treated with non-MTX combined therapy

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Conflict of interest: None

[Objectives] We investigate whether non-MTX DMARDs affect the effectiveness of TCZ in patients treated with non-MTX combination therapies. [Methods] We analyzed 56 TCZ-administered RA patients, 28 of which received TCZ monotherapy, and 28 of which received a non-MTX DMARDs combination therapy. We assessed effectiveness at 52 weeks by DAS28-ESR, SDAI, CDAI, and Boolean. [Results] Pre-TCZ administration background evaluation included age, disease duration, and history of prior administration of biologics and DAS28-ESR, in the monotherapy group was 56.9±12.7 years, 8.9±7.5 years, 54%, and 7.0±1.4; while in the combination group it was 58.9±13.1 years, 10.9±7.2 years, 43%, and 6.9±1.3. The 52-week remission rate between the monotherapy and combination groups were: 84.6% and 83.3% (DAS28-ESR); 28.0% and 22.7% (SDAI); 34.6% and 26.1% (CDAI); and 38.5% and 21.7% (Boolean), respectively. No difference was observed in all indices. The Boolean component completion rate at 52-weeks between the monotherapy and combination groups were, respectively, 76.9% and 87.5% (TJC≤1); 76.9% and 83.3% (SJC≤1); 46.2% and 25.0% (patient VAS≤1); and 92.3% and 87.5% (CRP≤1). [Conclusion] TCZ demonstrated high efficacy regardless of the concomitant administration of non-MTX DMARDs combination therapy.

P1-090

Evaluation of radiographic destruction after tocilizumab for rheumatoid arthritis with residual knee joint symptoms

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Conflict of interest: None

[Objectives] We investigated the effect of tocilizumab in inhibiting the knee joint damage in patients who had symptoms of swelling or tenderness. [Methods] The subjects consisted of 8 patients (14 joints) treated with tocilizumab and who had presented with symptoms in the knee joint. The change in disease activity and X-ray image of the knee joints with time up to 2 years from the start of treatment were evaluated by CDAI and Larsen grade, respectively. The change in presence/absence of tenderness or swelling with time was also examined. [Results] CDAI score improved with time, although progression of damage was observed in 2 knee joints. In patients who showed improvement in swelling at 3 months from the treatment and whose tenderness disappeared at 6 months from the treatment, inhibition effect of tocilizumab on the progression of damage to the knee joint was observed in all cases. [Conclusion] In our previous study, we reported that the risk factors that limit the effect of TNF-inhibitors on the progression of knee joint damage with symptoms were residual symptoms. In the present study, a similar tendency has been observed in tocilizumab.

P1-091

Relationship of ultrasound evaluation and disease activity in response to tocilizumab treatment in patients with rheumatoid arthritis

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Conflict of interest: None

[Objectives] The aim of this study is to evaluate the relationship of ultrasound evaluation and disease activity in response to tocilizumab (TCZ) treatment in patients with rheumatoid arthritis (RA). [Methods] 12 RA patients were receive TCZ 8 mg per kg bodyweight intravenously every 4 weeks. Clinical, laboratory, and power doppler ultrasonography were performed at baseline, 1, 2, 3, 4, 8, 12, and 24 weeks. Power Doppler signals were graded from 0 to 4 and presented as 100% before TCZ treatment. [Results] The changes of power Doppler signals were 100%, 84%, 85%, 81%, 88%, 116%, 81%, 77% at baseline, 1, 2, 3, 4, 8, 12, and 24 weeks. In five patients, power Doppler signals were improved at 1 or 2 weeks. Then, we divided 12 patients into the group which Doppler signals were improved at 1 or 2 weeks (called as the improved group, n=5) and the group which were worsened at 1 or 2 weeks (called as the worsened group, n=7). The DAS28 tended to be low scores in the improved group as compared in worsened group at 4, 12, 24 weeks. The value of rheumatoid factor at baseline was significantly low in the improved group. [Conclusions] The RA patients who were improved in power doppler ultrasonography of joint within 2 weeks after treatment with TCZ had high effectiveness of TCZ.

P1-092

Tocilizumab subcutaneous injection (TCZ-SC) is effective for patients with rheumatoid arthritis (RA) in clinical practice

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Conflict of interest: None

[Objectives] To examine the efficacy and safety of tocilizumab subcutaneous injection to rheumatoid arthritis (RA) patients in clinical practice. [Methods] We examined the disease activities of the RA patients who started the TCZ-SC in Konan Kakogawa Hospital since June 2013. [Results] Patient characteristics: 24 females, 3 males, age 62.6 ± 14.4 years old, body weight 49.7 ± 8.9 kg. Fourteen patients have never used TCZ (TCZ-Naive group). Thirteen patients was switched from TCZ intravenous injection (TCZ-Switch group). Changes of DAS28-ESR from baseline to last-observation in all patients group, TCZ-naive group, and TCZ-switch group was 3.59 to 3.10 (p=0.0479), 4.56 to 3.59 (p=0.0313), and 2.71 to 2.65 (p=0.8125) respectively. (Wilcoxon signed-rank test). Only one case in TCZ-Switch group discontinued treatment due to insufficient efficacy. [Conclusion] TCZ-SC was effective to RA patients in clinical practice in both TCZ-naive and TCZ-switch patients. Since the small dosing period, and also number of cases, we plan to add more in the announcement, to be considered in abstract creation.

P1-093

Supplemental treatment of leukocytoapheresis during tocilizumab mitigated disease activity of rheumatoid arthritis; report of two cases

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Conflict of interest: None

[Objectives] Several clinical trials have demonstrated that leukocytapheresis (LCAP) therapy is a safe and effective for patients with refractory rheumatoid arthritis (RA). However, the additive role of LCAP with biologic agent remains unknown. Here, we show two cases of RA patients who were successfully treated with LCAP as a supplemental treatment of tocilizumab (TCZ). [Case 1] A 65-years-old man with 3-year history of RA who had an inadequate response to abatacept (ABT), tacrolimus (TAC), salazosulfapyridine (SASP) and prednisolone (PSL). As substitution treatment, TCZ and methotrexate (MTX) were newly administrated. We added on LCAP at the second administration of TCZ, because of sustained high disease activity. He achieved Boolean remission after 22 weeks treatment with TCZ. [Case 2] A 60-years-old woman with 21-year history of RA who had an inadequate response to multiple biologics such as infliximab, etanercept, golimumab, and ABT. Despite newly administrated TCZ in combination with MTX and PSL, high disease activity sustained. We added on LCAP at the third administration of TCZ and she achieved low disease activity after 22 weeks treatment with TCZ. [Conclusion] These two cases indicate that LCAP might amplify the effect of TCZ in RA.

P1-094

Tocilizumab prominently decreases serum oxidative stress in patients with rheumatoid arthritis accompanying improvement of disease actirivy; comparative study with methotrexate

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Conflict of interest: None

[Objective] To evaluate how serum oxidative stress (d-ROM) changes in RA patients after tocilizumab (TCZ) treatment. [Methods] Eleven RA patients induced with TCZ were registered as TCZ-group. The mean age was 54 years old, RA disease duration was 9.2 years. The dose of methotrexate (MTX) was 4.9mg/week. As a control, 7 RA patients treated with only MTX were registered (MTX-group). The mean age was 64, RA disease duration was 4.7 years. The dose of MTX was 6 mg/week. The disease activity score (DAS)28 (4)-ESR was calculated at before and 3, 6, and 12 months after treatment of TCZ or MTX. serum reactive oxygen metabolites (d-ROM) were measured using free radical analytic device. [Results] In TCZ-group, DAS28 was significantly decreased at 3 months (2.19) compared to before treatment (4.77), and remission was kept at 6 and 12 months (1.51 and 1.48). In MTX-group, DAS28 was 5.09 before treatment, and finally showed significant decrease at 12 months (2.81). In TCZ-group, d-ROM was significantly decreased at 3 months (237U. CARR) compared to pretreatment phase (392). On the other hand, d-ROM was 576 U.CARR. before MTX treatment and significantly decreased to 403 at 6 months. [Conclusion] TCZ rapidly decreases disease

activity and serum oxidative stress even at 3 months after treatment.

P1-095

Maintenance rates of clinical remission for tocilizumab treatment-Evaluation of treatment for two years-

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Conflict of interest: None

[Objectives] In T2T treatment, clinical remission rates and maintenance rates are the important purposes. We evaluate the effectiveness of maintenance rates for RA patient who treated with tocilizumab (TCZ). [Methods] 303 patients who started tocilizumab treatment at TBCR (Tsurumai Biologics Communication Registry) from June 2008 to August 2008, and who has been observed for two years or more enrolled. In analysis, the patients who attained both the group which reached remission within 6 months and the group which reached remission for at least 24 months was set to "sustained remission". [Results] The average age were 58 years old and the average RA disease duration were 11 years. Average DAS28-ESR after tocilizumab treatment was 5.6, 3.1, 3.0 and 3.0 at 0, 6, 12 and 24 months. Clinical remission rates at 6 months was 39%, and maintenance rates at 24 months was 76%. On multivariate analysis, low value of Steinblocker Stage and DAS28-ESR were extracted as significant factor. [Conclusion] Although tocilizumab treatment can be attained high remission rates and maintenance rates, most important factor for "sustained remission" was low RA disease activity and non-joint destruction at the baseline.

P1-096

Investigation of Serological and Clinical Factors Affecting Outcome on Efficacy of Tocilizumab

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Conflict of interest: None

[Objectives] Investigating association between clinical responses by Tocilizumab (TCZ) and serological and clinical factors. [Methods] 70 RA patients who started TCZ between May 2008 and May 2011 were divided in groups by means of RF, anti-CCP Ab, ANA, γ-globulin, MMP-3, and disease activities. Following evaluations were performed among those groups: drug retention rate, DAS response, DAS remission rate, and ΔTSS by 104 w. Patient backgrounds were analyzed for identifying factors affecting efficacy of TCZ. [Results] Patients with high RF showed a higher rate of DAS remission and it was significant at 24 w. A better DAS response at 52 w was found in patients with high anti-CCP Ab but ΔTSS was more progressed. DAS response and remission rate at 104 w were better in patients with low anti-CCP Ab. Patients with low disease activity showed a better efficacy of TCZ, significantly higher retention rate at 52 w and remission rate at 24 w and 52 w. Good responders at 104 w had significantly lower values of mHAQ, RF, and anti-CCP Ab. [Conclusion] Although it was reported elsewhere that high RF is indicative for good response of TCZ therapy, our data indicated that patients without autoantibodies showed a good response to TCZ, which may be due to difference in patient backgrounds.

P1-097

Tocilizumab as a Promising First-line Drug for Treatment of Rheumatoid Arthritis

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Conflict of interest: None

[Objectives] The aim of this study was to examine differential relationships of inflammatory cytokines IL-6 and TNFα by comparing clinical parameters that changed during the administration of TCZ or ETN to patients with early or established RA. [Methods] The influence of TCZ on WBC and platelet counts in the 7 early RA and in the total cohort of 33 RA was compared to the influence of ETN on 11 early RA and the total cohort of 38 ETN-treated RA at weeks 0, 12, and 24. [Results] In the 33 RA treated with TCZ, mean WBC counts (7708/μL) and platelets (29.4×10^4/μL) before treatment were significantly decreased (to 5970 and 20.8×10^4 respectively) at week 12. In the 38 RA treated with ETN, the mean WBC (7804/μL) and platelet (31.7×10^4/μL) counts before treatment were also reduced (to 6911 and 25.4×10^4 respectively) at Week 12. The decrease in mean platelet counts was significantly greater in RA treated with TCZ than in those treated with ETN ($p<0.05$). In the early RA, in particular, the decreases in WBC and platelet counts were more drastic after treatment with TCZ than after treatment with ETN. [Conclusion] TCZ may be a more suitable than ETN as a first-line therapeutic option for early RA patients that have thrombocytosis and/or leukocytosis, parameters which may be influenced by IL-6.

P1-098

Trial of Tocilizumab treatment interval extension for rheumatoid arthritis based on disease activity and serum IL-6 levels

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Conflict of interest: None

[Objective] To examine whether extended injection intervals of Tocilizumab (TCZ) for patients with rheumatoid arthritis (RA) can maintain clinical remission after a clinical remission has been achieved and serum IL-6 levels have been reduced. [Methods] Seventeen RA patients receiving the administration of TCZ over 24 weeks were enrolled. If a patient achieved DAS28-ESR <2.6 for more than three months and a serum IL-6 level <35 pg/ml, the injection interval was prolonged for 1-2 weeks at a time, and the disease activity and serum IL-6 levels were observed. [Results] Eight patients underwent an extended injection interval. Before injection interval extension, the average age was 55.5±11.6 years, RA disease duration was 3.8-37.0 years, TCZ administration period was 25-175 weeks, 4 patients had MTX, the average DAS28 was 1.41±0.63, and the mean serum IL-6 level was 13.4±7.2 pg/ml. The TCZ injection interval was extended to 5-7 weeks. The final average DAS28 was 1.92±0.76 and the serum IL-6 level was 0.9-17.2 pg/ml. Six patients maintained remission, and 2 patients showed conversion to low disease activity. [Conclusion] If RA patients with TCZ achieve clinical remission and show declining serum IL-6 levels, the TCZ injection interval can be extended safely without flare-ups.

P1-099

Pregnancy outcomes in rheumatoid arthritis patients treated with tocilizumab

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Conflict of interest: None

[Objectives] Tocilizumab, such as inhibitors of interleukin-6, are widely used to treat rheumatoid arthritis (RA). This retrospective study

investigated Tocilizumab use before or during pregnancy in RA patients and the result and pregnancy outcomes. [Methods] Five RA patients with 7 pregnancies were identified and observed from the 1356 patients that are registered in our hospital. [Results] 7 pregnancy (5 patients) of patients in the TCZ use five cases (one case of preterm low birth weight infants), abortion was 1 cases, during pregnancy were 1 cases. They age were from 28 years to 42 years. Five cases was (washout period was from 2 months to 11 months) pregnant after Biologics free. One case was continued TCZ during pregnancy. Medical condition had worsened during pregnancy are two cases, there were two cases of what deterioration was observed after delivery. [Discussion & Conclusion] TCZ is a pregnancy risk category C drug, according to the US FDA. Japanese drug information states that TCZ should be administered to pregnant patients only if the benefits outweigh the risks; therefore, TCZ use in pregnant RA patients is not necessarily prohibited. the data on TCZ and pregnancy in humans were too limited to make conclusions on safety or suggestions on prescriptions.

P1-100

Efficacy of replacing subcutaneous TNF inhibitor therapy with a subcutaneous tocilizumab preparation

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Conflict of interest: None

[Objectives] We evaluated the efficacy of a subcutaneous tocilizumab preparation (TCZ-SC) in patients who exhibited an inadequate response to subcutaneous TNF inhibitors. [Methods] We retrospectively analyzed the data of 19 patients who were available for observation for more than 8 weeks after TNF inhibitor therapy was switched to TCZ-SC therapy. The clinical remission rate was determined on the basis of DAS28ESR, SDAI, and CDAI assessments. MMP-3 normalization rates and drug continuation rates were also investigated. [Results] The mean age of the patients was 55.2 years, the mean weight was 61.5 kg, and the mean DAS28-ESR and MMP-3 values were 3.69 and 224.5, respectively. The remission rate after 12 weeks was 66.7%, 25.0%, and 12.5% according to DAS-ESR, SDAI, and CDAI, respectively. The MMP-3 normalization rate was 40% and the drug continuation rate was 100%. There were no dropouts because of adverse events. [Conclusion] Subcutaneous administration of biological preparations in patients with rheumatological disease is effective and safe. Because of poor response to subcutaneous TNF inhibitor therapy, we considered the IL-6 inhibitor TCZ-SC, which acts on a different target, to be an effective alternative that was easy to use and resulted in high remission and continuation rates.

P1-101

Biological effect of Regulatory T cell by Tocilizumab in rheumatoid arthritis patients

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Conflict of interest: Yes

[Objectives] Regulatory T (Treg) cell have an important role on pathology of rheumatoid arthritis (RA). It was reported that Treg cells RA patients were less than that of in healthy persons, and were those of RA patients showed lower disease activity. IL-6 has a role of enhanced differentiation of Th17 and differential inhibitory of Treg cells. The purpose of this study is to assess the relation between the clinical effect by Tocilizumab (TCZ) and the biological effect on Treg cells. [Methods] To eight patients with inadequate effect by DMARDs, 8mg/kg of TCZ were administrated every four weeks. The number of Treg cells, disease activity, and serum cytokine level were measured at 0, 4 12, and 24 weeks. [Results] The disease activities were significantly improved by TCZ. The number of Treg cells had gradual tendency to be increased. Compared the SDAI remission group with non remission group at 24 weeks, the number of Tregs cells on the remission group had tendency to be increased at 12 and 24 weeks, although Treg cells level was equivalent at 0 week. [Conclusion] Present study suggested that TCZ had possibility to improve further the disease activity by the improvement of Treg cells level, because it was shown thet Treg cells level in SDAI remission group was increased by TCZ.

P1-102

Increase of medium and large sized joint destruction in patients with rapid radiographic progression during treatment with Tocilizumab

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Conflict of interest: None

[Objectives] To compare mediun and large (M-L) sized joint destruction in rapid radiographic progression (RRP) group with non-RRP group RA patients who have been treated with Tocilizumab (TCZ) for 1 year. [Methods] All patients took radiographs of both small and M-L sized joints. The modified total sharp score (mTSS) were assessed to find RRP (ΔmTSS /year>3). Average Larsen grade in 12 M-L sized joints was expressed as total Larsen score (TLS). The chi-squared test and the Wilcoxon test were used for the statistical analysis. [Results] Nine RRP patients (ΔmTSS /y: 10.4) were compared with 26 non-RRP patients (ΔmTSS /y: -0.5). Among baseline clinical factors, mTSS / year ($p<0.01$), serum CRP, SJC, DAS28-ESR ($p<0.05$) were significantly increased in RRP group. Out of 108 M-L sized joints examined in RRP group, there were progressions in 8 joints and improvements in 4 joints. Out of 312 M-L sized joints examined in non-RRP group, there were progressions in 3 joints and improvements in 5 joints. The changes of TLS were significantly higher in RRP group ($p<0.05$). [Conclusion] RRP group during 1 year TCZ treatment had high risk for joint damage with high mTSS /year, CRP at baseline. Progression of M-L sized joint destruction was significantly observed in RRP group compared with non-RRP group.

P1-103

Review of tocilizumab (TCZ) effect for rheumatoid arthritis (RA)

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Conflict of interest: None

[Objectives] To evaluate effectiveness of tocilizumab (TCZ) for rheumatoid arthritis (RA) in our hospital. [Methods] From November, 2010 to March, 2013, 20 RA patients who started to use TCZ were enrolled. They had been observed about the disease activity of RA (DAS28-CRP, SDAI, CDAI) in before and after 24 weeks, rate of clinical remission and taking MTX and PSL. [Results] They were 3 male and 17 female, and the mean age at started TCZ was 60.6 years old. The number of the cases which use TCZ for the first time was 6 patients. The disease activities before started are 4.75±0.62/29.4±8.0/25.6±7.2 in DAS28-CRP/SDAI/CDAI. On the other hand, in 24 weeks of medical treatment starts were 2.59±0.40/10.4±3.0/10.3±3.0 respectively. In 24 weeks, CDAI remission was 3 patients, and Boolean remission was 1 patient. Although the significant difference did not accept to CDAI 24 weeks after setting in a Bio-naive group and not Bio-naive groups ($p=0.59$), in the Bio-naive group, the disease activity suited the low tendency. In this group, a big difference was not observed in CDAI in 8 and 24 weeks, the improvement of the disease activity was accepted at the treatment start early stage. [Conclusion] By the Bio-naive group, it was suggested that a low disease activity can be achieved more at an early stage.

P1-104

The Efficacy in the Prevention of Bone and Joint damage treated with tocilizumab during week 12

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Conflict of interest: None

[Objectives] The efficacy in the prevention of bone and joint damage on DAS28ESR during week 12 of TCZ was evaluated. [Methods] From June 2008 to January 2013 administration to subjects who were administered TCZ until Week 52, and the subjects were 22 patients on carring out evaluation of bone and joint damage in X-rays (vdH total Sharp score ((TSS)). The difference between TSS prior to administration and 52 weeks in 11 subjects of DAS28ESR <2.52 in week 12 (low group) was compared with that in 11 subjects of DAS28ESR ≧2.52 in week 12 (moderate group). [Results] The average age were 62.7/55.3 years old and the average RA disease duration were 11.7/3.2 years moderate /low group, respectively. Progress was inhibited with the average change of TSS at low/moderate group is 0.5/-0.6. [Conclusion] The possibility that DAS28ESR at week 12 of TCZ can't be used to predict the inhibition of bone and joint damage after 1 year of administration was suggested.

P1-105

Clinical outcome of tumor necrosis factor inhibitor and interluikin-6 receptor inhibitor in biologics naïve patients with rheumatoid arthritis

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Conflict of interest: None

[Objectives] The present study retrospectively assessed the efficacy of tumor necrosis factor inhibitor and tocilizumab in biologics naïve patients with rheumatoid arthritis (RA). [Methods] A retrospective study of 65 RA patients who treated the first biologics for 24 weeks. Responses of subjects treated with TNFi (n=31; etanercept 11, adalimumab 9 and golimumab 11) were compared with those treated with tocilizumab (TCZ; n=24). Disease activity was assessed by the Disease Activity Score 28-ESR, the Simplified Disease Activity Index (SDAI) and the Clinical Disease Activity Index (CDAI). The physical functional status was measured using the modified health assessment questionnaire (MHAQ). [Results] In the evaluation between patients who treated with TNFi and TCZ, a significant improvement from baseline was seen in DAS28-ESR, SDAI, CDAI and MHAQ for all patients at 24 weeks. At 24 weeks DAS28 values were significant improved in the patients treated with TCZ compared those with TNFi. However, there were no significant differences in SDAI, CDAI and MHAQ values between the TNFi and TCZ treated groups at 24 weeks. [Conclusion] These results suggest that clinical outcomes were similar for both treatments in in biologics naïve patients with RA.

P1-106

Study of extended interval tocilizumab infusions for patients with rheumatoid arthritis

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Conflict of interest: Yes

[Objectives] Tocilizumab (TCZ) infusion therapy is repeated every 4 weeks for patients with rheumatoid arthritis (RA) with dose of 4mg/kg. However, patients prefer less frequent hospital visits when their disease activities are low and stable. In this study we investigated the intervals of TCZ infusion therapy for patients with RA. **[Methods]** We investigated the patients treated with extended interval TCZ infusions by July 2013 in our hospital. **[Results]** Twenty-five patients were treated with TCZ (average age 57.9 y, disease duration 15.5 y, TCZ infusion 27.5 times (3-60). Ten were treated by TCZ as first biologics, 11 as second, and 4 was third. Administration was ceased in 3 patients (1 by infections, 2 by secondary insufficiency). One was transferred by move and 1 was suspended by pregnancy. Twelve were treated by extended interval TCZ infusions routinely, of which intervals were average 5.5w (7 by 5w, 4 by 6w, 1 by7w). Average CDAI was 3.57 and DAS28-ESR was 1.52. Seven were also treated by immunosuppressive as MTX, 6 were by steroids, and 4 were by NSAIDs. Eight had exacerbation when the intervals were further extended and were maintained in the existing intervals. **[Conclusion]** TCZ infusion intervals may be extended for 1-2 w with keeping low and stable disease activity.

P1-107

Clinical evaluation of subcutaneous tocilizumab injection (TCZ-SC) at the author's institution

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Conflict of interest: None

【Objective】To evaluate the clinical efficacy and safety of TCZ-SC in RA patients.【Methods】Clinical efficacy and safety of TCZ-SC were evaluated on 37 RA patients responding poorly to MTX (2 in bio naive, 4 in swich biologies to TCZ-SC and 31 in the intravenous TCZ infusion (TCZ-IV)→ TCZ- SC) treated in our hospital that were enrolled on RA patients responding poorly to MTX. Safety and efficacy of the treatment were assessed to 12 weeks.【Result】With regard to safety, there were 15 onsets of adverse events in 6 of the 9 patients, however, all were not serious and the outcome was recovery with no dropout cases. The average DAS28ESR before treatment was 3.72. It improved to 2.32 in 12 weeks. TCZ-SC was also effective for RA patients who failed to be treated by anti-TNFtherapy.【Conclusions】Safety is comparatively high if attention is paid to infection and so on. Our study suggests that the usefulness of TCZ-SC is considered high for patients that respond poorly to MTX. TCZ-SC demonstrated comparable efficacy and safety to TCZ-IV.

P1-108

Efficacy and safety of subcutaneous tocilizumab treatment

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Itabashi Chuo Medical Center

Conflict of interest: None

[Objectives] To evaluate the early therapeutic efficacy/safety of subcutaneous tocilizumab (TCZ SC) treatment. [Methods] Consecutive 20 RA patients (pts) were enrolled. The RA pts were received TCZ SC biweekly. The disease activity and drug efficacy were evaluated at baseline (BL) and at 2, 4, and 8 wks. The patients were assigned to a naïve to a biological therapy (naïve) group, switching from TCZ intravenous infusion (IV) group, and switch from other biologics (switching) group, and the findings were compared. We assessed the influence of weight. Fisher's exact test, Wilcoxon rank sum test, and Wilcoxon signed rank test were used for statistical analysis. [Results] The simple disease activity index score in all cases significantly decreased from BL to 2, 4, and 8 weeks (from 11.64 to 8.81, 7.30, and 3.61, respectively). Efficacy was higher in the naïve or switching group, although the switching from TCZ IV group also exhibited efficacy. The efficacy of TCZ SC did not significantly differ in terms of weight. Compared to the BL levels, the levels of matrix metalloproteinases after 4 weeks of therapy changed from 237.8 to 77.5 ng/mL and from 320.4 to 246.9 ng/mL in the TCZ IV and TCZ SC groups. [Conclusion] The efficacy of TCZ SC was not associated with the pretreatment or weight.

P1-109

A Report of 5pregnancy in 4 RA patients treated with Tocilizumab untill they got pregnant. Data from TBC Registory

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Conflict of interest: None

[Objectives] many report of pregnancy with Etanercept is published and reviewed. Although few report was reported with Tocilizumab (TCZ). We report pregnancy with TCZ from data of TBCR (Tsurumai Biologics Communication Registory) [Methods] 5pregnancy in 4 RA patients treated with Tocilizumab untill they got pregnant are reported from TBCR. [Results] They are 28, 34, 39, 43 y.o. respectively. All patients had treated with ETN as first biologics, but ETN was not effective enough. They were treated with TCZ monotherapy or combination with PSL after ETN till their pregnancy was recognized. 4 deliveries in 3patients was normal.

1deliver in 1patient was spontaneously aborted. [Conclusion] When ETN is failed, TCZ is also useful as Second Biologics. Many reports were available in ETN treated till pregnancy was recognized, but TCZ is less reported. In TBCR data, 1 of 5 delivers (20%) was spontaneously aborted. Generally reported, spontaneous abortion occur in 10~20%. We have to accumulate more case report like this.

P1-110

Short-term outcomes of subcutaneous tocilizumab for rheumatoid arthritis

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Conflict of interest: None

[Objectives] Since 2013, subcutaneous tocilizumab (TCZ-SC) has been available as treatment for rheumatoid arthritis (RA). Here, we present short-term outcomes for patients who were administered TCZ-SC. [Methods] Fifteen patients with RA were administered TCZ-SC. Of these, we analyzed 11 patients for whom 8 weeks had passed since initiation of treatment (8 women and 3 men; mean age, 64.1 years; mean weight, 55.4 kg; concomitant MTX use, 3 patients; bio-naïve, 4 patients; switched from TCZ-IV, 5 patients, and switched from other biologics, 2 patients). We assessed the efficacy and safety of TCZ-SC in this population. [Results] CRP was found in 10 of 11 patients, but became negative by 8 weeks. With respect to clinical efficacy, CDAI remission was observed by 8 weeks in the 2 bio-naïve patients, and the effects were maintained in all 5 patients who switched from TCZ-IV. Side effects included papules in 1 patient, although there were no patients who stopped treatment due to side effects. All 11 patients underwent continuous TCZ-SC treatment. [Conclusion] Although the results are from short-term treatment, we identified cases of CDAI remission early in treatment, suggesting that TCZ-SC is promising as an effective treatment for RA.

P1-111

Our experience in using the subcutaneous (SC) formulation of Tocilizumab (TCZ)

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Conflict of interest: None

[Objectives] Here we report our experience in using TCZ subcutaneous (SC) formulation for 6 RA patients who have been treated since July 2013. [Methods] Subjects were 6 RA patients (a man and 5 women) with the average age 63.5 (28-74). 4 patients is biologics-naïve, while 2 patients switched the medication from etanercept (ETN) or infliximab (IFX) to TCZ. The reason for switching the medication is because of the side effects of ETN and the inadequate response to IFX. 3 patients received the combination of TCZ and methotrexate (MTX), while 3 received TCZ monotherapy. We made a clinical evaluation of these RA patients according to DAS28-CRP, SDAI, and HAQ. [Results] The clinical evaluation of all subjects was maintained or improved, though the treatment term is short. No significant adverse events were seen. [Conclusion] TCZ SC formulation will shorten administration time and the auto-injector will make patients avoid trouble such as needle-stick accident and infection risk. TCZ, however, has some demerits. It is true that the therapeutic efficacy is important, but patients' satisfaction with TCZ use is also important. We need to treat more RA patients with TCZ to further evaluate its benefits.

P1-112

Clinical experience and positioning of Iguratimod at the author's institution

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Hokkaido Medical Center for Rheumatic Diseases

Conflict of interest: None

[Objectives] Early intervention with DMARDs is the recommendation after rheumatoid arthritis is diagnosed. Clinical experience with the novel anti-rheumatoid drug, Iguratimod (IGU) is hereby reported. [Methods] Clinical progress of 70 RA patients on IGU was investigated using DAS28, joint ultrasonography, adverse events etc. Co-administration with MTX and Bio agents was also examined. [Results] RA therapy has undergone a major paradigm shift since the appearance of methotrexate (MTX) and Bio agents. Represented by MTX, DMARDs are leading RA therapy. Launched in September 2012, IGU is expected to be a new treatment option. Usefulness of IGU was investigated at this institution and the results as well as image assessment by joint ultrasonography are reported. GSUS (gray scale) involves visualization of bone erosion, intraarticular fluid, synovial hypertrophy and measurement of joint thickness. In PDUS (power Doppler), neovascularization in inflamed joint synovial membrane is visualized as a blood flow signal and the extent of inflammation in joint cavities is assessed. [Conclusion] Iguratimod is effective as a novel anti-rheumatism drug. Alone it is effective in mild RA, and together with MTX in highly active RA. Furthermore, it is useful when combined with Bio agents.

P1-113

Analysis of serological changes in the course of tofacitinib therapy in the patients with rheumatoid arthritis

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Conflict of interest: None

[Objective] Antibodies against citrullinated peptides (ACPA) and Rheumatoid factor (RF) are well known as diagnostic or prognostic markers in the patients with rheumatoid arthritis (RA). As several studies indicated that ACPA is involved in the pathogenesis of RA, therapy with lowering titer of ACPA is thought to be effective to lead true remission. The purpose of this study is to examine changes of antibodies against citrullinated peptides (ACPA) and rheumatoid factor (RF) during therapy with tofacitinib. [Methods] We enrolled 15 patients with RA, participating in long-term extended clinical trial of tofacitinib. We obtained clinical and serological data of patients at two points (; before the treatment and after 56 weeks of treatment), then analysed changes of ACPA and RF levels between the two visits and the effect of treatment response. [Results] In 53% (8/15) of study patients, ACPA titer declined after treatment with tofacatinib of 56 weeks. The median relative changes after 56 weeks were −22% for ACPA and −21.7% for RF. There was no significant correlation between changes of ACPA titer and age, disease duration, changes of Disease activity score (including SDAI). [Conclusion] ACPA and RF levels declined after 56 weeks of therapy with tofacitinib in Japanese patients with RA.

P1-114

Effects of irbesartan on IMT in the patients of connective tissue disease or rheumatoid arthritis with hypertension. -additional examination on the effect of ARB/CCB combination drugs in hypertensive patients- (5th report)

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Conflict of interest: None

[Objectives/Methods] Oral steroids often cause secondary hypertension and progress atherosclerosis for connective tissue disease or rheumatoid arthritis. We had reported that irbesartan (100mg/day; for 52weeks) could inhibit increasing IMT and showed long period observational effi-

cacy and safety past each 3years. In this conference, as additional examination (5th Report), we report the effect of ARB/CCB combination drugs in the patients who did not achieve the goal of treatment on hypertensive patients except numbers of discontinuation in this study subjects. [Results] As a result, we observe that it can be well control lowering blood pressure with no cardiovascular incidents and serious adverse events. [Conclusion] In conclusion, it suggests that irbesartan or irbesartan/amlodipine combination drugs are useful for secondary hypertension of connective tissue disease and rheumatoid arthritis.

P1-115

2 cases of the RA patients with residual severe pain were treated using fentanyl transdermal system

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Conflict of interest: None

[Objectives] We will report the two cases of RA patients with the residual strong pain using fentanyl patch. [Methods] Case 1. 69 y.o.-female. The onset of RA was 22 years ago. Infliximab was started at 4 years ago. And, tramadol/acetaminophen (TRAM/APAP) was started at two years ago. But, her severe pain remained. We decided to use fentanyl patch, one of strong opioids. Pain VAS: 72mm/0 M, 78mm/1M, 30mm/2M. No adverse effect was happened. Case 2. 81 y.o.-male. The onset of RA was 40 years ago. Etanercept (ETN) was started at two years ago. TRAM/APAP was used for his pain. But, MTX had to be stopped, because thyroid tumor was pointed out. ETN was continuing to use because of his strong hope. Severe pain was happened, we started to use fentanyl patch. Pain VAS: 100 mm/0M, 100 mm/1M, 53 mm/3M. His severe pain was gradually decreased. [Conclusion] Fentanyl patch can be an option for the residual severe pain of RA patients despite optimal treatment of inflammation.

P1-116

Early stage hepatic dysfunction associated with Iguratimod treatment for rheumatoid arthritis

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Conflict of interest: None

[Objectives] To assess the safety of Iguratimod in patients with rheumatoid arthritis (RA) particularly with relation to early stage hepatic dysfunction. [Methods] subjects were 59 patients with RA who were registered in the Tsurumai Biologics Communication Registry and began therapy with Iguratimod by May 2013. Subject characteristics were as follows: 49 women and 10 men; mean age, 65.1 years; mean disease duration, 109.6 months. We assessed safety over the course of 24 weeks of treatment. [Results] Of the 59 patients, continuous administration of Iguratimod was possible in 37 patients. Reasons for discontinuation in the remaining 22 patients were as follows: hepatic dysfunction, 5 patients; digestive symptoms. Of the 4 patients who re-initiated Iguratimod therapy, 2 had hepatic dysfunction, 1 had digestive symptoms. [Conclusion] Iguratimod is administered to the elderly and those with advanced RA, as well as those treated with MTX and those contraindicated to biologics therapy. Hepatic dysfunction improved upon discontinuation, but improvements were also noted in some patients who continued on Iguratimod, suggesting that one option is to continue treatment with careful monitoring even when hepatic dysfunction becomes apparent.

P1-117

Clinical effect of iguratimod in patients with rheumatoid arthritis

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Conflict of interest: None

[Objectives] To analyze the efficacy and safety of iguratimod (IGU) in patients with rheumatoid arthritis (RA). [Methods] IGU was used in 19 patients with RA treated at the affiliated clinics to Akita orthopedic group on rheumatoid arthritis (AORA) from January 2013. Ten patients (1 man and 9 women, mean age 64 years, man duration of illness 7.3 years), who were followed up for at least 24 weeks of treatment with IGU, were included in this study. MTX had been administrated to all patients (mean dose 6.2 mg), PSL to 9 patients (mean dose 2.8 mg), and biologics to 2 patients. We evaluated persistence rate, DAS28-CRP, SDAI, CDAI, MMP-3 and reasons for discontinuing at 24 weeks. [Results] Six patients (60%) were administered continuously in 24 weeks. The mean DAS28-CRP, CDAI, SDAI, and MMP-3 scores of 4.77, 23.35, 26.19, and 191, respectively decreased to 2.23, 4.88, 5.34, and 155 at 24 weeks after initiation. The reasons for discontinuing were adverse events in 2 cases, change of biologics in a case, and other in a case. [Conclusion] These data suggest that IGU could become an option for the treatment of patients with RA during administration of MTX.

P1-118

Efficacy and Safety of Long-term Administration of Tofacitinib in Patients with RA

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Conflict of interest: Yes

[Objectives] To assess the long-term administration of tofacitinib in patients with RA. [Methods] Subjects were 8 non-smokers with RA (including 7 women) enrolled in the phase II trial (A3921040) and long-term administration trial of tofacitinib. Mean age was 57.3±1.1 years and mean disease duration was 13.8±3.5 years. When patients are not feeling well, they stop taking tofacitinib and call the coordinator. [Results] Mean observation period was 3.5±0.4 (min 1.6 – max 4.4) years. Mean DAS28-ESR was 5.7±0.3 before administration, 2.5±0.3 at week 48, and 2.4±0.1 at week 144. Mean time until attaining DAS28-ESR remission was 38 weeks. A patient withdrew because of soft tissue infection. Infectious diseases in all patients during the whole period were as follows: 15 cases of nasopharyngitis, 3 cases of apical periodontitis, and 1 case each of bronchitis, acute gastroenteritis, herpes labialis, influenza, cystitis, and tinea pedis. Adverse events were no more numerous than those of biologics. At the end of the trial, an indeterminate result of QFT was obtained in a patient due to insufficient production of IFNγ in the positive control. [Conclusion] Tofacitinib showed good efficacy and tolerability with optimal patient management. QFT may be available for assessment of immunocompetence.

P1-119

Effect of biological agents for orthopaedic surgery in rheumatoid patients

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Conflict of interest: None

[Objectives] We retrospectively evaluated the outcome of the surgery for rheumatoid patients using biologics. [Methods] This study included 130 cases who underwent surgical operations. 83 joint replacement, 12 arthrodesis, 10 resection arthroplasty, 9 surgery for infection and 16 other operations were performed. Biologics were used as follows; etanercept for 55, tocilizumab for 39 and others for 36 patients. We reviewed the frequency of surgical site infection (SSI). In patients undertaken total knee arthroplasty (TKA), we also reviewed joint destructions by X-ray and intraarticular findings during surgery. [Results] The SSI was 3.1%.

TKA was performed for 44 patients. Inflammatory bone destructions were recognized in 6 patients by the last preoperative X-ray findings. 35 patients were followed up for about 19 months with X-ray. All of them had joint destructions more than Larsen grade II at the start of biologics and 20% of them had progressed joint destructions. It was relatively amenable performing surgery as a result of improved inflammatory synovitis and bone quality. [Conclusion] We should care for SSI in the surgery for the patients treated with biologics. Although biologics cannot prevent the existing joint destructions from progressing, they have positive effects for surgery.

P1-120

Evaluation of the operated rheumatoid patients treated with biologics

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Conflict of interest: None

[Objectives] To evaluate the operated RA patients treated with biologics. [Methods] 34 patients with biologics were evaluated, who treated with orthopedic surgery between January 2010 and October 2013. Their mean age was 60.6 years and mean duration of illness was 15.5 years. Duration of interruption before surgery is 4 weeks in Iniximab (IFX), Tocilizumab (TCZ), Abatacept (ABA) and 2 weeks in Etanercept (ETN) and Adalimumab (ADA). [Results] The number of total knee arthroplasty (TKA) was 15, arthroscopic synovectomy of knee joint was 1, arthroplasty of forefoot was 12, arthroplasty of wrist or hand was 4, total elbow arthroplasty was 1, and resection of lipoma was 1. Mean DAS28ESR (4) before the operations was 3.9±1.1, in detail, 3.7±0.9 in TKA, 4.0±1.2 in forefoot plasty, 3.5±1.1 in upper limbs plasty. Mean CRP before the operations was 0.5±0.9, in detail, 0.6±0.6 in TKA, 0.1±0.2 in forefoot plasty, and 0.3±0.7 in upper limb plasty. CRP in patients with forefoot plasty was lower than in patients with TKA before operation. The number of each biologics was as follows: IFX 7, ETN 15, ADA 5, TCZ 6, ABA 1. There was no perioperative infection. Flare up of disease was seen in 7 patients with ETN and 1 patient with TCZ. [Conclusion] Inflammation of operated patients was controlled with biologics.

P1-121

Present status of orthopedic surgery for rheumatoid arthritis under the treatment with biologics

Hiroshi Nakamura[1], Kenji Takahashi[1], Kenji Takenouchi[1], Masahito Koiwa[2], Toshikazu Kamada[3], Akiko Sato[4], Yoshihiko Satake[4], Hidemi Kawaji[4], Shinro Takai[4]
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Conflict of interest: Yes

[Objectives] To examine the status of recent orthopedic surgery under the treatment with biologics and compare those in the past. [Methods] The number of orthopedic surgery operated for RA under the treatment with biologics between 2011 and 2013 was 29. The procedures, biologics, causes of surgery and perioperative adverse events were investigated, and compared with those operated before 2008. [Results] Application rates of biologics in orthopedic surgery for RA was 4.6% in 2003-2006, 10.2% in 2007-2008 and 37.7% after 2011. Surgery in the hand and the foot occupied 52% of the cases and rates of arthroplasty in the lower extremities decreased (TKA 17%, THA 3% and TEA 10%). Thirty one percent of the patients were treated with tocilizumab. Insufficient response to biologics and delay of introduction occupied 31% and 10% of the causes, respectively. Biologics were discontinued and restarted according to the guideline of JCR. No perioperative adverse events associated with biologics were found. [Conclusion] Increase of orthopedic surgery under the treatment with bilogics may reflect patient's demand for higher QOL. Orthopedic surgery will continue to be required in the cases that showed insufficient response to biologics.

P1-122

Effects of biologic agents for rheumatoid arthritis patients undergoing total knee arthroplasty

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Conflict of interest: None

[Objectives] The aim of this study is investigate the effects of biologic agents for rheumatoid arthritis (RA) patients undergoing total knee arthoplasty (TKA). [Methods] We performed 244 TKA with RA from 2007 to 2012. We evaluated 51 cases which were preoperatively treated with biologic agents. The average RA disease duration was 10.5 years. They used biologic agents for average 2.0 years when they had TKA. We investigated postoperative complications and blood examination at three time points- before using biologic agents, after using biologic agents, and 3 months after TKA respectively. [Results] We found one case of infection and two cases of delayed wound healings. The average CRP (mg/dl) showed 5.8, 2.0 and 1.4 at three points respectively. After using biologic agents, the average CRP was significantly lower than before, however, there was no statistical difference between pre-operation and post-operation. On the other hand, the average ESR showed 71.3, 49.2, and 49.9 respectively, and there were no statistical difference among them. [Conclusion] TKA with biologic agents did not induce serious incident. Biologic agents caused decreasing hematological inflammatory response, however, it was thought that TKA has small effect to the hematological inflammatory response.

P1-123

Analysis of perioperative complications after surgery in patients treated with biological DMARDs

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Conflict of interest: None

[Objectives] To evaluate perioperative complications in patients treated with biological DMARDs. [Methods] We collected surgery cases with biological DMARDs from January, 2002 to September, 2013. Incidences of postoperative infections, delayed wound healing were extracted from the data for comparison with patients without these postoperative events. A total of 57 cases were collected. The biological DMARDs used are five IFX (s), 20 ETN (s), three ADA (s), six TCZ (s), and one ABT in 35 cases, and, as for the orthopedics operation, five emergency case operationswere seen. Other department operation is 22 cases (seven kidney internal medicine, three surgery, three gynecology, three otolaryngology, two urology department, two cardiovasucular surgery, and respiratory-organs surgery, ophthalmology, and dentistry oral surgery each). The biological DMARDs used were two IFX (s), ten ETN (s), three ADA (s), and seven TCZ (s), and the emergency case operation was four cases. [Results] Postoperative infection did not produce a standby operation and an emergency case operation. Two patients of an orthopedics operation had delayed wound healing. [Conclusion] In order to analyze perioperative complications by biological DMARDs use, many analyses of an example are more nearly required.

P1-124

The evaluation of neutrophil CD64 expression in the perioperative stage of joint arthroplasty in patients with rheumatoid arthritis

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Conflict of interest: None

[Objective] To examine sequential changes of neutrophil CD64 expression in the perioperative stage in patients with rheumatoid arthritis (RA). [Methods] From 15 RA patients (17 joint arthroplasties; TKA 10, THA 4, TSA 2, and femoral head replacement 1), peripheral blood samples were obtained at before (baseline) and 1, 2, and 3 weeks after surgery. CD64 expression per neutrophil was measured by flowcytometry. Average age was 68 years old and RA duration was 14.7 years. Eleven patients were treated with biologics (etanercept;4, tocilizumab;3, adalimumab;2, infliximab;1, and abatacept;1). [Results] No perioperative infection was observed. The value of CD 64 was 955 molecules/cell at baseline, 1213 at 1 week, 1091 at 2 weeks, and 1011 at 3 weeks after surgery. The ratio of change was 1.28, 1.16, and 0.85 at 1, 2, and 3 weeks. No significant difference was detected by statistical analysis. In only one case, the ratio of change was above 2.00, but neither local redness nor swelling was detected and infection was ruled out. [Conclusion] The data from this study showed no significant change in CD64 expression though rapid phases after surgery were not measured. These data suggest CD64 can be a possible basis for proper diagnosis of postoperative periprosthetic infection in RA patients.

P1-125

Prosthetic joint infection in two rheumatoid arthritis patients under treatment with biologic agents

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Conflict of interest: None

[Case 1] A 60-year-old female RA patient had been treated with tocilizumab (TCZ). She had had left total ankle arthroplasty 4 months ago. At 26 days after the infusion of TCZ, redness, swelling and pain of the left lower leg appeared. Body temperature was 36.8℃, CRP was 0.05, WBC was 8,500, and neutrophil fraction was 72.5%. MRCNS was detected by aspiration from left ankle and blood. At 5 days after the onset of the symptom, debridement was performed. Infection was resolved with LZD. Treatment with abatacept was initiated at 3 months after the last TCZ introduction. The recurrence of infection was not recognized under ABT treatment for 15 months. [Case 2] A 50-year-old female patient had been treated with infliximab (IFX). She had had bilateral total knee arthroplasty six years ago. At 11 days after the infusion of IFX, she developed high fever and left knee pain. CRP and WBC was elevated to 10.15 and 20,000, respectively. Joint fluid was cloudy brown, and nuclear cell count was 68,000. At next day of the onset of the symptom, debridement was performed. Bacteria was not detected. Infection was resolved with CEZ. Recurrence of infection was not recognized under IFX treatment for 11 months. [Conclusion] Early diagnosis of prosthetic joint infection under TCZ treatment is difficult.

P1-126

Synovectomy for severe swelling at wrists in patients with rheumatoid arthritis receiving biologic agents: a report of two cases

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Conflict of interest: None

Objectives: Synovectomy is sometimes applied for sustained synovitis at large joints such as shoulders and knees. Here we present two cases of RA who showed severe joint swelling at their wrists and underwent synovectomy under treatment with biologics. Case 1: A 73-year old man presented right wrist pain and severe swelling. He received weekly 10 mg of MTX and monthly 50 mg of GLM therapy, but joint destruction progressed, eventually underwent synovectomy at 22 weeks after GLM administration. Case 2: A 71-year old man presented left wrist pain and abnormal swelling. He had undergone synovectomy for his left wrist three times. He received weekly 8 mg of MTX and monthly 480 mg of TCZ therapy, but underwent synovectomy at 14 and 30 weeks after TCZ administration. Discussion: These two cases showed single arthritis at their wrists. In these cases, therapeutic effects cannot be evaluated by regular disease activity like DAS28, therefore physical and radiological findings are more important. The two cases were initiated treatment with biologics before synovectomy to avoid flare of synovitis, however, joint destruction progressed by the surgery. Optimal time of initiating biologics therapy and surgical intervention should be determined.

P1-127

Total Knee Arthroplasty in Rheumatoid Arthritis with Biologic Agent`s Therapy-Comparison between Arthloplasty before Biologic and Biologic before Arthroplasty-

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Conflict of interest: None

Introduction: The objective of this study was to demonstrate clinical outcome between Surgery before Biologic and Biologic before Surgery for Total knee Arthroplasty (TKA). **Materials and Methods:** Thirty patients were the subject of the study. There were 32 joints in Arthroplasty before Biologic (AB group) and 23 joints in Biologic before Arthroplasty, respectively. We estimated the patients characteristics, the laboratory data, the clinical outcomes, DAS 28 and complications after surgery. **Results:** No significant difference was noted in the patients characteristics, the clinical outcomes, DAS 28. Conversely, post operative knee range of motion in BA group have a significant better than AB group ($P<0.05$). There was one deep infection in AB group. In BA group, three were the superior infections. **Discussion and Conclusion:** This study showed that Biologic before surgery for TKA supposed to be more effective in the postoperative knee motion and the perioperative care than Arthloplasty before biologic.

P1-128

Steroid injection effect in wrist joint pain of RA

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Conflict of interest: None

[Objectives] Arthroplasty is generally conducted in RA patient with wrist joint disorder. Since many patients do not wish operation, triamcinolone acetonide 40 mg and 1% lidocaine 5 ml were injected into distal radioulnar joint to investigate the improvement of pain & motion and the adverse reaction of triamcinolone acetonide. [Methods] Of the 65 patient (56 females and 9 males) underwent injection during the period from 2009.11. to 2013.11. Larsen Classification assessed fourteen, 17, 20 and 14 cases as Grade I, II, III and IV, respectively. The injection was given in 40, 15 and 10 cases to both hands, right hand and left hand, respectively. [Results] Many cases were injected 1 to 4 times/year, however, a few received 5 to 13 injections. As the results of injection, the pain disappeared or decreased after injection and range of the wrist motion improved. There were no subcutaneous atrophy or depigmentation described as the adverse reactions of triamcinolone acetonide. X-ray test indicated joint narrowing progressed in some but not in others. Whether this is due to RA deterioration or an adverse reaction of injection is not clear. [Conclusion] The injection of triamcinolone acetonide is considered worthwhile for the patients who don't want under operation.

P1-129

Progression of hand lesion is related with cervical and/or lumbar spinal instabilities in patients with rheumatoid arthritis

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Conflict of interest: None

[Objectives] We investigated the relations of hand lesion and cervical

and/or lumbar spinal instabilities in patients with rheumatoid arthritis (RA). [Methods] One-hundred and twenty two patients (16 men and 106 women, mean age 65 (41-84) years) were enrolled. Instabilities of cervical spine were defined as atlantodental interval > 3 mm, Ranawat-value < 13 mm and anteroposterior translation at middle to lower cervical spine > 3 mm by plain radiograph. Instability of lumbar spine was defined as anteroposterior translation > 3 mm. Hand lesion was evaluated with Steinbrocker's classification. [Results] Thirty-eight cases (31%) exhibited cervical spinal instability and 42 cases (34%) lumbar spinal instability. Seventeen cases (13%) showed cervical and lumbar spinal instabilities. Hand lesions were classified into stage I in 34 cases (28%), stage II in 28 cases (23%), stage III in 40 cases (33%) and stage IV in 20 cases (17%). Compared with stage I and II, the instabilities of cervical spine (P=0.0001), lumbar spine (P=0.00091) and instabilities of cervical and lumbar spine (P=0.0072) were observed significantly higher in stage III and IV. [Conclusion] A progression of hand lesion was associated with spinal instabilities in lumbar spine as well as cervical spine in patients with RA.

P1-130

Nano-fiber scaffold induces osteogenesis and chondrogenesis of human mesenchymal stem cells

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Conflict of interest: None

[Objectives] We have described the new ability of mesenchymal stem cells (MSCs); inhibition of osteoclastogenesis and differentiation into osteoblasts in inflammatory circumstances. We herein show the cooperative behavior of electrospun poly- (lactide-co-glycolide) fiber (Nano-fiber) in osteogenesis and chondrogenesis of MSCs. **[Methods]** Human MSCs (hMSCs) derived from healthy donors, rheumatoid arthritis (RA) or osteoarthritis (OA) patients seeded on plastic plate or Nano-fiber were cultured *in vitro*. **[Results]** hMSCs seeded on Nano-fiber differentiated into osteoblasts and chondrocytes detected by RUNX2 and SOX9 respectively, without any induction (day 7). Extracellular matrix of cartilage turned to be positive before day 14. Nano-fiber changed the cell-shape of hMSCs to osteocyte-like cells with dendrite at day 28. Simultaneously, osteocyte marker DMP-1 was detected. 56 days-culture resulted in mineralization. RA or OA-derived hMSCs reproduced these results indicating the possibility of this treatment strategy in joint repair. **[Conclusions]** Nano-fiber is a supportive scaffold for not only regeneration of bone but cartilage. More investigation on Nano-fiber-MSC therapy will carry a boon on patients with destructed joints.

P1-131

Staging and mechanism of coxalgia of hip osteoarthritis using X-ray and MRI

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Conflict of interest: None

[Objectives] The Pathophysiology of OA is largely unknown. It has been reported that bone edema, necrosis, microfracture might affect it. The aim of this study is to better understand the staging and mechanism of coxalgia of hip OA. [Methods] We enrolled various staged OA, Group A) in patients without or a slight degree of joint pain, Group B) in patients with a joint pain. MRI examination was performed when the patients complained of joint pain. Plain radiograph was also taken within 3 months of onset. We then evaluated the progression of OA based on images. [Results] In Group A, most cases did not progress to further staged OA by plain radiograph and braod bone signal alterations by hip MRI were not seen in all patients. In Group B, it progressed to further staged OA by plain radiograph in almost all patients. Also, broad bone signal alterations were observed by hip MRI in most patients with joint pain. There was no statistically significant difference between those groups. [Conclusion] In this study, broad bone signal change by hip MRI was not seen in patients without joint pain. On the other hand, broad bone signal changes were seen in most patients with joint pain.

P1-132

The Periostin expression and role in Osteoarthritis

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Conflict of interest: None

[Objectives] The Periostin (PN) expression was indicated by array analysis of rodent OA model. However, in human, there are no reports about that expression in OA. This research was conducted to investigate PN expression and that role in human OA. [Methods] PN mRNA expression in OA cartilage, synovium was detected by qPCR, and PN protein expression in OA cartilage was detected by immunostaining. Moreover, to investigate the role of PN, OA related genes were reviewed in human chondrocytes, synoviocytes stimulated by PN. [Results] We analyzed PN expression in degeneration cartilage which were obtained from OA patients. Main positive staining was detected in ECM and chondrocyte surrounded by degenerative area. However, PN qPCR didn't show constant trend in OA synovio/chondrocyte. For further investigation, we examine in vitro PN affect to synovio/chondrocyte. PN addition to these cells induced upregulation of inflammatory cytokines, MMPs dose dependently. Moreover, the chondrogenic marker expression also decreased by addition of PN. [Conclusion] The PN expression was detected in chondrocyte and matrix of OA cartilage. PN induced the expression of degenerative and inflammatory markers in vitro. It is suggested that PN expression and deposition might accelerate OA degeneration.

P1-133

The C1q expression in osteoarthritis cartilage

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Conflict of interest: None

[Objectives] Complement is serum protein working for natural immunity. In particularly, C1q was reported other many roles. Reentry, it is revealed that C1q can stimulate Wnt/beta-catenin signaling. Wnt/beta-catenin is important for osteogenesis and chondrogenesis, homeostasis, and osteoarthritis (OA). This research conducted to examine the C1q effect to OA. [Methods] We prepared two rat OA models; surgery and chemical administration, and detected C1q by immunostaining. Moreover, we also stained at human OA cartilage. In vitro analysis, we traced the beta-catenin signaling in osteoblast and mesenchymal cells stimulated by C1q. Furthermore, we reviewed C1q effect to their osteo/chondro differentiation. [Results] The C1q expression was detected in deeper area of rat chemical OA cartilage, and also in human OA cartilage with degenerative degree. However, in vitro analysis, beta-catenin signaling could not be detected in osteoblast and mesenchymal cells stimulated by C1q. Moreover, the differentiation effect by C1q also could not be found. [Conclusion] It is indicated that C1q had some roles in OA by rat, human immunostaining. But, in vitro analysis didn't show any significant results.

P1-134

Study of pseudogout cases in our hospital

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Conflict of interest: None

【Purpose】Pseudogout is arthritis induced by CPPD crystals. We report study and research the cases of finally diagnosis of pseudogout. 【Method】We targeted 86 cases (40-94 years, 77.8 years average, male

33, female 53) and was diagnosed with pseudogout in our hospital between 2004 to 2013. Survey items were 1) maximam value of WBC, CRP and temperature 2) onset region 3) treatment 4) OA change and calcification in the radiograph 5) patient history.【Result】1) WBC 4,900~17,500/μl (average 9,249/μl), CRP 0.1~36.1mg/dl (average 14.2mg/dl), temperature 35.2~40.8℃ (average 37.9℃). 2) 80 cases of knee joints 106 knees, 8 cases of ankles 12 feet, 4 cases of shoulder joints 6 shoulders, 3 cases of elbow joints 3 elbows, 3 cases of wrists 5 hands and 2 cases of cervical vertebrae. 3) 65 cases of NSAIDs administration alone, 3 cases of oral steroid, 10 cases of intra-articular steroid and 2 cases of arthroscopiy. 4) Of the 49 cases of knee joint 83 knees, OA 45 cases 76 knees, calcification 39 cases 65 knees, of the 3 cases of ankle joints 5 feet, OA 1 case 2 feet, calcification 2 cases 3 feet. 5) 31 cases of hypertension, 14 cases of diabetes mellitus, 10cases of ischemic stroke.【Conclusion】Pseudogout is common in the knee and is causing various symptoms such as repeating attack, simultaneous multiple arthritis.

P1-135

A case of erosive osteoarthritis mimicking rheumatoid arthritis

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Conflict of interest: None

A 63-year-old female suffered left wrist-joint pain with swelling in 200X. Left finger-joint (2^{nd}, 3^{rd} and 5^{th}) deformities were detected in 200X+1, and then the pain and deformities were spread to right-thumb IP and other right finger joints (2^{nd}, 3^{rd} and 5^{th}) in 200X+2. Although the patient was initially diagnosed as RA, her symptoms have been gradually worsened. Laboratory data (when treated with prednisolone 4.5 mg) were as follows: CRP 0.01 mg/dl, ESR 5 mm/h, anti-CCP 0.5 U/ml, RF 21 IU/ml, and ANA<40. Hand X-ray exhibited erosive and osteoproliferative changes in her bilateral finger and thumb joints. Hand MRI further exhibited Gd-enhancement in her right thumb IP and MCP joints. Upon diagnosis with erosive osteoarthritis, the patient was treated with prednisolone (5mg) and loxoprofen (120mg). Due to the progression of her arthritis, she underwent arthrofixation therapy of the right thumb IP, left thumb CM and left DIP joints in 200X+5. Administration of methotrexate and biologic agents are now considered to treat this progressive arthritis. Here we report a progressive case of erosive osteoarthritis in focusing its differential diagnosis.

P1-136

Bilateral lipoma arborescens of the knee: a case report -a study of cytokines in synovial fluids-

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Conflict of interest: None

【Introduction】Lipoma arborescens (LA) is a rare, benign intra-articular lesion characterized by villous proliferation of the synovium. We report a case of bilateral LA of the knee and data of cytokines in synovial fluids.【Case peport】A 38 year-old male presented with the complaint of swelling of the bilateral knee for 8 years. Blood tests showed CRP of 0.4mg/L, anti-CCP antibody and rheumatoid factor were negative. Approximately 150 mL of fluid was aspirated from the right knee and 250mL from the left. Testing of synovial fluids revealed IL-1β of 25pg/mL, IL-6 of 594pg/mL, TNF-α of 1.2pg/mL. MRI showed synovial proliferation with high signal intensity on T1 and T2 image. The patient was treated by arthroscopic synovectomy of the bilateral knee and followed up for 12 months with no recurrence.【Discussions】Some authors report that LA may induce a secondary osteoarthritis (OA). In other study, our data of synovial fluid revealed IL-1β of 8.2pg/mL, IL-6 of 43.7pg/mL, TNF-α of 1.7pg/mL in OA patients (5knees), and 19.3pg/mL, 4130pg/mL, 11.1pg/mL in rheumatoid arthritis (RA) (9knees). In this case, IL-1β and IL-6 were higher than OA patients, IL-1βwere approximately equal to RA. It was suggested that destructive process of LA was different from OA based on a result of cytokines.

P1-137

Relationship between the history of total knee arthroplasty and the level of d-dimer

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Conflict of interest: None

[Objectives] We use serum d-dimer as a screening test for detecting preoperative deep vein thrombosis (DVT) for inspection before total knee arthroplasty (TKA). In this study, we investigated the relationship between the history of total knee arthroplasty and the level of d-dimer. [Methods] We reviewed data from 151 patients (160 knees) who underwent unilateral primary TKA for the treatment of osteoarthritis at our hospital between January and September 2013. We divided them into two groups—111 knees without the history of TKA as Group A and 49 knees with the history of TKA as Group B. The average serum level of d-dimer was compared. The correlation between the period of first TKA and the level of d-dimer also investigated. [Results] The average serum d-dimer were 0.97μg/mL in Group A and 1.5μg/mL in Group B ($p<0.05$). There was a weak negative correlation between the period from first TKA and the level of d-dimer ($R=-0.25$). [Conclusion] The serum d-dimer level in patients with the history of TKA was significantly high even though DVT had not been detected by echogram. D-dimer level had a weak negative correlation with the period from first TKA. Therefore, patients who undergo second TKA soon after first TKA should be carefully monitored.

P1-138

Efficacy and Safety of Daily Teriparatide Treatment for 2 years in Osteoporosis in Patients with Rheumatoid Arthritis

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Conflict of interest: Yes

[Objectives] Efficacy and safety of daily teriparatide (TPTD) for 2 years in osteoporosis (OP) in RA patients and to analyze predictors for efficacy at 24month (m). [Methods] 29 RA patients (all female) in whom 24m had past from initiation of TPTD were used. Patients' characteristics, BMD of lumbar spine (LS-BMD), BMD of total hip (TH-BMD), bone turnover markers (BTM), drug retention rate and reason of stopping TPTD were investigated. Predictors of efficacy in LS-BMD and TH-BMD at 24m were also investigated. [Results] Mean age was 70.9 years old. Mean RA duration was 19.8 years. Rate of previous fracture was 79.3%. %increase of LS-BMD at 6, 12, 18, 24m were 7.0, 11.5, 11.6, 12.1 %. %increase of TH-BMD at 6, 12, 18, 24m were 2.3, 4.3, 5.2, 6.0%. BTMs were increased to the peak at 6-12m and decreased afterward. Drug retention rate was 82.8% at 24m. Reason of stopping TPTD was vascular event in 3 cases. Predictor for efficacy in LS-BMD at 24m was good %increase in LS-BMD at 6m. Predictors for efficacy in TH-BMD at 24m were low mHAQ and good %increase in LS-BMD and TH-BMD at 6m. [Conclusion] TPTD was effective in OP in RA patients. Early efficacy was collerated with efficacy at 24m but BTMs were not. Efficacy for TH-BMD was decreased in patients with low activity of daily living.

P1-139

Predict factor for change of bone mineral density in RA patients from TOMORROW study

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Conflict of interest: None

[Objectives] Bone mineral density (BMD) of rheumatoid arthritis (RA) patient more decreased than that of healthy volunteer. We investigated the change of BMD (ΔBMD) in RA and volunteer. The predict factor for ΔBMD was analyzed in RA. [Methods] We analyzed TOMORROW study, which is a prospective cohort for age and sex matched RA and volunteers. BMD were measured at three points (whole body, lower limb, lumber) by DXA. We compared ΔBMD in RA and volunteer between 2010 and 2013. We investigated the predict factor for ΔBMD in RA by univariate analysis. [Results] 192 RA and 194 volunteers were entry. ΔBMD of RA was -0.2% (whole body), -0.1% (lower limb), and 3.1% (lumber). That of volunteer was 0.4% (whole body), -0.1% (lower limb), and 2.2% (lumber). ΔBMD of lumber increased significantly in both groups ($p<0.0001$). There was not significantly deference between groups. In RA, ΔBMD of lumber in bisphoshonete user was significantly higher than that in non-bisphoshonete user (6.2% vs 1.8% $p=0.0001$). Change of disease activity and biologics agent were not influenced for ΔBMD. [Conclusion] The reason of increase in BMD of lumber was reflected degenerative changed of lumber. Bisphoshonete was more important factor influenced for ΔBMD than change of disease activity and biologics agent in RA.

P1-140

Opportunistic screening for osteoporosis using computed tomography scans obtained for other indications in patients with rheumatic diseases

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Conflict of interest: None

[Objectives] To evaluate computed tomography (CT)-derived bone mineral density (BMD) assessment compared with dual-energy X-ray absorptiometry (DXA) measures for identifying osteoporosis by using CT scans performed for other clinical indications in patients with rheumatic diseases. [Methods] In 87 patients who underwent CT and DXA within a 6-month period and whose doses of steroid and treatment drugs for osteoporosis were allowed to be changed within a 3-month period between April 2012 and March 2013 in our center, we measured CT-attenuation values (in Hounsfield units: HU) of trabecular bone of the L1 vertebral level (L1-CT) and DXA BMD. [Results] L1-CT was significantly positively correlated with Young Adult Mean (YAM) values and T-score of DXA BMD (correlation coefficient 0.592, 0.596 both $P<0.001$). An L1-CT threshold of 70 HU for T-score$\leqq$-2.5 and 120 HU for YAM values<80% had a sensitivity of 60% and 94.6%, a specificity of 89.6% and 62%, a positive predictive value of 42.9% and 64.8%, and a negative predictive value of 94.5% and 93.9%. [Conclusion] CT images obtained for other reasons that include the lumber spine can be used to identify patients who have rheumatic diseases with osteoporosis or normal BMD without additional radiation exposure or cost.

P1-141

Investigation of effects on bone metabolism of anti-TNF-α biologics and bisphosphonates in patients with rheumatoid arthritis

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Conflict of interest: None

[Objectives] Our purpose is to investigate effects on bone metabolism of anti-TNF-α Biologics and bisphosphonates (BPs) among patients with rheumatoid arthritis (RA). [Methods] We selected 18 cases of patients with RA who received BPs for the first time and investigated effects on bone metabolism of BPs. 40 cases of patients with RA who already took BPs more than 6 months (BPs group) and 40 cases of those who received BPs and anti-TNF-α Biologics (BPs+anti-TNF-α group) were subjected to this study as well. We investigated bone resorption markers (NTX, TRACP5b), bone formation markers (BAP, osteocalcin), cartilage metabolic markers (MMP-3, COMP), mineral density (BMD) and inflammatory situation with ESR, CRP, DAS28 (ESR) and DAS28 (CRP). [Results] BPs led to low bone turn over and lumbar BMD was significantly increased ($P<0.05$). COMP is significantly lower in BPs+anti-TNF-α groups than BPs group ($P<0.05$) and CRP of BPs+anti-TNF-α group is significantly lower than that of BPs group ($P<0.05$). In addition, percent change of MMP-3 during 6 months was significantly reduced among BPs+anti-TNF-α group compare to BPs group ($P<0.001$). [Conclusion] Our data suggested that anti-TNF-α Biologics treatment for patients with RA has a potential for indirect suppression of cartilage destruction.

P1-142

Effects of disease activity on bone turnover and oxidation stress markers level in early rheumatoid arthritis

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Conflict of interest: None

[Objectives] To evaluate the effects of disease activity of rheumatoid arthritis on bone turnover and oxidation stress markers. [Methods] Consecutive fifteen patients with rheumatoid arthritis, 53% women, mean disease duration of 1.5 year were included. The levels of serum TRACP-5b (tartrate-resistant acid phosphate-5b) and P1NP (procollagen 1N-terminal peptide). and urinary pentosidine were measured at diagnosis of rheumatoid arthritis. [Results] In patients of whom disease durations were less than one year, urinary pentosidine levels correlated with the Disease Activity Score using 28 joints (DAS28). Serum TRACP-5b, P1NP levels did not correlate with DAS28. [Conclusion] This study demonstrated that high disease activity affects against pentosidine formation, oxidative damage, but not against bone formation and resorption in patients with early rheumatoid arthritis.

P1-143

Short term effect of denosumab on serum calcium concentrations in patinets with rheumatic disease

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Conflict of interest: None

[Objectives] To investigate short term effect of denosumab on serum calcium levels after first administration in patients with rheumatic diseases. [Methods] From June to September 2013, patients with rheumatic disease admitted to our hospital for treatment of osteoporosis with denosumab. They were administered with denosumab in day 1, and were monitored serum calcium levels every other day until day 15. 1 μg of alfacalcidol was given from day 1. [Results] Of 8 patients enrolled, 6 patients with rheumatoid arthritis and 1 patient with polymyalgia rheumatica completed the protocol. Demographics shows: mean ± SD age 72.5 ± 7.2, body mass index 20.3 ± 1.74 kg/m2, lumber bone mineral density T score -2.1 ± 1.03 at the spine L2-4. 7 patients (87.5%) were given oral grucocorticoid, and the mean dose of predonisolone was 9.6 mg/day. The mean albumin-adjusted calcium was 9.5 mg/dl in day 1 and lowest in day 7, 9.2 mg/dl. It recovered to 9.5 mg/dl in day 15. [Conclusion] It is appropriate for detecting hypocalcemia to monitor calcium level one week after administration of denosumab in patients with rheumatic diseases.

P1-144

Calcium values in osteoporosis patients administered Denosumab under activated vitamin D3 medication

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Conflict of interest: None

[Objectives] Denosumab is new drug for osteoporosis. Medication of vitamin D3 with calcium agents or active vitamin D3 is recommended to avoid from hypocalcemia due to be administered Denosumab. We studied osteoporosis patient's serum calcium value after one week administered Denosumab under activated Vitamin D3 medicated. [Methods] We enrolled sixteen patients (one male and fifteen females) who administered Denosumab from October to November 2013. All patients were medicated activated vitamine D3 without calcium agents. Age range was from 55 to 78. Patients profiles is following, Nine Rheumatoid arthritis (inclued three biologics treated patients) and seven collagen diseases. Twelve patients were treated with bisphosphonate. Thirteen patients were medicated activated vitamin D3. Denosumab was administered after confirmed calcium value was normal. Serun calcium and albumin were measured after one week Denosumab administered and serem calcium values adjusted with sererm albmin were calculated. [Results] The adjusted serum calcium values under activated vitamin D3 medicated after one week Denosumab administered were all within normal range. No hypocalcemia was detected. [Conclusion] Activated vitamin D3 monotherapy can avoid from hypo-calcemia due to administered Denosumab.

P1-145

Two cases of non-traumatic femoral head fractures under the administration of daily teriparatide after the surgery for proximal femoral fracture

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Conflict of interest: None

Successful efficacy of daily teriparatide (TPTD) treatment against osteonecrosis of jaw has been reported, and is also expected to have therapeutic effects against osteonecrosis of femoral head. Meanwhile, in the early phase of administration, bone loss of proximal femur is sometimes observed which is concerned to raise femoral fracture risk. We report two cases (case 1; 72-year-old woman whose femoral neck fracture [Garden type 2] was treated by Hansson pins, followed by 5-months daily TPTD / case 2; 42-year-old woman whose trochanteric fracture [Evan's type 1 group 2] was treated by intramedullary nail, followed by 9-months daily TPTD), who suffered non-traumatic femoral head fractures after operation of proximal femoral fracture, even though they were treated by daily TPTD. In both two cases, femoral neck bone mineral density was considerably low at the time just before the injury (Young Adult Mean; 30% in case 1, 46% in case 2). Careful consideration may be needed for the administration of daily TPTD to the patients with low bone mass at proximal femur after the fixation surgery of the proximal femur fracture.

P1-146

The impact of the use of TNF inhibitor and IL-6 inhibitor on patients with rheumatoid arthritis

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Conflict of interest: None

[Objectives] The aim of this study was to assess the plasma concentrations of bone quality markers in patients with rheumatoid arthritis (RA) who were receiving biologics. [Methods] Thirty-six RA patients (5 male, 31 female; median age: 65 years) were included in this study. Twenty-three patients received TNF-inhibitor, and 13 patients received IL-6 inhibitor. Pentosidine, homocysteine, intact P1NP, TRACP-5b, CRP, ESR, and MMP-3 levels, the DAS28-ESR, DAS28-CRP, CDAI, and SDAI scores, and the BMD (lumbar spine and proximal femur) were assessed. We compared these parameters between patients being treated with TNF-inhibitor (T group) and those being treated with IL-6 inhibitor (I group). [Results] Homocysteine, intact P1NP, TRACP-5b, CRP, ESR, and MMP-3 levels, the DAS28-ESR, DAS28-CRP, CDAI, and SDAI scores, and the BMD showed no significant differences between the two groups. However, the pentosidine levels were significantly lower in the I group than the T group ($p<0.5$). [Conclusion] In this study, the levels of bone quality markers were significantly lower in the I group. These results suggest that biologics, especially IL-6 inhibitor can improve not only the disease activity, but also the bone quality in RA patients.

P1-147

The relationship between severely suppressed bone turnover detected in X ray (SSBT-Xp) and lateral bowing of the femur among patients with rheumatic diseases under bisphosphonates treatment

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Conflict of interest: None

[Objectives] To clarify the relationship between severely suppressed bone turnover in X ray (SSBT-Xp) finding and lateral bowing of the femur among patients with rheumatic diseases under bisphosphonates (BP) treatment. [Methods] One hundred and one patients (175 lower extremities) with rheumatic diseases taking BP were included. The mean age was 54.5 years old (19-82), 90 (89.1%) were females, the mean disease duration was 13.9 years (1.2-43.7) and all of them were taking prednisolone (PSL); the mean dose was 9.8mg daily (0.5-25). The mean duration of BP usage was 4.8 years (0.5-13.5). The X ray of hips and femurs were examined and those who beaking was detected in lateral cortices were defined as SSBT-Xp. Lateral bowing of the femur were evaluated using Kiura's method. [Results] SSBT-Xp (+) was detected in 10 lower extremities (5.7%). No one among patients with SSBT-Xp (+) but 21 lower extremities among SSBT-Xp (-) showed lateral bowing of the femur (p=0.611). The mean of the femur bowing ratio was also not different between SSBT-Xp (+) and SSBT-Xp (-) [46.5% (28.6-57.7%) vs. 48.8% (15.4-75.0%), p=0.511]. [Conclusion] The incidence of SSBT-Xp (+) in patients with rheumatic diseases under BP treatment was not related to lateral bowing of the femur in this study.

P1-148

A Patients Preference Survey for Osteoporosis Medication on 679 Patients : Development of a Questionnaire for the Persistence and Adherence

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Conflict of interest: None

[Objectives] Bisphosphonates are the first-line therapy for osteoporosis treatment though the long-term persistence and adherence remain low. To explore patient preferences, we performed a cross sectional survey. [Methods] A questionnaire was newly developed and distributed to all patients and the attending doctor. A total of 679 questionnaires out of 765 were completed, and the data were evaluated. [Results] 556 men and 83 women were enrolled. All patients assumed oral bisphosphonates. 66%

of the patients were assuming weekly bisphosphonates, 24.4% were assuming monthly bisphosphonates, and 8.7 % were assuming daily bisphosphonates. Interestingly, 42 patients answered to assume daily bisphosphonates while the attending doctor reported to prescribe the daily bisphosphonates to 78 patients. In the multivariate logistic regression model, compared with daily bisphosphonates, weekly bisphosphonates was significantly associated with "forgetting to take a medication" (odds ratio 2.01 [95% CI 1.10-3.65]; P<0.05). [Conclusion] Our newly developed questionnaire revealed that weekly drug regimen was significantly associated with incompliance. Considering with that less number of patients answered "hassle" for monthly drug regimen, the regimen can be a best for the adherence.

P1-149

Study of cases of collagen disease complicated by osteonecrosis or osteomyelitis of the jaw

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Conflict of interest: None

[Objectives] To investigate risk factors for osteonecrosis of the jaw (ONJ) and osteomyelitis of the jaw (OMJ) in patients with connective tissue disease (CTD). [Methods] We examined the clinical characteristics of 5 patients with CTD complicated by ONJ or OMJ treated at our department. [Results] The original disease was systemic lupus erythematosus in 2 cases (1 complicated by rheumatoid arthritis [RA]), scleroderma in 2 cases (1 complicated by RA), and RA in 1 case. There were 4 women and 1 man, with a mean age of 52.2 (39–65) years. Three patients had a history of smoking, and all patients had diabetes and arthritis. All patients received steroids and 3 received immunosuppressants, particularly calcineurin inhibitors. ONJ or OMJ occurred after tooth extraction in 4 patients, 3 of whom received bisphosphonates (BPs) concomitantly and 1 who stopped BP use 3 months before extraction. The remaining 1 patient had not taken BP drugs, but developed OMJ after gingivitis due to cyclosporine administration. [Conclusion] This study suggests that steroid administration, BP administration, tooth extraction, and diabetes, as well as arthritis and calcineurin inhibitor administration are risk factors for ONJ and OMJ in CTD patients.

P1-150

The clinical features and treatment progress of atypical femoral fractures in our facility

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Conflict of interest: None

【Objective】To examine the clinical features in patients with atypical femoral fracture.【Methods】Seven cases (8 femora) were diagnosed with atypical femoral fracture. The age was 36 to 87 year old, and each case was female. Treated bisphosphonates (BP), serum bone specific alkaline phosphatase (BAP), serum 25-(OH)-D, and treatment progress were examined. Iliac bone was subjected to bone histomorphometry.【Results】The underlying disease was 3 of systemic lupus erythematosus, 2 of osteoporosis, 1 of rheumatoid arthritis and 1 of polymyalgia rheumatica. Treated BPs were alendronate in 5 cases and risedronate in 2 cases. Bone specific alkaline phosphatase (BAP) was 8.8 IU/l, and 25-(OH)D was 19.6 ng/mL. Osteosynthesis was performed in each case. Delayed union were observed in 2 femora and then revision surgeries were performed. BP treatment was ceased and teriparatide was treated in 6 cases. The fracture union is acquired in 2 femora. In bone histomorphometry, osteoid parameter was severely decreased in 4 out of 6 cases.【Conclusion】Low BAP, low 25-(OH) D concentration, and low osteoid parameter strongly suggest the association between atypical femoral fracture and severely suppressed bone turnover. Union rate was 25 %, which is not so high. Careful follow up is required.

P1-151

Association of *TRIM21* (Ro52) SNP with systemic lupus erythematosus

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Conflict of interest: None

[Objectives] *TRIM21*, a member of the tripartite motif-containing (TRIM) family, encodes the autoantigen Ro52. TRIM21 is induced by type I interferon, and has many functions, one of which is inhibition of IRF and NFkB pathways. Thus, it is possible that TRIM21 itself may play a role in the occurrence or pathogenesis of autoimmune diseases. Thus far, several small-scale studies suggested the association of *TRIM21* polymorphism with primary Sjögren syndrome (pSS) or systemic lupus erythematosus (SLE), although it remains to be established. In this study, we made an attempt to examine whether a SNP within intron 1 previously reported to be associated with production of anti-Ro52 antibody in pSS (Imanishi et al., 2005) is associated with susceptibility to SLE. [Methods] A case-control association study was performed for rs7947461 on 530 Japanese patients with SLE and 518 healthy controls. Genotyping was performed using TaqMan SNP genotyping assay. [Results] Significant decrease of T/T genotype frequency was detected in SLE (P=0.04, odds ratio 0.72, 95% CI: 0.53-0.99). [Conclusion] These results suggested association of *TRIM21* polymorphism with occurrence of SLE.

P1-152

a case of overlap syndrome conbined with SLE and multiple myositis diagnosed by arrhythmia

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Conflict of interest: None

The patient is a 43-year-old man. He had the arrhythmia of atrial flutter in 39-year-old, ventricular premature contraction in 40-year-old and sinus arrest and non-sustained ventricular tachycardia in 41-year-old. He also had the high level of CK continuously from the age of 39-year-old without symptom. In the 41-year-old, the proteinuria and thrombocytopenia newly appeared. He was diagnosed with overlap syndrome of polymyositis and SLE by the investigation of antinuclear antibody, anti-DNA antibody, renal biopsy, MRI, EMG and muscle biopsy. The findings of cardiac biopsy showed the fibrotic change with irregular cardiac omission. After the therapy by prednisolone and tacrolimus, the proteinuria, the high level of CK, thrombocytopenia were improved. This is the rare case of overlap syndrome which the main findings are arrhythmia.

P1-153

Analysis of 43 SLE patients who died during hospitalization (JUDE cohort study)

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Conflict of interest: None

[Object] Analyzing the cause of death and the type of the SLE patient and consider the underlying disease of the recent SLE patient and the association to the cause of death. [Method] Extracted 43 death examples that our Hospital could analyze than approximately 500 SLE patients with a history of the hospitalization from 2002 to 2012 and analyzed disease types in the last during the cause of death, a contraction of a disease period. [Result] Among 43 cases that they analyzed this time, as for the age at mean death, 56.0±12.4 years old, the sex ratio are 1:7.6. The mean contraction of a disease periods from the last onset to the death are 19.8±12.0 year. The ratio of type at admission was 39% of lupus nephritis, arthritis 19%, cytopenia 16%, exanthem 12%, NPSLE 7%. The ratio about the cause of death was order of 32% of infectious diseases, malignant tumor 21%, underlying disease 19%, 12% of cardiovascular system. Lupus nephritis was 57%, and the cause of death of the underlying disease was the most. [Conclusion] The death due to complications accounts for approximately more than 80% in 43 SLE death examples, and the prophylaxis for these risk factors is important to further life prognosis improvement.

P1-154

The relationship between the activation route of complement system and clinical features in SLE patients

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Conflict of interest: None

[Objectives] To investigate the relationship between the activation route of complement system and clinical and laboratory features in SLE patients. [Methods] SLE patients were devided into two groups according to the activation route of complement system: 1. patients in that the complement system was activated mainly through the classical pathway (CP group) and 2. patients in that the complement system was activated mainly through the alternative route (AP group). Clinical and laboratory features were compared between the groups. [Results] We could observe more frequent presence of arthritis and nephritis in CP group compared with AP group. The prevelence of anti DNA antibody and disease activity index (SLEDAI) were significantly higher in CP group than those in AP group. The frequency of thrombosis was significantly lower in CP group than that in AP group. [Conclusion] These results are consistent with previous reports that the activation of complement system via classical pathway is firmly connected with the pathogenesis of SLE.

P1-155

Maternal and fetal outcomes in systemic lupus erythematosus

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Conflict of interest: None

[Objectives] To investigate the relationship among preterm birth, miscarriage, light for dates, perinatal complications, and the maternal or fetal outcomes in women with systemic lupus erythematosus (SLE). [Methods] We investigated 69 pregnancies in 44 SLE patients from 1996 to 2013 them retrospectively. The rate and the risk of preterm birth, miscarriage, neonatal birth weight, perinatal complications and the dose of corticosteroid treatment were assessed. [Results] The mean patient age, the mean dose of prednisolone (PSL), and the average of delivery weeks was 31.8 years and 8.9 mg/day and 36.9 weeks, respectively. The incidence of miscarriage, preterm birth and perinatal loss was 10.4%, 17.4% and 2.8%, respectively. The average neonatal birth weight was 2550 g. We found high incidence of miscarriages in lupus anticoagulant (LAC) positive patients compared with LAC negative patients (p=0.0008). Birth weight was negatively correlated with PSL dose (r=-0.356, p=0.022). Fetal malformations were not observed. Six patients were exacerbated underlying SLE, but 5 patients had good outcomes with the increase in PSL dose. [Conclusion] In pregnancy complicated with SLE, patients with Lac have a risk of miscarriage, and low birth weight was associated with high dose of PSL.

P1-156

Safety of early discharge practice with high dose steroids for lupus patients

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Conflict of interest: None

[Objectives] To evaluate safety of early discharge practice with high dose steroids for lupus patients. [Methods] We retrospectively extracted all patients admitted deu to lupus during the period of April, 2006 to November, 2013. Electric chart review was performed to collect the patients charateristics, doses of steroid, and any compications which required readmission after discharge. [Results] Fifty patients were admitted due to lupus flare. Mean age (SD) at the time of admission was 40.5 (15.6) yrs. All but 4 patients were female. Mean and median duration of hospitalization were 17.8 days and 13.0 days, respectively. The number of the patiets devided based on steroid dose (PSL) at the time of discharges were as follows: 11 with more than 50mg/day, 20 with 40mg to 50mg, 10 with 30 to 40mg, and 11 with less than 30mg. Seven patients required readmission because of infection: 3 with gastroenteritis, 3 with herpes zoster, and 1 with cellulitis. At the time of re-admission, the mean duration after first discharge was 569.3 days, and the dose of steroid was PSL 10.8mg/day. [Conclusion] Early discharge practice with high dose steroids may be safe for lupus patients.

P1-157

A case of lupus proctitis and mesenteric panniculitis presenting as lower abdominal and anal pain

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Conflict of interest: None

A 45-year-old woman was diagnosed with SLE from photosensitivity, pancytopenia, anti-DNA antibody, and ANA in 2005, and was in remission (SLEDAI 2) with prednisolone (PSL) 7 mg/day and tacrolimus 3 mg/day in 2012. She was admitted to our hospital in the end of June 2013 because of her lower abdominal and anal pain, and increase in hair loss. Urine occult blood, pyuria, hair loss, hypocomplementemia, and high titer of anti- ds-DNA (SLEDAI 14) were observed. The pelvic contrast CT showed elevated levels of adipose around the rectal and rectal wall thickening. Rectal mucosal biopsy was performed to rule out infectious proctitis. It showed an inflammatory cell infiltration, mainly not neutrophils but lymphocytes. From these, she was diagnosed as lupus proctitis and mesenteric panniculitis. Since we initially could not distinguish infectious proctitis, cefmetazole 1g twice a day was administered, but was not effective. We finally increased PSL to 40 mg/day, and got trend toward improvement in pain and CRP after a week. We also confirmed improvement of pelvic CT findings. Lupus proctitis is a rare clinical condition, so we reports here.

P1-158

Male lupus manifestation in our hospital

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Conflict of interest: None

[Objectives] SLE predominantly occurs in females during their childbearing age. Generally, male lupus is rare and a female-to-male ratio is 10:1. Several characteristics of male lupus has been already reported, such as higher rate of haematological abnormalities, renal involvement

comparing with females. However, the characteristics of male lupus remains unclear. Therefore, we researced male lupus in our hospital, to know more about the characteristics of male lupus. [Methods] We retrospectively researched SLE cases who were newly diagnosed from January 2006 through October 2013 in our hospital. We analyzed by age at diagnosis, laboratory data, clinical features, SLEDAI, treatment. [Results] 30 patients consisting of 6 male (20%) and 24 females (80%) newly developed SLE in 8 year. Several clinical manifestations were significantly dominant in male lupus patients than females; such as older age at diagnosis (female 43.4±17.0, male 61.8±18.2), negative ratio of the lupus anticoagulant, and relatively higher C4. Although there was no significant difference in the distribution of the organ damages, it seems a fewer frequency of skin involvement in male lupus. [Conclusion] We report the characteristics of male lupus in our hospital compared with some review of the previous literature.

P1-159

A study on the association of structural and functional deletion polymorphisms of *LILRA3* and systemic lupus erythematosus

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Conflict of interest: None

[Objectives] The leukocyte Ig-like receptor (*LILR*) is a gene family in 19q.13.4. LILRA3 is the only secreted protein among LILRs, but its function remains unclear. *LILRA3* has a deletion polymorphism lacks most of the coding region, and its allele frequency is especially high in the Japanese (71.0%). Besides, *LILRA3* has non-functional alleles resulting from a shared splice site SNP. Association of the deletion with multiple sclerosis, and increased expression of LILRA3 in SLE have been reported in Caucasian, but association with autoimmune diseases has not been published in Japanese. In this study, we genotyped for *LILRA3* deletion and the splice site SNP, and examined their association with SLE. [Methods] 780 Japanese SLE patients and 773 healthy controls were used. *LILRA3* deletion was genotyped by PCR-SSP, and splice site SNP was genotyped by TaqMan SNP genotyping assay. [Results] Association between the deletion and SLE was not detected. However, analyzing the deletion and the non-functional alleles in combination, a tendency towards decrease of the individuals without functional *LILRA3* allele was observed in SLE. [Conclusion] Considering the previously reported increased expression of LILRA3 in SLE, our observations may suggest that *LILRA3* deficiency might be protective against SLE.

P1-160

The results of International Conference on Cutaneous Lupus Erythematosus Questionnaire in Japan

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Conflict of interest: None

【Objectives/Methods】Recently Reich A. et al. performed the questionnaire survey about the treatments of cutaneous lupus erythematosus (CLE). To elucidate the trends in Japan, we tallied the replies form 28 dermatological institutions including 23 university hospitals.【Results】1. Lifestyle guidance. About a half of replies always informed the influence of ultraviolet rays and recommended the protection from them. Only a quarter always recommended smoking cessation. 2. How to assess the treatment efficacy. Physician Global Assessment were mainly used. QOL measures or Patient's opinions was also used. 3. The details of the rate about the drug efficacy. Ultra-potent corticosteroids, oral corticosteroids and calcineurin inhibitor ointment were evaluated to be efficacious, and low-potent corticosteroids were evaluated to be not efficacious regardless of the CLE type. Many replies had no opinions about the efficacy of immunosuppressants or Dapson, but most of the others evaluated to be efficacious.【Conclusion】The guidance about ultraviolet rays and smoking should be done thoroughly. Systemic therapeutic options are not so many and most of them are off-label use. Hydroxychloroquine, which may be going to be available in Japan, will be an useful option.

P1-161

Distal femoral osteonecrosis in systemic lupus erythematosus successfully treated with teriparatide

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Conflict of interest: None

A 60 year-old woman was admitted to a previous hospital for right femoral pain in mid-December 2010. She was diagnosed with necrotizing fasciitis, and developed acute renal failure. She was transferred to our hospital in late December, and was diagnosed with systemic lupus erytematosus (SLE) from positive tests for anti-dsDNA and anti-nuclear antibodies, pericarditis, and persistent proteinuria. Congestive heart failure, disseminated intravascular coagulation, and hemorrhagic duodenal ulcer complicated with SLE were observed, but these were ameliorated by the therapy including oral predonisolone (PSL) 20mg daily. After discharge, risedronate 17.5mg weekly was initiated for the prevention of osteoporosis, and PSL dosage was gradually tapered to 10 mg daily. However, in July 2012, left hip and knee pains appeared. She was readmitted in February 2013 because of gait disturbance. MRI revealed osteonecrosis (ON) of her bilateral distal femurs. Teriparatide (TP) treatment of 20 μg daily resulted in gradual improvement of gait disturbance. TP is reported to be effective on bisphosphonate-related ON of the jaw. However, the effect of TP on other ON had not been documented. The present case suggests that TP may be effective on distal femoral ON secondary to SLE.

P1-162

Clinical characteristics of systemic lupus erythematosus associated with hemophagocytic syndrome as a primary manifestation

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Conflict of interest: None

[Objectives] To assess the clinical characteristics of systemic lupus erythematosus (SLE) associated with hemophagocytic syndrome (HPS) as a primary manifestation. [Methods] Four patients (3 female and 1 male) with SLE associated with HPS as a primary manifestation were evaluated to clinical symptoms, laboratory findings and treatment. [Results] The mean age was 25.5 years old (range 22-33). All patients had fever, 3 had lymphadenopathy and 1 had hepatosplenomegaly. Three patients had nephritis, but no myocarditis, pericarditis and central nervous system syndrome. WBC, Hb and Plt were 1010-2720 /μl, 9.6-13.5 g/dl

and 59-168×10^3 /μl, respectively. The mean ferritin was 3657 ng/ml and the mean LD 625 U/l. All patients were positive for anti-dsDNA Ab, anti-SS-A Ab and 2 were positive for anti-RNP Ab. Blood cell count improved in mean 8.6 (range 7-10) day, after the initiation of prednisolone. In 3 cases, proteinuria and hypocomplementemia were improved after add tacrolimus. [Conclusion] SLE associated with HPS as a primary manifestation presented nephritis in 25% in previous reports, but in 75% in our department. Steroids therapy was useful for cytopenia in SLE associated with HPS as a primary manifestation.

P1-163

Characteristics of three systemic lupus erythematosus with retinopathy

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Conflict of interest: None

[Objectives] Systematic lupus erythematosus (SLE) is an autoimmune disease that affects multiple organs. Lupus retinopathy influences QOL for visual disorder. Thus, we analyzed characteristics of pts which had SLE with retinopathy in our hospital. [Methods] We examined three pts from 2011 to 2013. [Result] All pts were women at 35-47 years old. About the eye ground, two pts had soft exudate and hemorrhage, and one had central serous chrioretinopathy. All pts had arthritis, positive antinuclear antibodies (Ab) and anti-RNP Ab, and hypocomplementemia. Anti cardiolipin Ab and lupus anticoagulant were negative in all pts. Immune complex, anti-dsDNA Ab, anti-Sm Ab were seen in two pts each. Two had CNS lupus. All pts were treated with oral prednisolone 1mg/kg/day, and two needed steroid pulse. All pts had improved clinically with no ocular symptoms. [Discussion] 3-20% of pts with SLE has retinopathy and it is thought to be caused by infarction due to immune complex and antipospholipid Ab, and vasculitis. In our pts, all pts had specific autoantibodies for SLE and two had immune complex positive and CNS lupus each. [Conclusion] We experienced three SLE pts with retinopathy. For SLE pts, ophthalmological examination should be considered without visual manifestations.

P1-164

A case of autoimmune pulmonary alveolar proteinosis during the treatment of systemic lupus erythematosus

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Conflict of interest: None

A 63-year-old woman was diagnosed as pandysautonomia and Sjogren's syndrome in 1988, and was diagnosed as having systemic lupus erythematosus (SLE) in 1992. She was given 50mg/day (1mg/kg) of prednisolone (PSL). Her SLE was improved, and the dose of PSL was tepered to 9mg of PSL and 300mg of mizoribine (MZB). In August 2009, she felt exertional dyspnea. High-resolution computed tomography of her chest revealed scattered ground–glass opacities in the peripheral side of both lung fields. Her medicine changed from MZB to 50mg/day of azathioprine in November 2010 because of the elevation of serum KL-6 level (1734U/ml). But her respiratory symptoms did not improve. Bronchoalveolar lavage showed eosinophilic granular material and autoantibody against GM-CSF was positive. We reported a rare case of SLE associated with aPAP and reviewed the literatures.

P1-165

A case of systemic lupus erythematosus complicated with pneumatosis cystoides intestinalis

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Conflict of interest: None

Case report: In December, 2012, a 76-year-old woman who hospitalized with a diagnosis of alveolar hemorrhage. Steroid pulse therapy started instantly. At a later date, she was given a diagnosis of SLE by laboratory findings. About one month later, she suffered from cytomegalovirus infection, and immediately ganciclovir treatment was performed, but the five days later, free air with the peritoneal irritation sign was found, and she was diagnosed perforation of the digestive tract with pneumatosis cystoides intestinalis from an examination for abdomen CT. The clear perforation part was unidentified in the urgent laparotomy, and she was followed up by drainage conservatively. A few days later, cytomegalovirus infection and pneumatosis cystoides intestinalis was improved and discharged about three months after hospitalization. It is reported that the etiology of pneumatosis cystoides intestinalis is possibly-associated with the collagen disease such as SLE or scleroderma, viral infection such as CMV, and steroid therapy. In this case, it is difficult to specify a cause for it. We reports a rare case and discuss it.

P1-166

Spontaneous rupture of the flexor digitorum profundus tendon as a complication of corticosteroid therapy for systemic lupus erythematosus

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Conflict of interest: None

[Introduction] Finger tendon rupture as a complication of systemic lupus erythematosus (SLE) is uncommon. Here, we describe a case of a patient with SLE who presented with spontaneous rupture of a flexor tendon. [Case] 50-year-old woman with SLE was treated with prednisolone for pulmonary hypertension. The patient reported the sudden onset of pain in the right hand after performing a strong pinch grip and was subsequently unable to flex the distal interphalangeal (DIP) joint of the right index finger. She was diagnosed with rupture of the flexor digitorum profundus (FDP) tendon of the right index finger complicated by Kienböck's disease. Tendon repair was performed after the corticosteroid dose was tapered. Intraoperative findings revealed that the FDP tendon was ruptured in the carpal tunnel. The FDP tendon of the index finger was repaired using a side-to-end anastomosis to the flexor digitorum superficialis tendon of the index finger. Five months postoperatively, the patient was able to flex the DIP joint of the right index finger. [Conclusion] Although corticosteroid therapy is required for SLE patients with significant organ involvement, doctors should be aware of the possibility of tendon rupture as an adverse effect of glucocorticoid use.

P1-167

A case of late-onset systemic lupus erythematosus with various symptoms like IgG4-related disease

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Conflict of interest: None

A 71-year-old man was diagnosed with severe angina pectoris and valvular heart disease. The patient was referred to our department due to pancytopenia, anti-ds-DNA antibody positivity, low complement, and joint pain, and systemic lupus erythematosus (SLE) was suspected. However, pancytopenia was improved naturally after the surgery for the heart disease. Three months after the surgery, the patient's serum levels of IgG, IgG4, IgE were elevated, and adenopathy of lymph node around the kidney appeared. Lymph node biopsy of inguinal node showed poor infiltration of IgG4. Thus, we diagnosed the patient SLE not IgG4-related disease. Here, we present a rare case of SLE with atypical symptoms and data.

P1-168

The analysis of 423 SLE patients that survived long-term. From - JUDE cohort study -

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Conflict of interest: None

[Objectives] Although it was improved, the prognosis of patients with SLE needs long-term treatment management. We determine clinical features and the factors associated with the relapse from 423 SLE patients that we were able to observe in our hospital for a long term. [Methods] We conducted JUDE (Juntendo University Database of Erythematosus) cohort study in SLE cases in our hospital. We analyzed it about clinical course, a relapse rate, and the factor which contributed to recurrence. The definition of the recurrence obeyed SLENA-SLEDAI flare composite. [Results] The SLE case that was able to chase for a long term the clinical course after initial treatment was 423. The average of age at onset was 29.7 years old, and the sex ratio was 7:93. At the time of initial treatment, the ratio of which had febrile symptom was 32.9%, arthritis 54.9%, cutis symptoms 47.3%, mouth ulcer 14.7%, leukopenia 36.4%, thrombocytopia 11.4%, hemolytic anemia 2.4%, nephropathy 31.4%, and central nerve lesions 5.9%. The average of the number of relapse during this observation was 0.51 times, and 135 cases (31.9%) was relapsed more than once. To have pleurisy or serositis contributed to relapse rate. [Conclusion] In 423 SLE patients, it contributed to relapse to have pleurisy or serositis at initial treatment.

P1-169

A case of late-onset steroid resistant SLE remissed by low-dose azathioprine

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Conflict of interest: None

A 86-year-old female had a continuous fever with leukocytosis, elevated CRP levels, and left-sided pleural effusion on her chest CT in mid February 2013. Antibiotics could not improve her symptoms, then platelet count decreased to 4,000/μl for several weeks in April. Further exam revealed that she had oral ulcer and tested positive for antinuclear, anti-dsDNA, and antiphospholipid antibodies. She was diagnosed as SLE and prednisolone (PSL) 30mg/day was initiated, then transferred to our hospital in early May. On admission, pleural effusion had disappeared and platelet counts had increased to 60,000/μl. Tacrolimus (TAC) 1mg/day was started on 4th day and PSL was tapered to 25mg/day, but one week later platelet count decreased to 36,000/μl. We stopped TAC and performed steroid pulse therapy followed by PSL 30mg/day. After we initiated azathioprine (AZP) 25mg/day on 21st day, thrombocytopenia was gradually improved. PSL was tapered and she was discharged on 62nd day. Late-onset SLE is rare and often has clinical features different from those of early-onset SLE, leading to a delayed diagnosis. But it had less common occurrence of severe manifestations and better prognosis. This case was steroid resistant, but could attain lasting remission with a combination of PSL and low-dose AZP.

P1-170

Splenic infarction, antiphospholipid antibodies in a patient with systemic lupus erythematosus

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Conflict of interest: None

A 40-year-old man with systemic lupus erythematosus (SLE) developed a massive splenic infarction. SLE was diagnosed in 1999 on the basis of pleurisy, and treated with prednisone. In May 2013, while he was still taking prednisone (PSL) 8mg daily, the patient was admitted because of exertional dyspnea and left back pain. Chest computed tomography demonstrated multiple atelectasis in base of bilateral lungs. We diagnosed as organizing pneumonia associated with SLE and PSL 60mg daily was started. Within five days of therapy, the dyspnea and CT image were improved. Routine abdominal computed tomography revealed splenic arterial and venous thromboses and a massive splenic infarction, and this splenic infarction suggested to cause the back pain. Low-dose aspirin and heparin were started to prevent recurrent thrombosis. Laboratory data showed a mild elevation of FDP, D-dimer, soluble fibrin monomer. The lupus anticoagulant test was positive, whereas the serum levels of complements, anti-ds-DNA antibodies, anticardiolipin antibodies, and anti-β2GP1-protein antibodies were within normal range. Based on the laboratory and imaging findings, a diagnosis of antiphospholipid syndrome (APS) was supposed. We report a rare case of spontaneous isolated splenic infarction in a man with SLE and APS.

P1-171

Successful long-term treatment of refractory thrombocytopenia with low dose danazol therapy in a patient with antiphospholipid antibody syndrome (APS), mixed connectve tissue disease (MCTD), and Sjögren's syndrome (SS)

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Conflict of interest: None

We report a case of 72 years old female who has past medical history of diabetes mellitus and acute myocardial infarction. In July 2001, she visited our hospital for the first time because of Raynaud phenomenon and sausage like swelling of fingers. She was diagnosed as MCTD with positive anti-U1-RNP antibody. She was also diagnosed as SS with positive anti-SSA and anti-SSB antibody. Since July 2006, her blood platelet counts gradually decreased from 200000/ul to 20000/ul with hypocomplementemia and rising of anti-DNA antibody. Anti-Helicobacter pylori antibody was negative. Platelet associated IgG was high, lupus anticoagulant and anticardiolipin antibody were positive respectively. The result of bone marrow biopsy was normal. The platelet counts were decreased in spite of stopping almost all medication except for prednisolone. So we diagnosed as autoimmune thrombocytopenia followed by APS, SS or MCTD. The thrombocytopenia was refractory to high dose prednisolone (60mg/day), azathiopurine (50m/day), and cyclosporin A (150mg/day). The platelet counts rose over 80000/ul after administration of low dose danazol (100mg/day) for 1 year. This is a rare case of successful lont-term treatment of thrombocytopenia by low dose danazol therapy in a patient with APS, MCTD, and SS.

P1-172

A case of Mixed Connective Tissue Disease associated with Kikuchi-Fujimoto disease

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Conflict of interest: None

【Case】 A 32 year-old woman was admitted to our hospital presenting polyarthralgia and fever. She presented bilateral cervical, left supraclavicular and left axillary lymphadenopathies with tenderness. Moreover, she developed tender edematous erythema in her face, swollen fingers, Raynaud's phenomenon. Laboratory examinations also showed pancytopenia (Systemic Lupus Erythematosus: SLE-like) and positive anti-U1-RNP antibody. Therefore, she was diagnosed as Mixed Connective Tissue Disease (MCTD), additionally diagnosed as Sjogren's syndrome (SjS) due to positive anti-SS-A/SS-B antibodies and significant lymphocytic infiltration in the salivary glands. Furthermore, biopsy specimen from cervical lymph node demonstrated the infiltration of CD68 positive his-

tiocytes with focal necrosis and intercellular nucleoclasts, therefore, she was finally diagnosed as MCTD and SjS associated with Kikuchi-Fujimoto disease (KFD). Oral prednisolone 40mg daily was initiated and her symptoms were improved.【Conclusion】Previous reports demonstrated about the relationship between SLE and KFD. The case of MCTD or SjS associated with KFD is rare, and we discuss the pathophysiology.

P1-173

Significance of anticoagulation therapy for Steroid resistance refractory 2ndary APSDiscussion about cross talk of coagulation system and complement system in APS

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Conflict of interest: None

[Objectives] To discuss about cross talk of coagulation and complement system in APS [Methods] Case Report [Results] Case: 37 years old woman. She developed SLE in 2002 and she visited a hospital for treatment in A Hospital and had medical treatment. On the other day, blood test showed hypocomplementemia and increased it in quantity on PSL30mg/ day, but the hypocomplementemia aggravated it. She was hospitalized, and the steroid was uploaded on PSL60mg/ day. However, without improvement of hypocomplementemia / left lower extremity edema, she transferred to our department in July, 2012. As for her, it was accepted lower extremities phlebothrombus of in vein US. A blood test showed anti-cardiolipin IgG antibody, anti-beta 2 GP I antibody, lupus anti-coagulant positive and we diagnosed it as APS and started anticoagulation therapy. Thrombus reduced after anticoagulant therapy immediately. We showed improvement of hypocomplementemia with it. [Conclusion] Complement and coagulation system consist of proteolyses cascade by a lot of serine protease both, and it was thought when these two cascade are independent in before, but there is coherence to these two system by recent study mutually. Through this case, we consider cross talk of two cascade of a coagulation system and complement system in APS.

P1-174

A case of secondary anti-phospholipid syndrome with abdominal angina

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Conflict of interest: None

55-yrs female suffered from systemic lupus erythematosus (arthritis, photosensitivity, lymphopenia, hypocomplementemia, positive for antinuclear antibody, anti-DNA antibody and anti-Sm antibody, class II of lupus nephritis). Treated with high dose steroid, she improved in clinical remission. Abdominal pain and diarrhea after meals, and 10 kg of body weight loss appeared since October 2012. Colonoscopic examination showed multiple ulcers in colon, biopsy specimen revealed no CMV infection, no inflammatory bowel disease. She admitted our hospital in Mar 2013. We suspected lupus enteritis because of edema of intestinal wall in CT scan, multiple ulcers in stomach, duodenum and colon. However, 3D-CT and angiography revealed stenosis of at the origin of the celiac artery, superior and inferior mesenteric artery. At coagulation test, it was positive for PTT-LA, anti CL β 2GPI antibody and anti PS/PT antibody. We diagnosed secondary anti-phospholipid syndrome with abdominal angina. We performed bypass surgery of celiac and superior mesenteric artery. She improved symptom and nutritional status. It was highly suggestive for slowly progressive thrombosis.

P1-175

Two cases of esophageal cancer that concurrently developed immunologic thrombocytopenic purpura accompanied by positive antiphospholipid antibodies

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Conflict of interest: None

<Case Presentation> Case 1. A 76-year-old man, complaining of swallowing difficulty, was diagnosed with esophageal cancer. His platelet (Plt) count, albeit normal two years before, was 1.1 $\times 10^4/\mu L$ and bleeding continued from the tumor. He was diagnosed with immunologic thrombocytopenic purpura (ITP), accompanied by positive antiphospholipid antibodies (APA) and deep venous thrombosis (DVT). The bleeding stopped with Plt rising up to $7.1\times10^4/\mu L$ by 25 mg predonisolone (PSL), and he became capable of oral intake after an endoscopic intervention. Case 2. An 82-year-old man, suffering from bloody stool, was diagnosed with esophageal cancer. His Plt count had dropped from normal to 1.2 $\times 10^4/\mu L$ at the diagnosis, and he was diagnosed with ITP accompanied by autoimmune hemolytic anemia and positive APA. High-dose PSL improved hematological abnormality, but he afterwards suffered from DVT and pulmonary embolism. For both patients, esophageal cancer could not be treated and they finally had a fatal outcome. <Discussion> Although rare, ITP can occur as a paraneoplastic event among solid tumor patients. When accompanied by APA, the risk of thrombosis increases. As malignancy is commonly seen in daily practice, it is necessary to deepen understanding of malignancy-related autoimmunity.

P1-176

A rare case of mixed connective tissue disease complicated with mesenteric panniculitis

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Conflict of interest: None

Mesenteric panniculitis is a rare complication in patients with rheumatic diseases. Here, we describe a case of mixed connective tissue disease (MCTD) complicated with mesenteric panniculitis. A 36-year-old woman was admitted to antibiotic-resistant fever and abdominal pain. We diagnosed MCTD due to presence of Raynaud's phenomenon, puffy fingers, malar rash, arthritis, cervical lymphadenopathy, dermal sclerosis of fingers, systemic inflammatory response, positive anti-U1RNP antibody and myogenic change in needle electrode examination. Mesenteric panniculitis was shown by examination of CT, Ga scintigraphic test and MRI. The patient was treated with 60 mg/day of prednisolone (PSL). The symptoms and laboratory results became well. Now, we are tapering the dose of PSL with no sign of relapse. Mesenteric panniculitis was reported by Ogden et al in 1960. It was a non-specific inflammatory disease with degeneration, necrosis and fibrotic change of mesenteric fat tissue. Physical stimulation, infection, autoimmune reaction, ischemia, and bleeding were thought to be a possible cause. When patients with MCTD have significant abdominal pain, we should consider mesenteric panniculitis as differential diagnosis.

P1-177

A case of mixed connective tissue disease with splenic infarction

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Conflict of interest: None

[Case] In December 2010, a 34-year-old woman presented to our hospital with arthralgias and swollen hands. The presence of anti U1-ribonucleoprotein antibodies, Raynaud's phenomenon and lower diffusing capacity of carbon monoxide established a diagnosis of mixed connective tissue disease (MCTD). In June 2013, she had developed fever, arthralgias, lower abdominal pain and a butterfly rash. Elevation of C-reactive protein (17.9 mg/dl) was observed. Enhanced computed tomography (CT) of her abdomen revealed inflammation of the pelvic cavity due to acute appendicitis. Antibiotics were administered, following which her symptoms and laboratory findings improved. In August 2013, she developed left upper abdominal pain and fever. C-reactive protein level increased to 7.9 mg/dl. Enhanced CT of the abdomen showed multiple splenic infarctions. Antibiotics were administered to prevent abscess formation and her

condition improved. One month later, she again presented with left upper abdominal pain and fever. CT showed massive necrosis of the spleen. Antiphospholipid antibody was negative. [Conclusion] Splenic infarction is a rare disorder and can occur in a variety of clinical situations. We present the case of a patient with splenic infarctions with pelvic cavity inflammation and MCTD.

P1-178

The changes of biochemical parameters of the patients with systemic sclerosis who were administered anti-interleukin-6 receptor antibody tocilizumab for three years

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Conflict of interest: Yes

[Objectives] Systemic sclerosis (SSc) is an autoimmune disease of uncertain etiology. There are many reports which present the possible involvement of interleukin-6 (IL-6) in the pathogenesis of SSc. We have reported the skin changes of SSc patients who were administered anti-IL-6 receptor antibody tocilizumab (TCZ). Here we present their blood biochemical data to know the influence of TCZ on the internal organs. [Methods] Three patients were administered TCZ for three years. One of them had pulmonary fibrosis and two of them had renal involvement due to SSc. One patient showed severe dysfunction of bowel tract. Serum creatinine which represents kidney function, alanine aminotransferase (ALT) which represents liver function, amylase which represents pancreas function, and nutrition data (total cholesterol and albumin) were evaluated retrospectively. [Results] The creatinine levels did not have a common tendency, though two patients had impairment of renal function. The movement of ALT levels varied according to a case. CK level augmentations were observed in some cases. [Conclusion] A common tendency of biochemical data was not observed. Since there are few cases who received TCZ for long period, it is necessary to repeat such a study.

P1-179

A case of diffuse cutaneous systemic sclerosis (dcSSc) with progressive interstitial lung disease (ILD) successfully treated with peripheral blood stem cell transplantation (PBSCT)

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Conflict of interest: None

Severe ILD complicated in dcSSc is one of the most serious conditions in rheumatic diseases. Here, we present a case, 34 year-old female with dcSSc associated with progressive ILD that was improved in response to PBSCT. She noticed Raynaud's phenomenon and puffy fingers 6 years ago. She refered to our hospital 5 years ago and diagnosed with anti Scl-70 antibody-positive dcSSc. She had esophageal lesion and ILD with %VC 65 and %DLCO 69. She started 30mg/day of prednisolone and monthly IVCY 500mg, then 3mg/day of tacrolimus after 6 times IVCY. However, her respiratory function gradually deteriorated and she couldn't go up the stairs 3 years ago. At that time, her %VC was 45 and %DLCO was 30. Considering progressive nature of ILD and her age, we decided to perform PBSCT and it was successfully done. Her respiratory function was improved to %VC of 52 and %DLCO of 73 in 18 months after PBSCT. On the other hand, her anti Scl-70 antibody titer was not changed. The mechanisms of action in PBSCT for autoimmune diseases are supposed to be reset of immune system or complete suppression of immune cells through administration of fatal dose cyclophosphamide; otherwise, unable to give. In this case, suppression of pulmonary fibroblast by high dose CY was most likely mechanism of action.

P1-180

Pulmonary hypertension associated with left heart dysfunction: Our experience of 3 cases with connective tissue diseases

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Conflict of interest: None

[Objectives] Pulmonary hypertension (PH) in connective tissue diseases (CTD) is associated not only with pulmonary arterial hypertension (PAH) (Pre-capillary PH) but with post-capillary PH. **[Methods]** We will present 3 CTD patients with post-capillary PH. **[Results] Case 1:** 78 year-old female. She developed limited systemic sclerosis (lc-SSc) in 2005. In 2010, treatment was started for hypertension. She noticed dyspnea in 2012 (WHO-FC II). By right heart catheterization (RHC), she was diagnosed as post-capillary PH because pulmonary capillary wedge pressure (PCWP) was elevated to 18mmHg. Myocardial fibrosis was found. **Case 2:** 78 year-old female. She had MCTD since 2000. In 2011, she noticed dyspnea (WHO-FC II). Elevation of PVR (260dyn.sec/cm^5) (TPG =19mmHg) and PCWP (23mmHg) was seen by RHC. Mixture with pre and post-capillary PH was considered. **Case 3.** 63 year-old female with lc-SSc (1998-) and hypertension treated with losartan. Beraprost and bosentan were introduced for Raynaud and interstitial lung disease. In 2010, she had exerbation of dyspnea (WHO-FC II). RHC showed an elevation of PCWP to 15mmHg with normal PVR. **[Conclusion]** Post-capillary PH is important in CTD. It can be accompanied with PAH **(case 2)** or developed during the treatment with pulmonary vasodilators **(case 3)**.

P1-181

Successful treatment with mycophenolate mofetil (MMF) for scleroderma heart disease

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Conflict of interest: None

【Introduction】Scleroderma heart disease is a major risk of death in systemic sclerosis (SSc).【Case】The patient, a 53-year-old woman with a 5-year history of SSc, presented with pretibial edema of acute onset and deterioration of breathlessness. She had had Raynaud's phenomenon, progressive diffuse scleroderma, dyspnea on exertion, positive anti-Topo-I andtibody >500 and elevated KL-6. She had been treated with PSL, tacrolimus, IVCY and azathioprine. When she presented acute edema, the electrocardiogram showed complete AV block. Then, the pacemaker implantation operation was performed. At the same time, she developed massive pericardial effusion and was diagnosed as pericarditis due to SSc. Myocardial scintigraphy demonstrated focal defects in part of anteroseptal and inferio-posterior walls, however, coronary angiography showed no significant stenosis. Therefore, it was considered that her cardiac involvement derived from scleroderma heart disease. PSL was increased and MMF was initiated, then her symptoms are stabilizing without flare-up of heart failure and pericarditis.【Conclusion】Recent reports showed that MMF improved skin involvement and stabilized pulmonary function in diffuse progressive SSc. MMF might be considered as a new treatment for scleroderma heart disease.

P1-182

Thrombotic thrombocytopenic purpura accompanied by portal hypertension and nodular regenerative hyperplasia in a patient with systemic sclerosis

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Conflict of interest: None

A 41-year-old woman was admitted for an elevated creatinine level and persistent diarrhea. At the age of 16 years, she was diagnosed with systemic sclerosis (SSc). At 34 years old, she developed systemic lupus erythematosus and portal hypertension because of chronic liver injury and splenomegaly. At 37 years old, the patient underwent Hassab operation. A liver specimen obtained during surgery revealed nodular regenerative hyperplasia. On admission, she was initially diagnosed with scleroderma renal crisis because of red blood cell fragmentation. Because platelet count decreased further during ACE inhibitor treatment, thrombotic thrombocytopenic purpura (TTP) was suspected as a complication despite normal ADAMTS-13 activity. After steroid pulse therapy, plasma exchange (PE) was started. The patient's kidney function recovered and the platelet count increased to 1,00,000/μL after the seventh PE cycle, and PE and HDF were then stopped. However, on day 45 and 51 after admission, the patient experienced varix rupture and died on day 52. Pathological analysis revealed hemorrhagic shock induced as the cause of death. We report the case of a patient with SSc who developed several complications related to endothelial cell injury, as indicated by the pathological findings.

P1-183

Therapeutic efficacy of immunosuppressants for systemic sclerosis associated with early stage of interstitial lung disease

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Conflict of interest: None

[Objectives] Interstitial lung disease (ILD) in a patient of systemic sclerosis (SSc) is generally slowly progressive, but in a few cases, acute progressive ILD also exists. Currently, cyclophosphamide (CYC) is a recommendable drug for SSc-associated ILD (SSc-ILD), and no other medications have evidence of therapeutic efficacy. We report the clinical course of CYC resistant SSc-ILD patient to whom mycophenolate mofetil (MMF) and cyclosporine A accompanied with steroid pulse (CSA-SP) were administered. [Clinical course] A 41-year-old male noticed raynaud phenomenon 3 years before admission, and visited our hospital with a complaint of exertional dyspnea. With scleroderma, ground grass opacities on chest computed tomography (CT) and positive antitopoisomerase-1 antibody titer, we diagnosed him as SSc-ILD. At first we started the therapy of intravenous CYC accompanied with low dose prednisone, but had no effect. Then, we changed the medication to MMF for half a year, next to CSA-SP. [Results] CSA-SP prevented our SSc-ILD patient from worsening of CT findings and pulmonary function. [Conclusion] In our SSc-ILD case, CSA-SP exhibited a possibility to prevent the progression of SSc-ILD. But in evaluating the drug efficacy, we must consider the participation of natural clinical course of SSc-ILD.

P1-184

Two cases of anti-RNA polymerase III antibody positive systemic sclerosis

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Conflict of interest: None

【Background】Antibodies to RNA polymerase III (RNAP-III ab) are found in patients with diffuse cutaneous systemic sclerosis (dc-SSc) and associated with increased risk of scleroderma renal crisis (SRC).【Case 1】A 82-year-old female was admitted with puffy finger in June, one year before X. Although antinuclear antibody was slightly positive (1:160, Speckled pattern), anti-topoisomerase I and anti-centromere antibodies were negative. Diagnosed as SSc with interstitial pneumonia (IP), she was observed without medication. When she was admitted to our hospital having dyspnea in April, X year, sclerosis spread over her fore-arms and RNA-III ab was positive. Pulse steroid therapy for IP, ACE inhibitor and plasma exchange for SRC were administered, but she was died on the 38th hospital day nevertheless.【Case 2】A 60-year-old female suffered from raynaud's symptom, ulcers of fingertips and skin sclerosis over 20 years. Prednisolone of 20mg/day for dyspnea was administered but not effective on 2 years before X. Diagnosed as SSc with positive RNA-III ab on X year, vasodilator was begun for her pulmonary arterial hypertension (PAH).【Conclusion】We experienced two cases of SSc with positive of RNAP-III ab. Both of them were sever cases. Case1 died due to SRC and case2 was complicated with PAH.

P1-185

A case of cryoglobulinemic vasculitis associated with limited systemic sclerosis

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Conflict of interest: None

【Case】A 58 year-old Japanese woman was admitted to our hospital with an intractable ulcer, Raynaud's phenomenon, swelling of extremity and pericardial effusion. These symptoms had gradually worsened. General examination showed scleroderma of extremity and rash. Laboratory data revealed that levels of serum CRP, C1q, C3, C4, CH50 and anticentromere antibody were 1.5 mg/dl, 17.5 μg/ml, 30.7 mg/dl, 3.1 mg/dl, <10.0 U/ml and >240.0 U/ml, respectively. Cryoglobulin was positive. HBs antigen and HCV antibody were negative. Histological findings of biopsy specinum on a right lower arm or a left upper leg demonstrated hyperplasia of the collagen fibers or leukocytoclastic vasculitis, respectively. Because of proteinuria and microhematuria on admission, a percutaneous renal biopsy was performed. The renal biopsy revealed membranoproliferative glomerulonephritis, compatible with cryoglobulinemic vasculitis (CV). Therefore, she was diagnosed with CV appearing in the progression of limited systemic sclerosis. We initiated intravenous corticosteroid pulse therapy (1g×3 days) followed by oral 40 mg/day prednisolone and she improved.【Conclusion】Herein we report a rare case of CV associated with limited systemic sclerosis.

P1-186

A Case of scleroderma followed by thrombotic microangiopathy

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Conflict of interest: None

A 71-year-old male was diagnosed as rheumatoid arthritis in February, 2012. Although he was treated, he stopped the medication in March, 2013 because symptoms were improved. In April, he had shortness of breath on exertion and was referred and admitted to our hospital. On admission, his blood pressure was 212/116 mmHg and had edema of the lower extremities. His laboratory examination revealed anemia with the fragmentation of blood cells, low haptoglobin concentration, thrombocytopenia and renal dysfunction. The renal biopsy specimen revealed fibrin thrombi in the capillaries of glomeruli. He was diagnosed as thrombotic microangiopathy (TMA) with the malignant hypertension. Anemia and thrombocytopenia were improved only by an antihypertensive treatment, but renal dysfunction continued. In mid-August, his fingers, hands, forearms and feet became swollen. In late September, the edematous skin rapidly became firm and thickened. His skin sclerosis extended to the face and trunk. The skin biopsy specimens revealed the swelling and proliferation of collageneous fibers and were consistent with scleroderma. We had the difficulty to investigate the cause of TMA because of lack of scleroderma at first. We report this case with bibliographic consideration.

P1-187

A case of generalized morphea mimicking systemic sclerosis

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Conflict of interest: None

A 66-year-old woman presented to our department with a 4-month history of gradually worsening skin tightness in the bilateral lower leg. She saw her docter regularly for hypertension and hyperlipidemia, using no medication. She didn't have a present or past history of diabetes mellitus. The physical examination revealed skin tightness over bilateral forearm and trunk besides lower leg. Her skin distal to the wrist and ankle was normal. She had no history of raynaud phenomenon and her nail fold capillary was normal. An ANA test was positive at 1:160 with a homogenous pattern. Tests for antibodies to centromere, scl-70, and RNA polymerase III were negative. Chest CT, echocardiogram, and gastroenterological endoscopy showed normal findings. A skin biopsy from forearm showed pathological findings compatible with scleroderma. Initially, she was suspected of having systemic sclerosis, because she had proximal skin tightness. Finally, she was diagnosed with generalized morphea, because she didn't have sclerodactyly or history of raynaud phenomenon. To exclude a diagnosis of generalized morphea is required in the classification criteria for systemic sclerosis. Clinical suspicion for generalized morphea should be raised, especially in patients without sclerodactyly or raynaud phenomenon.

P1-188

A patient who developed scleroderma-myositis overlap syndrome complicated by thrombotic microangiopathy during treatment for interstitial pneumonia

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Conflict of interest: None

[Case] A 59-yo female. [Chief complaints] dyspnea. [Course] In July 2012, interstitial pneumonia was diagnosed. In late August, dyspnea was deteriorated, and admitted to our hospital on October 1. Systemic sclerosis and dermatomyositis was diagnosed. Anti ARS antibodies was subsequently found to be positive. Prednisolone is administrated from October 9. However, thrombocytopenia, and renal dysfunction were detected. Because schizocytes were found, thrombotic microangiopathy (TMA) was diagnosed. Plasma exchange was started on next day. However, renal failure progressed, and hemodialysis was initiated. Plasma renin activity was high, raising suspicion of high-renin renal crisis. However, her blood pressure tended to decrease. Renal function showed no improvement, necessitating the introduction of maintenance dialysis. ADAMTS13 activity was mildly depressed at 43.6%, and negative for its inhibitor. [Conclusion] Although some cases of scleroderma complicated by TMA have been reported, according to our literature search, there are no reports on anti-ARS antibody-positive scleroderma-myositis overlap syndrome. In our case, TTP or high-renin renal crisis was suspected to be a cause of TMA, but the diagnosis was difficult due to a lack of typical findings of either condition.

P1-189

Two cases of pneumatosis intestinalis with abdominal free gas which could be managed conservatively –Dermatomyositis and Systemic Sclerosis

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Conflict of interest: None

Case1: A 30-year-old woman. The patient was diagnosed with Dermatomyositis in 2001, receiving low-dose steroid temporarily, thereafter, the symptoms were calm. She has recurrently reported the symptoms of pseudo-obstruction from January 2011, and received conservative treatment. In July 2013 routine follow-up chest X-ray revealed free gas under the right diaphragm. She admitted for five days with medical treatment performed conservatively. Case 2: A 79-year-old man. The patient was diagnosed with Systemic Sclerosis (SSc) in 2004, and the current disease activity has settled down with low-dose steroid. He's have repeating constipation and diarrhea, bowel dysmotility associated with SSc was considered. By chance, abdominal free gas was shown on contrast CT examining for his back pain in November 2013. Because the abdominal symptom was same as usual without peritoneal irritation, he could be observed as an outpatient. Clinical significance: SSc or other similar collagen disease are occasionally complicated with pneumatosis intestinalis, which rarely may involve abdominal free gas. It is important that we recognize these complications to avoid unnecessary surgical intervention. We report here, including image findings, mechanisms of the onset, and consideration of the literature.

P1-190

Clinical study of the initial treatment of dermatomyositis and polymyositis

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Conflict of interest: None

[Objectives] Clinical study of the initial treatment of dermatomyositis and polymyositis. [Methods] We have analyzed retrospectively 32 patients who were treated in our hospital since 2003. [Results] There were 14 males (43.8%) and 18 females (56.2%). The mean age±SD of onset was58.9±14.9 years old. Their serum CK value was 4273IU/L (38-60586). 19 patients (59.4%) have been complicated by interstitial pneumonia. Steroid therapy has been carried out in all of them. 12 of them received Steroid pulse therapy, 3 of them received IVIG as an add-on treatment. The initial treatment of 17 patients was prednisolone (PSL) alone. 9 patients (52.9%) of them had a relapse during the course. The initial treatment of 15 patients was the combination of prednisolone and immunosuppressant. Only 2 patients (13.3%) of them had a relapse during the course. [Conclusion] We concluded that the combination of prednisolone and immunosuppressant to be effective in the initial treatment in dermatomyositis and polymyositis.

P1-191

Serum interferon-α is a useful biomarker in patients with anti-melanoma differentiation-associated gene 5 (MDA5) antibody-positive dermatomyositis

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Conflict of interest: None

【Objectives】To investigate the clinical importance of the measurement of serum type I interferon (IFN) in patients with anti-melanoma differentiation-associated gene 5 (MDA5) antibody (Ab)-positive dermatomyositis (DM).【Methods】We studied 30 patients with DM: 10 who were anti-MDA5 Ab-positive and 20 who were anti-MDA5 Ab-negative. Serum IFN-α, IFN-β, interleukin 18 (IL-18), ferritin and the titer of anti-MDA5 Ab were measured by enzyme-linked immunosorbent assay. The associations between the IFNs with the other variables were examined.【Results】Rapidly progressive interstitial lung disease (RPILD) was confirmed in 10 patients. The presence of clinically amyopathic dermatomyositis (CADM) and RPILD as well as the serum concentrations of IFN-α and ferritin were significantly higher in the anti-MDA5 Ab-positive DM patients compared to the anti-MDA5 Ab-negative DM patients. Clear positive correlations were found between IFN-αand the titer of anti-MDA5 Ab ($r = 0.54$, $p = 0.0037$) and between IFN-α and ferritin ($r = 0.49$, $p = 0.0086$).【Conclusion】Considering the good correlations of IFN-αwith the titer of MDA5 Ab and ferritin, serum IFN-α can be used as a useful biomarker in patients with anti-MDA5 Ab-positive DM.

P1-192

8 cases of dermatomyositis with malignant neoplasm

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Conflict of interest: None

[Purpose] Dermatomyositis (DM) is associated with malignancies in a significant minority of cases. This study is to clarify the characteristics of malignancy in DM. [Method] Eight cases of DM with malignancy were seen for these three years in our hospital. The criteria of Bohan and Peter was used for diagnosing. We examined kinds of malignancy, presence of muscle weakness, CK levels, findings of EMG and muscle specimens, auto- antibodies, existence of interstitial lung disease (ILD), and prognosis. [Result] Five of eight cases are "definite", and the other three are "probable" DM. Two cases were gastric cancer, one had both of gastric and lung cancers, three were breast cancers, one was multiple myeloma, and the other one was cancer of unknown origin. The elevations of CK levels were seen in six cases. Six cases complicated with ILD. Five cases were ANA-positive. The anti Jo-1 antibody positive case was only one. The all eight cases had progressive malignancy, and three cases died. Other anti ARS antibodies except for JO-1 were measured in four cases, and only one case had anti-PL7 antibody. Anti-p155/140 antibody was not measured in all cases. [Conclusion] We experienced eight cases of DM with malignancy. Adenocarcinomas of the stomach and breast accounted for almost cases.

P1-193

A dermatomyositis patient developing chronic myeloid leukemia is able to experience improvement in the quality of daily life, following treatment with imatinib mesylate

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Conflict of interest: None

Abstract A female patient was originally diagnosed with dermatomyositis in 1985 at the age of 58 because of the presence of interstitial pneumonia and skin lesions. Early in 2008, she experienced a high fever for one week, and essential thrombocytosis was suspected. She was sent to the University Hospital whereupon tests revealed a WBC count of 11,200/μl accompanied by myelocytes at 2.5%, basophiles at 11.5%, and thrombocytes at 1,491,000/μl. The reciprocal translocation between chromosome 9 and 22 [t (9;22) (q34;q11.2)] was observed in all 20 cells analyzed by G-banding and she was diagnosed with chronic myelogenous leukemia (CML). Daily administration of 400mg of imatinib mesylate (IM) was started on April 1, 2008, and the patient's WBC and thrombocyte counts had dropped to 5,500 and 168,000, respectively, by the end of April. We discuss the rare association between dermatomyositis and CML and the effect of IM in improving daily life and significantly decreasing the HAQ score from 1.87 to 0.875 in this particular dermatomyositis patient because IM may inhibit IL-6 production.

P1-194

Detection of fasciitis associated with dermatomyositis by power doppler ultrasonography

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Conflict of interest: None

[Objectives] We have previously demonstrated that fasciitis as a common lesion of dermatomyositis (DM) can be detected early after disease onset by en bloc biopsy combined with magnetic resonance imaging (MRI). Recently, it has been reported that power doppler ultrasonography (PDU) is useful for detection of inflammation and vascularity in rheumatoid arthritis. We examined whether fasciitis is detectable by PDU in DM. [Methods] PDU was performed to detect fasciitis in 3 newly diagnosed patients with DM and 2 newly diagnosed patients with polymyositis (PM). The presence of fasciitis was confirmed by MRI and en bloc biopsy. [Results] Fasciitis was detected in 2 patients with DM by MRI and en bloc biopsy, and was not detected in 2 PM patients and a DM patient. The increased small blood vessels were histologically observed under the fascia in the patient with DM who did not have fasciitis. PDU showed increased blood flow near the fascia in all the patients with DM, while it did not in all the patients with PM. [Conclusion] PDU showed abnormal increased blood flow where the fasciitis or the increased small blood vessels near the fascia were detected by en bloc biopsy. These results suggest that PDU is useful for detection of fasciitis and diagnosing early stage DM.

P1-195

A surviving case of rapid progressive interstitial pneumonia in dermatomyositis complicated with macrophage activation syndrome and cardiomyopathy

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Conflict of interest: None

[Introduction] Recently, adverse prognostic factors of dermatomyositis have been reported, such as clinically amyopathic dermatomyositis, high serum ferritin level, a positive anti-melanoma differentiation-associated gene (MDA) 5 antibody, and elevated AaDO2 level. Additionally, cardiomyopathy, rapid progressive interstitial pneumonia (RPIP), and macrophage activation syndrome (MAS) can be fatal complications. [Case] A male patient in his fifties presented with skin eruptions and dyspnea. He was diagnosed with RPIP complicating DM presenting multiple adverse prognostic factors including a positive anti-MDA 5 antibody, high ferritin level (2919 ng/mL), and high AaDO2 level (96 mmHg), and additionally developed MAS and cardiomyopathy. RPIP and MAS improved with 1mg/kg/day of corticosteroid, 325 mg/day of cyclosporine, and 2500 mg of intravenous cyclophosphamide. However the cardiomyopathy had newly developed despite strong immunosuppressive therapy. Therefore we chose intravenous high-dose immunoglobulin therapy (IVIg; 400 mg/m^2 for 5 days), and cardiac function improved dramatically (EF 23 to 51%). [Conclusion] We were able to successfully treat this severe case of dermatomyositis with multiple adverse prognostic factors with intensive combination therapy and close monitoring.

P1-197

Two cases of relapsing polymyositis with noticeable inflammation of distal lower limb by the diagnostic imaging

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Conflict of interest: None

New classification of idiopathic inflammatory myopathy (IIM) defined three major entities, polymyositis (PM), dermatomyositis (DM) and sporadic inclusion body myositis (s-IBM). We report the clinical, electrophysiological and pathological characteristics of two relapsing patients with a rare form of IIM fulfilling the diagnostic criteria for PM. They were treated with immunosuppressive agents included steroid for typical PM, but it was difficult to control their PM activity. They presented with a subacute, proximal and distal symmetrical further weakness in lower limbs. By Gallium scintigraphy and MRI, we detected inflammation of distal lower limb, not proximal. One patient underwent muscle biopsy of left lower limb, which showed an active myositis without rimmed vacuoles. Another patients could not undergo biopsy for several reasons. They

shared similarity with negative for anti Jo-1 antibody and positive for anti SS-A antibody. They responded to immunosuppressive therapy. Some cases were identified in the literature. It is important to recognize that sometimes PM patients present atypical findings at the time of flare-ups.

P1-198

A case of lung-dominant connective tissue disease treated with intravenous cyclophosphamide pulse therapy

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Conflict of interest: None

【Case】A 60-year-old woman was admitted with a complaint of fever for a month in July, 2013. Laboratory analysis revealed elevated serum KL-6, and ground grass opacity (GGO) appeared on her chest CT. She was diagnosed with interstitial pneumonia (IP) and infection was excluded with various examinations. Immunological examination revealed hyperferritinemia and anti-SS-A antibody, but negative of anti-Jo-1 antibody. We suspected of connective tissue disease-related IP, but could not establish the diagnosis. We treated with oral administration of 1mg/kg/day of predonisolone (PSL) and oral cyclosporine because of deterioration of her condition. These treatments were effective but follow-up CT scan showed new lesion of GGO. So we added intravenous cyclophosphamide pulse therapy (IVCY) and she got improvement in chest CT scan findings, and serum KL-6 and ferritin level.【Discussion】We experienced a case of lung-dominant connective tissue disease, resistant to high dose of PSL and of which IVCY contributed to stabilization. Afterward it was reported that anti-MDA-5 was positive, so it is suspected that this case is progressive interstitial lung disease due to clinically amyopathic dermatomyositis (DM). It was difficult to make diagnosis because of lack of characteristic rash of DM.

P1-199

Increased KL-6 in dermatomyositis not by interstitial pneumonitis but by adenocarcinoma: a case report

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Conflict of interest: None

KL-6 was initially identified by generating monoclonal antibodies towards human lung cancer. Later, the high sensitivity and specificity of serum level of KL-6 for interstitial pneumonitis (IP) made it useful for evaluating the disease activity of IP. Dermatomyositis (DM) is well known to be associated with malignancy and also appears as a para-neoplastic syndrome. A 58-year-old woman admitted our hospital because of fever, rash, and myalgia in July 20xx. She was diagnosed as having DM by typical skin findings and pathology of biopsied skin. KL-6 was within normal range and the chest CT did not show a sign of IP. No malignancy was identified in spite of the extensive screening. She was treated with prednisolone at 60 mg/day and the dose was gradually tapered. In July of 20xx+1, the rash of DM relapsed and increased serum level of KL-6 was identified. The CT revealed not the sign of IP but an abnormal mass in the abdomen. The laparoscopic examination showed a disseminated poorly differentiated adenocarcinoma of unknown origin. KL-6 is present in alveolar type II epithelial cells, but its expression has been confirmed in lung adenocarcinoma, pancreatic cancer and breast cancer. Careful examination of malignancy is required in a patient of elevated KL-6 without a sign of IP.

P1-200

A case of onset by malignant tumor-related dermatomyositis (DM) as a prodrome of adult T cell leukemia/lymphoma (ATLL)

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Conflict of interest: None

【Case】Age: 64-year, Gender: Male【History of present illness】He noticed erythema and edema of his face from Mar/2013. He felt fatigue and both thigh myalgia, noticed his rash appeared from Apr. He felt it became difficult to squat down and stand. PSL15mg was prescribed for him by a dermatologist, but he became the hospitalization in a close inspection purpose because a symptom turned worse.【After admission course】He had six items of diagnostic criteria, we diagnosed him as DM. We conducted many examinations, and then malignant tumor was not found. He took the steroid therapy for DM, and his symptoms were improved, but sIL-2R was still elevating. Because he suffered from ileus from the end of May, we enforced abdominal CT and found a large number of lymphadenopathy in abdominal cavity. We detected a T cell type malignant lymphoma by the biopsy used a small intestine endoscope, and we diagnosed him as ATLL. He entered the blood internal medicine to take.【Consideration】We experienced one case of DM which merged ATLL. He had typical rash and we suspected malignancy but we could not find it. We found ATLL in his episode of care. A case of the ATLL following DM symptoms is very rare, and we report this case.

P1-201

A case of eosinophilic granulomatosis with polyangitis (EGPA) developed intra-abdominal abscess

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Conflict of interest: None

【Case report】A 65-year-old healthy man complained of stomachache, and was diagnosed with intra-abdominal abscess in February, 2013. Antibiotics and drainage were effective with abscess, but fever and elevation of CRP continued. Purpura and numbness appeared in his legs, and renal function worsened in April. The laboratory data revealed eosinophilia and elevated level of IgE and PR3-ANCA. He was found to have vasculitis at skin biopsy, and was diagnosed with EGPA. We treated with oral administration of 50mg/day of predonisolone (PSL). The laboratory data improved, but he had bloody stools at the 8th day of the start of steroid treatment. The multiple ulcers confined to transverse colon were found by colonoscopy, so we added cyclophosphamide. Despite these therapy, colonic perforations occurred at the 34th day, requiring emergent surgery. Postoperative course was good, although lung abscess and disorder in healing wound occured after operation.【Discussion】We experienced a case of EGPA with PR3-ANCA that developed intra-abdominal abscess, requiring emergent surgery for perforation of multiple ulcers localized in the mesentery of transverse colon. The prognosis of EGPA with gastrointestinal involvement is generally poor, but we could save the patient in this case.

P1-202

A case of microscopic polyangiitis with thrombocytopenia and several positive autoantibodies

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Conflict of interest: None

A 83-year-old man had acute thrombocytopenia and polyclonal hypergammaglobulinemia. Antinuclear antibody (homogeneous pattern 160x, nucleolar pattern 160x), MPO-ANCA (>300 U/ml), PR3-ANCA (5.5 U/ml) and anticardiolipin antibody (20.6 U/ml) in serum were positive. The diagnostic criteria for microscopic polyangiitis was fulfilled by elevated C-reactive protein, purpura, interstitial pneumonia and leukocytoclastic vasculitis according to skin biopsy. SLE was also considered because of low serum complement and positive immunocomplex, but it was not definitive. Swelled lymph nodes in neck and mediastinum made thought of Castleman's disease, but serum IL-6 level was not elevated. Lymph node biopsy was not performed due to severe thrombocytopenia. Because no reason was shown to explain thrombocytopenia nothing but PA-IgG, it was similar to idiopathic thrombocytopenic purpura. 30mg/day of prednisolone was initiated, but it showed poor effect. High-dose methylprednisolone (250mg×3days) was done, and tacrolimus was added on prednisolone. Afterwards, platelet count and interstitial pneumonia recovered. We report an interesting case of microscopic polyangiitis with thrombocytopenia and several positive autoantibodies.

P1-203

A case of ANCA related nephritis with almost normal urinalysis

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Conflict of interest: None

[Objectives] To discover the pathology of interstitial nephritis related to microscopic polyangiitis, thorough a case of an old woman. [Methods] A 74 year-old woman admitted our hospital presenting fever, frequent urination, and general fatigue. Her blood test showed elevated levels of imflammatory response. She was firstly treated with antibiotics as pyelonephritis which took no effect. Throughout her admittion, her urinarysis was almost normal but her serum creatinin level raised from 0.80 mg/dl to 2.12 mg/dl in ten days. Scintigraphy scan showed gallium uptake in both her kidney. [Results] Renal biopsy revealed that she had severe vasculitis in her small to medium sized vessels in her kidney, which lead to interstitial nephritis. [Conclusion] This case only showed slight problems in urinarysis, because there were few lesions in the arteriole and the more smaller vessels.

P1-204

Myeloperoxidase-antineutrophil cytoplasmic antibody associated vasculitis accompanied by tubulointerstitial nephritis without glomerular lesions: Two Case Reports

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Conflict of interest: None

[INTRODUCTION] Renal involvement in myeloperoxidase-antineutrophil cytoplasmic antibody (MPO-ANCA) associated vasculitis (AAV) shows mainly crescentic glomerulonephritis. We herein describe two cases of AAV acompanied by TIN without glomerular lesions. [CASE PRESENTATION] A 76-year-old female had suffered from myalgia and fever. Her laboratory findings revealed elevation of C-reactive protein and MPO-ANCA (411U/mL). Her urinary N-acetyl-β-D-glucosaminidase (NAG) and urinary β2 microglobulin (β2MG) levels were elevation. Renal biopsy specimen showed tubulointerstitial nephritis (TIN) without glomerular lesion, and necrotizing vasculitis in interlobular and arcuate arteries. She was diagnosed with AAV accompanied by TIN and received prednisolone (PSL) oral administration. A 77year-old male had suffered from general malaise and fever. His laboratory findings revealed elevation of MPO-ANCA (353U/mL), urinary NAG and urinary β2MG levels. Renal biopsy demonstrated TIN without glomerular lesions. These findings were compatible with TIN associated with AAV. He was treated with PSL oral administration and intravenous cyclophosphamide. [CONCLUSION] We have presented two cases of TIN suggesting to be rare renal manifestation of AAV adding review of the literatures.

P1-205

Elderly Onset Microscopic Polyangiitis Presented with Pulmonary-Renal Syndrome: A Case Report

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Conflict of interest: None

[Introduction] In microscopic polyangiitis (MPA), diffuse alveolar hemorrhage and renal dysfunction are related with poor prognosis. Survival rate and renal prognosis are low in the elderly. [Case] A 82-year-old man visited another hospital with complaint of general malaise. He was found to have acute renal failure of serum creatinine 9.38mg/dl, the right lung consolidation in the X-ray. He was referred to our hospital and brochoalveolar lavage revealed alveolar hemorrhage. MPO-ANCA was high. We diagnosed him as MPA with pulmonary-renal syndrome. We started intravenous pulse methylprednisolone, plasma exchange and hemodialysis. We added intravenous cyclophosphamide later. The renal function was improved. Dialysis was successfully withdrawn at 3 months from treatment onset. [Conclusion] Pulmonary-renal syndrome is defined as syndrome with glomerulonephritis and diffuse alveolar hemorrhage. ANCA associated vasculitis is the most common cause. Although we thought dialysis withdrawal was difficult in this case because of old age and severe renal dysfunction, he could leave dialysis. This case illustrates the importance of early diagnosis and aggressive treatment in the management of severe case of MPA with pulmonary-renal syndrome.

P1-206

A case of ANCA associated vasculitis (AAV) complicated with rapidly progressive glomerulonephritis (RPGN) and thrombotic microangiopathy (TMA) which may be suggestive for overlapping of AAV and Systemic lupus erythematosus (SLE)

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Conflict of interest: None

We report a case of ANCA associated vasculitis overlapped with SLE. A 37-year-old man visited our hospital with multiple joint pain and swellings in May 2013. He had negative ANA, positive anti-DNA antibody (10 IU/ml) and positive C-ANCA (5.5 EU). In late August, he began to suffer with sustained fever. He had proteinuria and microhematuria. The blood tests showed positive anti-DNA antibody (206 IU/ml), negative C-ANCA with no hypocomplementemia. Since he fulfilled diagnosis of SLE, we suspected lupus nephritis. In early September, his renal function deteriorated rapidly. We started methyl-predonisolone (PSL) 0.5g intravenously for three days with PSL 60mg/day (1mg/kg) afterward. Regardless of these treatments, we had to start hemodialysis in late Sptember. Moreover, he complicated with TMA. We administered plasma exchange. The histopathology of his renal biopsy was necrotizing crescentic glomerulonephritis, pauci-immune type which suggested AAV, so we added on mycophenolate mofetil for vasculitis. With the clinical improvement, we were able to quit hemodyalisis. This case showed clinical symptoms and laboratory findings suggested of SLE, but histopathologically suggested of AAV. We suspected of overlapping of SLE and AAV.

P1-207

Two cases of pulmonary-limited microscopic polyangitis who can be followed without treatments

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Conflict of interest: None

[Introduction] Pulmonary-limited microscopic polyangitis (plMPA) is one of the ANCA-associated vasculitis without extrapulmonary involvement and has the potential to progress to the systemic vasculitis (SV). In some patients aggressive treatments were necessary to inhibit progression, but in some unnecessary until exacerbation of interstitial pneumonia (IP) or persistent occult blood in urine (OB). We report two cases of plMPA who can be followed without treatments. [Case 1] A 75-year-old man was referred to our hospital for further evaluation of IP in February 2012. Laboratory findings showed elevation of MPO-ANCA and positive OB, but renal function was normal. He was diagnosed as plMPA and followed without treatments. Despite persistent OB, SV has not developed for 1 year and 7 months. [Case 2] A 70-year-old woman was referred to our hospital for further evaluation of elevated KL-6 and IP in July 2012. Laboratory findings showed elevation of ANA and MPO-ANCA, but an OB was negative and renal function was normal. She was diagnosed as plMPA and followed without treatments. Despite persistent mild inflammation and MPO-ANCA elevation, SV has not developed for 1 year and 3 months. [Clinical significance] Some plMPA patients can be followed without treatments.

P1-208

Clinical study of microscopic polyangitis complicated with interstitial pneumonia

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Conflict of interest: None

[Objectives] To evaluate the clinical characteristics and prognosis of patients with microscopic polyangiitis (MPA) complicated with interstitial pneumonia (IP). [Methods] We analyzed retrospectively 44 cases of MPA according to the Watts' algorithm from 2003 to 2013 at our hospital including prognostic changes and factor. [Results] The mean age of the 44 patients (21 males and 23 females) was 73.9±7.4 year-old. MPO-ANCA was positive in all cases. All patients steroid treatment is performed, immunosuppressive therapy was performed in 21 cases, steroid pulse therapy in 35 cases. 22 cases (male 12 cases, female 10 cases) complicated with IP. 5-year survival rate was bad significantly compared with non-IP cases, 58.3% in IP cases and 79.7% in non-IP cases. There was no significant difference between the two groups with respect to MPO-ANCA value, but BVAS in IP cases was significantly higher than non-IP cases, 17.0 ± 5.4 in IP cases and 12.6 ± 4.8 in non-IP cases. [Conclusion] BVAS of IP cases was significantly higher and worse prognosis than non-IP cases in the MPA.

P1-209

A case of giant cell arteritis which developed from lower leg edema and which complicated MPO-ANCA-positive interstitial pneumonia

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Conflict of interest: None

A 72-year-old woman was admitted to our hospital because of lower leg edema, headache and fever. Heart failure was not observed and renal function was within normal range. Chest computed tomography revealed interstitial pneumonia. Myeloperoxidase-antineutrophil cytoplasmic antibody (MPO-ANCA) level was 81 u/ml. Meanwhile, jaw claudication appeared. Temporal artery biopsy revealed temporal arteritis. She was diagnosed as giant cell arteritis (GCA) with MPO-ANCA-positive interstitial pneumonia. She was treated with prednisolone 50 mg/day and cyclophosphamide pulse therapy (500mg/month). Lower leg edema, headache, fever, jaw claudication and interstitial pneumonia was improved.

P1-210

An autopsy case of Eosinophilic Granulomatosis with Polyangitis who died due to pericarditis

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Conflict of interest: None

A 67-year old man was suffering from asthma for 20 years. Proteinuria and hematuria were detected from 9 months ago. From 2 months ago, he was admitted to initial hospital for systemic edema. He exhibited marked hepatomegaly, pericardial effusion, pleural effusion, ascites, and thrombosis in the right ventricle. Since high serum level of MPO-ANCA (236 U/ml), liver dysfunction, eosinophilia (44%) as well as marked increase of serum creatinine and IgE level were detected, Eosinophilic Granulomatosis with Polyangitis (EGPA) was suspected and oral steroid therapy was started. However, strong abdominal pain accompanied with liver dysfunction and severe metabolic acidosis occurred, then he was transferred to our hospital. Since dyspnea and hypoxemia progressed rapidly, he was treated by mechanical ventilation and CHDF, but he died on the next day. Autopsy findings demonstrated endocarditis with eosinophilia, as well as massive thrombi in whole right ventricle, which caused pulmonary artery obstruction and congestive liver. Cardiac diseases account for nearly half cause of deaths in patients with EGPA, however pericarditis is very rare. Herein, we discuss about the disease situation, referring to current related literatures.

P1-211

A case of periaortitis and hypoacusis in a patient with Microscopic PolyAngitis

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Conflict of interest: None

A 80-year old woman was admitted with fever, fatigue and right ear hearing loss. In 2002, she had had a low-grade fever, hematourea, and cough, and had visited our hospital. Chest computed tomography (CT) showed microcystic fibrosis of the lung. Renal biopsy showed segmental necrotizing glomerulonephritis. The serum level of MPO-ANCA was elevated. She was diagnosed Microscopic polyantiitis and treated with prednisolone (PSL). After treatment, the symptoms subsided and the PSL dose had been tapered and discontinued by 2011. In September 2013, the patient's serum levels of CRP and MPO-ANCA were elevated. She had unilateral sensorineural hearing loss. Contrast enhanced CT of the abdomen demonstrated circumferencial thickening of the abdominal aortic wall corresponding to vivid 18-fluorodeoxyglucose (FDG) uptake on positron emission tomography/computed tomography (PET-CT). Recently, the use of 18-FDG PET, either alone or in combination with contrast-enhanced CT, has emerged as a potential tool for the initial diagnosis and assessment of disease of aortitis caused by Takayasu arteritis. This case may also suggest that PET-CT is useful as a diagnostic tool in aortitis caused by MPA.

P1-212

Immune-mediated hearing loss: two case reports

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Conflict of interest: None

[Case1] 52-year-old female. She complained of arthralgia of maniphalanx, facial eruption and malaise after January in the year X. After that, she complained of bilateral hearing loss. She was referred to our hospital. She was complicated with fever, stomatitis, proteinuria, cytopenia, and elevation of antinuclear antibody and anti-DNA antibodies. She was diagnosed as SLE by skin biopsy. She was also complicated with polyarthritis. After beginning to treat with steroid, hearing loss were improved. [Case2] 80-year old-female. She complained of fever after the year Y. She was complicated with renal insufficiency. She was diagnosed as microscopic polyangiitis (MPA) by the examinations. Her treatment was started with prednisolone (PSL) 40mg daily after methylprednisolone pulse. AS her symptoms were improved, PSL was gradually reduced. She complained of malaise and right hearing loss after the year Y+11. She was diagnosed as recurrence of MPA. Her hearing loss was improved, when PSL was increased. Hearing loss with both cases were considered to be caused by immune-mediated hearing loss, because hearing loss appeared following exacerbation of autoimmune disease and was improved by steroid treatment. We reported both cases in addition to the study of the literatures.

P1-213

A case of MPO-ANCA-associated vasculitis with otitis media

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Conflict of interest: None

A 69-year-old Japanese woman experienced fever, cough, dyspnea and hearing loss of left ear, and was diagnosed as otitis media and alveolar hemorrhage due to myeloperoxidase anti-neutrophil cytoplasmic antibody (MPO-ANCA)-associated vasculitis (MPO-AAV) in July, 2012. She admitted to our hospital and was treated with corticosteroid, cyclophosphamide pulse, plasma pheresis and puncture of the eardrum. She improved but after leaving hospital and tapering PSL, elevation of MPO-ANCA titer was observed and she recognized left side and then bilateral difficulty of hearing again in July, 2013. An otolaryngologist suggested the possibility of AAV with otitis media. On admission, vasculitis was not proved by histological examination, but we diagnosed her as AAV with otitis media from absence of any other obvious causes, history of hearing loss and elevation of MPO-ANCA titer. After initiation of therapy with corticosteroid and azathioprine, her hearing ability ameliorated and MPO-ANCA titer reduced. This case suggests that otitis media is rare and one of the symptoms of vasculitis. It is important to make an early diagnosis for good prognosis of hearing ability in cases of AAV with otitis media, and we have to consider AAV for differential diagnosis.

P1-214

A rare case of microscopic polyangiitis (MPA) complicated by ischemic optic neuropathy (ION)

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Conflict of interest: None

A 59-year-old man having fever, myalgia and numbness was diagnosed with MPA as a result of positive MPO-ANCA test and renal biopsy. After high-dose steroid therapy followed by intravenous cyclophosphamide (IVCY) regimen, he had complete remission and was maintained with PSL 5 mg/day. Six years later, he had flare-up of MPA with fever, dry cough, myalgia and episcleritis. Labo tests showed high serum CRP 5.82 mg/dl, IgG4 153mg/dL and positive MPO-ANCA 6.8 U/ml. Soon after admission, he had sudden loss of visual acuity in his left eye up to light perception. Ga-enhanced MRI revealed involvement of the left optic nerve and fluorescent fundus angiography showed edematous left optic disk. Ophthalmologists diagnosed as arteritic ION. Giant cell arteritis (GCA) was unlikely because of no tenderness of temporal artery. To protect the opposite visual acuity, we performed steroid-pulse therapy followed by oral PSL and IVCY, resulting that almost all symptoms improved except loss of left visual acuity. Arterial ION is almost accompanied by GCA, involved in large and/or medium vessels, but rarely by ANCA-associated vasculitis. Loss of vision in both eyes may occur very abruptly and ION is therefore a medical emergency. We should make a close attention in MPA cases with elevated serum IgG4.

P1-215

Orbital myositis due to eosinophilic granulomatosis with polyangiitis

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Conflict of interest: None

A 47-year-old woman, who developed bronchial asthma in 2001 and eosinophilic gastroenteritis in 2005, was diagnosed as EGPA based on the ACR 1990 criteria. Her symptoms were stable on glucocorticoids for seven years. In January 2013, she presented with progressive proptosis of the right eye and diplopia. Physical examination revealed exophthalmos, conjunctival hyperemia, episcleritis and impaired abduction of the right eye. Laboratory analysis revealed an increased titer of MPO-ANCA and hypereosinophilia. MRI showed swelling of the extraocular muscles of the right eye and fluid in right ethmoid sinus. Since a biopsy of swollen extraocular muscles cannot be performed due to a high risk of complications, a biopsy specimen was taken from the right bulbar conjunctiva, and the pathological finding revealed dense infiltration of eosinophils with an epithelioid cell granuloma formation and phagocytized Charcot-Leyden crystals. It was speculated that unilateral proptosis was caused by the eosinophilic orbital myositis. Thirty milligrams of prednisone was started, and her proptosis and conjunctivitis dramatically improved. There are only two reports that describe orbital myositis associated with EGPA. We will discuss the differential diagnosis of eye presentation of autoimmune diseases.

P1-216

An autopsy case of Microscopic polyangitis (MPA) with pachymeningitis

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Conflict of interest: None

The patient was a 83 -year-old woman. She was developed rapidly progressive glomerulonephritis in October 2009. Exhibit of necrotizing crescent formation nephritis by renal biopsy, MPO-ANCA positive, interstitial pneumonia, was diagnosed with multiple microscopic vasculitis. We underwent (mPSL-pulse + PSL 30mg/day) steroid therapy, and became remission state, one month after the start of steroid therapy. She appeared left visual loss and left ptosis headache and left facial pain, than in April from March 2012. Her cranial nerve (II III IV V) were failure and the dural thickening admit the contrast effect in the left lead in the head contrast MRI. Wediagnosed ANCA associated pachymeningitis and strengthened the steroid treatment (mPSL-pulse + PSL 35mg/day). The cranial nerve symptoms other than visual acuity was improved, but the pachymeningitis was relapsed when we lose weight the amount of steroid (16mg/day). We enforcement the steroid pulse therapy in February 2013, in March. Since then, the disease was calm, but she passed away in septic shock due to aspiration pneumonia in September 2013. In the autopsy report, dura mater was thickening was observed. This case is a valuable autopsy cases of ANCA associated pachymeningitis, and reports.

P1-217

A case of posterior ischemic optic neuropathy with microscopic polyangiitis

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Conflict of interest: None

The case is a 75 years old woman, who was diagnosed microscopic polyangiitis with MPO-ANCA because of fever in a year ago. After starting corticosteroid, she improved and corticosteroid was reduced. The left eyesight completely disappeared, she consulted our hospital. There was no pupillary light reflex in the left. Including an ocular movement, there were no motor and sensory disturbance. There was no abnormality in cerebrospinal fluid, head CT and the funduscopy. For judging posterior ischemic optica neuripathy (PION) or neuromyelitis optica, we started methylprednisolone 1000mg per day for three days and followed by oral prednisolone 50mg per day. Head MRI on next day showed normal and we diagnosed PION. The left eyesight was gradually restored. However, the right side eyesight begun to lose in the fifth day. Because of no abnormality in examination, diagnosed bilateral PION, we continued therapy, and the right eyesight recovered in original on the 45th day. [Clinical significance] We report a case of administrating corticosteroid to PION with microscopic polyangiitis, the eyesight improved while it was complicated in the fellow eye.

P1-218

A Case report of IgA vasculitis with subarachnoid hemorrhage and Positive MPO-ANCA

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Conflict of interest: None

[Case Report] A 21-year-old male had developed rash of both the legs and was diagnosed as a Henoch-Schönlein Purpura by the dermatologist, and he was given prednisolone (PSL) 10 mg/day. After a week, he complained of a pain in back of head and visited the emergency room, CT brain showed subarachnoid hemorrhage (SAH). Besides brain MRI revealed multiple cerebral infarction, he treated conservatively and had no neurological sequela. On the 17th hospital day, skin eruption appeared in his legs, and he revealed with microscopic hematuria and positive MPO-ANCA. On the 27th day, renal biopsy was done which suggested purpura nephritis (ISKDC gradeIII). Considering the presence of both renal and cerebrovascular involvement, he was administered PSL40mg/day and intravenous cyclophosphamide (IVCY). Finally, he received five times IVCY and PSL was tapered, his urine sediment is improved. [Discussion] In IgA vasculitis patients, the incidence of nervous system dysfunction ranges from 0.9% to 6.9%. Intracranial hemorrhage and cerebral infarction were observed almost 20 each, but SAH is reported in only 5 patients, additionally other 4 patients were negative at MPO-ANCA. Our patient's Renal biopsy presented typical histologic feature of IgA vasculitis, however, MPO-ANCA might be associated with cerebrovascular involvement.

P1-219

A case of MPO-ANCA sero-positive granulomatosis with polyangitis (GPA) with choroidal tumor

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Conflict of interest: None

Granulomatosis with polyangitis (GPA) is a systemic disease of unknown etiology characterized by necrotizing granulomatous inflammation, tissue necrosis, and variable degrees of vasculitis in small and medium-sized blood vessels. A eighty four years-old Japanese woman, who had headache (frontal-temporal region) about 6 months admitted to our department. She had 3 month's history of ophthalnalgia and conjunctivitis. One month prior to admission, percutaneous coronary intervention (PCI) for myocardial infarction was performed. After PCI, low grade fever (37.0-37.5℃) was sustained, therefore, she was transferred our hospital for further examination. In laboratory data on admission, CRP (9.37mg/dl) and ESR (86.0mm/h) were elevated. Although PR3-ANCA was negative, MPO-ANCA was positive with high titers. Brain MRI demonstrated mucosal hypertrophy and liquid storage of maxillary sinus and a left choroid tumor with low intensity in T2W1 and high intensity in DWI. Tumor biopsy was performed, and a histological diagnosis of granulomatosis with polyangitis in choroidal tissues was made. She was treated by PSL 30mg/day. Her symptoms were improved, and the tumors were regressed by steroid therapy. Choroidal tumor could be another face of GPA, precise diagnosis should be needed in these cases.

P1-220

Minor salivary gland biopsy may not useful for a diagnosis IgG4-related disease without IgG4-Mikulicz disease

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Conflict of interest: None

[Objectives] In patients suspected of IgG4-related disease (IgG4-RD) without IgG4-related Mikulicz disease (IgG4-MD), we often experience that they cannot undergo biopsy except minor salivary gland biopsy (MSGB) or do not fulfill the IgG4 pathological criteria. To clarify whether MSGB is useful for diagnosis in those cases. [Methods] This study comprised a retrospective data collection at single-center. All patients were suspected IgG4-RD, and received MSGB for diagnosis from April 2012 and November 2013. The subjects of our investigation are eleven patients. We examined the pathologic results and final diagnoses. [Results] In four of five patients with suspected IgG4-MD who had typical symptoms for IgG4-MD, MSGB revealed positive pathological findings and was finally diagnosed as IgG4-MD. In 3 patients who had typical symptoms for IgG4-RD without IgG4-MD, MSGB revealed negative findings but was finally diagnosed as IgG4-RD. In 2 patients suspected with IgG4-RD who had no typical symptoms for IgG4-RD, MSGB revealed negative findings and was not diagnosed as IgG4-RD finally. [Conclusions] Our results suggest that MSGB is not useful for diagnosis of IgG4-RD without IgG4-MD.

P1-221

Clinical characteristics of patients with IgG4-related disease in Kitasato University Hospital

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Conflict of interest: None

[Objectives] IgG4-related disease (IgG4-RD) has been a newly established concept whose details in clinical practice have been clarifying. In this study, we present the series of patients with IgG4-RD in our hospital in the last 5 years. [Method] Ten patients clinically diagnosed as IgG4-RD in Kitasato University Hospital from 2008 to 2013 were exhaustively enrolled in this study. The clinical manifestations and serological parameters were retrospectively reviewed based on the medical records. [Result] Of 10 patients, 7 patients were male and 3 patients were female, and the ages at the diagnosis as IgG4-RD were 71.8 ± 8.1 years [mean±SD]. Serum IgG4 level were 1021 ± 704 mg/dl. Serum IgE levels were also elevated in all the 5 patients whose data are available (978 ± 526 IU/ml). None of the 10 patients presented autoimmune pancreatitis. Nine patients were successfully treated with moderate doses of prednisolone (PSL) (5~40 mg/day). Last one patient was follow-up without PSL. Thus, none of the 9 patients relapsed during the tapering of PSL into maintenance doses (5~12). [Conclusion] The results confirmed the efficacy of steroid in IgG4-RD. In addition, it is suggested that the elevation of IgE might be closely relate with that of IgG4.

P1-222

Membranous nephropathy associated with IgG4-related disease

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Conflict of interest: None

[Objectives] In IgG4-related disease (IgG4-RD), interstitial nephritis is known. But there are a few reports of membranous nephropathy (MN) with IgG4-RD. We studied to investigate the characteristics of MN with IgG4-RD. [Methods] Patients with IgG4-RD who was diagnosed as MN by renal biopsy in our hospital were enrolled. [Results] Five patients had established MN with IgG4-RD. Mean age was 74.4 years old, three male and two female. Cr was 1.1+-0.5 mg/dl, IgG 2,644+-1422mg/dl, IgG4 558+-726mg/dl, proteinuria 3.9+-4.9g/day. Phospholipase A2 receptor (PLA2R) was measured in four patients, and three patients were negative and one patient was positive. All patients showed granular IgG deposition in glomerular capillary by immunofluorescent staining of renal biopsy. IgG1 subclass was dominant in three of four patients who were positive PLA2R. Four of five patients were underwent steroid therapy, and proteinuria disappeared in three patients. [Conclusion] One patient who PLA2R was positive had MN before diagnosis of IgG4-RD, and it was thought to be primary MN. But IgG1 was dominant in most patients with IgG4-related MN, and it was characteristics of secondary MN. There is a possibility of secondary MN due to IgG4-RD rather than direct effect of IgG4.

P1-223

Three cases of IgG4-related disease diagnosed by nasal mucosa biopsy

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Conflict of interest: None

We report three cases of IgG4-related disease diagnosed by nasal mucosa biopsy. Case1: A 62 years old man developed swelling of the neck. Ultrasonography detected enlargement of the bilateral salivary glands. CT showed diffuse enlargement of the pancreas. Serum IgG4 was elevated to 490 mg/dl. PET/CT showed abnormal uptake in bilateral salivary glands and hilar lymph nodes, pancreas, and prostate. He developed nasal obstruction and bleeding. Nasal mucosa presented erosion and redness. The specimen of nasal mucosa revealed the infiltrations of IgG4-positive plasma cells. He was treated with PSL 35mg/day and his symptoms immediately improved. Case2: A 60 years old woman developed swelling of neck and eyelid. CT showed swelling of bilateral submandibular and lacrimal glands. Serum IgG4 was elevated to 1000 mg/dl. Although no abnormalities were found in the nasal mucosa, IgG4-positive plasma cell infiltration was observed in the specimen of nasal mucosa. She was treated with PSL 35mg/day, and her symptoms improved. Case3: A 32 years old man had a swelling of bilateral eyelid. Serum IgG4was elevated to 149mg/dl. MRI showed enlargement of bilateral lacrimal glands and thickening of nasal mucosa. The specimen of nasal mucosa revealed IgG4-positive plasma cells infiltration.

P1-224

IgG4-related disease manifesting as pericarditis

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Conflict of interest: None

A 78-year-old female presented to a local hospital with progressive exertional dyspnea. A CT scan revealed marked pericardial effusion, and pericardiocentesis was performed. Mach hemorrhagic pericardial fluid was obtained. ADA activity in the fluid was elevated to 107 U/ml. Serum level of IgG4 and was elevated. A contrast enhanced CT scan revealed pericardial effusion, poly-lymphadenopathy, enlargement of the pancreas, and bilateral hydronephrosis. We performed biopsy of inguinal lymph node, and denied malignant lymphoma. Immunostaining of the specimen demonstrated increased ratio of IgG4/IgG-positive cells at 53%. Althogh the diagnosis of IgG4-RD was made, it was necessary to exclude tuberculous pericarditis because of her past history of pulmonary tuberculosis and elevation of ADA activity in pericardial fluid. We performed biopsy of pericardium and drainage of pericardial effusion. PCR and culture of M.tuberculosis were negative. Specimen of the pericardium revealed diffuse fibrous thickening and patchy lymohoplasmacytes infiltration. Immunostaining demonstrated increased ratio of IgG4/IgG-positive cells at 51%. Therefore, we concluded pericardial effusion was not caused by tuberculosis but by IgG4-RD. We discuss in literature about IgG4-RD manifestating as pericarditis.

P1-225

A case of multicentric Castleman disease with infiltration of plasmasytes presenting IgG4

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Conflict of interest: None

Multicentric Castleman's disease (MCD) is a rare atypical lymphoproliferative disorder, which is characterized by various systemic manifestations. A 51-year-old woman had been detected hyper gamma-globulinemia and elevation of CRP from ten years ago. She was referred to our hospital due to her morning stiffness and joints pain. Laboratory findings demonstrated elevation of CRP (6.48mg/dl), IL-6 (9.3pg/ml), IgG4 (239mg/dl) and polyclonal hyper gamma-globulinemia. Her FDG-PET showed the patchy shadows of bilateral lung and multiple lymphadenopathy (axillar, interiliac and inguinal lymph node) with the abnormal uptake of [^{18}F]-FDG. Histopathological findings of the specimens obtained by inguinal lymph node biopsy revealed massive infiltration of plasma cells. There were no findings of malignant or atypical cells in lymph node. Pathological findings and high level of CRP and IL-6, she was diagnosed MCD. However, immunohistochemically, infiltrating plasmacytes are highly positive for IgG4 (IgG4/IgG=30-40%) and her serum IgG4 was elevation. She was a difficult case diagnosed IgG4-related disease or MCD. She was followed clinically without treatment because her symptoms are improving during examinations. This case indicated the close relationship between IgG4-related disease and MCD.

P1-226

A case of Castleman disease showing interesting disease progress

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Conflict of interest: None

【Objective】Multicentric Castleman disease (MCD) was one of the most important disease of differential diagnosis of IgG4RD. Well known renal complication of IgG4RD was membranous nephropathy (MN), on the other side, MCD comprise glomerulonephritis.【Case】A 68 y.o. male patient had been to a hospital due to nephrotic syndrome 9 years before. He was diagnosed to have MN, and treated by PSL and CsA with success. But proteinuria recurred and retreated with PSL with partial remission 2 year before. He noticed febrile episode 1 year before, degree of fever further deteriorate and become steroid resistant. Peripheral blood analysis showed pancytopenia, he was reffered to our hospital. On admission, severe anemia, and multiple lymph node swelling and the skin eruption was noted, Blood test showed severe pancytopenia with marked inflammation (CRP 14.8 mg/dl). Other abnormality of Alb1.7, Glob 8.9, IgG6390, IgG4 1100. with high IL6 level and lymph nose biopsy made the diagnosis of MCD. He was treated by steroids in combination of Tosilizumub with success to the present.【Conclusion】This time we pre-

sented the MN case progressed to inflammatory condition to the diagnosis of MCD. This case give us a hint of possibility of progression IgG4RD to MCD, or relation of two these condition.

P1-227

A rare case of MALT lymphoma complication in the patient with IgG4-related thyroiditis

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Conflict of interest: None

A 54-years old male was seen in the emergency department due to severe anemia on September 1st, in X. He was receiving synthetic thyroid hormone for Hashimoto's disease and has recently noticed anterior neck swelling. During upper gastrointestinal endoscopy, he had breathing difficulty. A marked thyroid swelling was found on CT scan, he was hospitalized to the hospital. Because of upper airway obstruction due to enlarged thyroids, tracheostomy was performed on the same day. In addition to high levels of serum IgG4 (938 mg/dL), the thyroid biopsy showed the characteristic histopathological appearance of IgG4-related disease, a dense lymphoplasmacytic infiltrate and a storiform pattern of fibrosis, and increased IgG4+ plasma cells, thus was diagnosed as IgG4-related thyroiditis. Glucocorticoid therapy with 40mg/day prednisolone (PSL) was stared followed by closing of the air duct. However, the PSL effect was reduced at 20 mg/day and then 100 mg/day azathioprine was added. He was discharged as thyroid swelling reduced, but further histopathological examination revealed the complication of MALT lymphoma with κ-monotype light chain restriction in IgG4-related thyroiditis.

P1-228

A case of IgG4-related disease presented renal cystic pseudotumor

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Conflict of interest: None

【Case】A 63 year-old woman without symptoms was pointed out multiple pulmonary tumors and right renal mass on CT for health check. FDG-PET/CT imagings showed increased FDG accumulations of right renal cystic tumor, bilateral pulmonary tumor and pancreatic body. Biopsy specimen from pulmonary tumor showed IgG4 positive inflammatory pseudotumor with fibrosis. For considering the possibility of renal cell carcinoma, right nephrectomy was performed. IgG4/IgG-positive cells ratio was over 50% on the kidney, and moreover the serum IgG4 level was 252 mg/dl. Therefore the patient was diagnosed as having IgG4-RD presented renal cystic pseudotumor.【Discussion】Histological findings of removed kidney showed that IgG4 positive plasma cells infiltrated along cyst wall of cystic pseudotumor in addition to tubulointerstitial nephritis. Immunostainings of the cyst wall demonstrated that positive stainings of EMA, PAX2 and PAX8, and negative of CD10. Therefore, it was indicated that cystic pseudotumor derived from collecting duct. In this case, the collecting ducts in the kidney medulla were reduced by inflammation and fibrosis, and the narrowing of the lumen was caused. Therefore, it was suggested that the cystic lesions were produced by dilation of collecting ducts of the proximal side.

P1-229

A case of new –onset IgG4-related disease during SLE treatment

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Conflict of interest: None

A 38-year old female with the swelling of submaxillary and parotid glands was admitted to our hospital. She was diagnosed as systemic lupus erythematosus (SLE) with nephrotic syndrome about 5 years ago and treated with PSL (8mg/day) and tacrolimus (1.5mg/day). Positron emission tomography/computed tomography revealed the swelling of submaxillary and parotid glands (4.8×2.8cm) and sinusitis. Then we obtained the submaxillary tissue and its surrounding lymph nodes to make a diagnosis. Both of biopsy specimen showed the infiltration of IgG4+ plasma cells and germinal-center hyperplasia partially. The serum level of soluble IL-2 receptor and IgG4 was both normal and serum IgG4/IgG ratio was 3.8%. This case was very unique onset of IgG4-related disease during SLE treatment. We messured large variety of serum citokine at once using Bio-Plex and got the unique data of high level of several citokine such as IL-17-A, IL-21 and IL-23.

P1-230

A patient with IgG4-related disease accompanied by intracranial vascular lesions

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Conflict of interest: None

[Patient] A 44-year-old woman was referred to our hospital for a left orbital mass. She had undergone two operations to remove benign neck tumors 14 and 15 years prior. She had an 8-year history of chronic headache and a 6-year history of exophthalmos. She was diagnosed with an orbital pseudotumor. Prednisolone (PSL) 40 mg/day was administered. After 4 months, PSL was stopped. thereafter, the orbital pseudotumor recurred. Therefore, she was referred to our hospital. Because her serum IgG4 levels were high (IgG 1,602 mg/dL, IgG4 526 mg/dL), she was suspected to have IgG4-RD. CT scan showed an orbital tumor, cardiac effusion, left renal pelvic tumor, periaortitis, and a thickened bladder wall. IgG4 staining of the lymph nodes from 15 years previously showed numerous IgG4-positive cells (>70/hpf). therefore, she was diagnosed with IgG4-RD. Brain-enhanced MRI showed an aneurysm in the right vertebral artery and inflammation around the adventitia of the bilateral internal carotid artery that seemed related to IgG4-RD. To avoid aneurysm rupture after steroid therapy, coil embolization was performed and PSL was administered 1 month after steroid initiation. [Discussion] Further studies are needed to clarify the clinical features of IgG4-related intracranial vascular lesion.

P1-231

The distinct expression pattern of mRNA for cytokines in IgG4-related kidney disease associated with renal cell carcinoma

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Conflict of interest: None

[Objectives] We treated a 61-years-old man with IgG4-related kidney disease (IgG4-RKD). He had been diagnosed as renal cell carcinoma (RCC) and received left kidney segmental resection at 59 years old. He have diagnosed as autoimmune pancreatitis (AIP). According to his clinical course it was clarified that the value of serum amylase and the number of peripheral eosinophils were increased after the development of RCC. We constructed a hypothesis that RCC might induce the development of AIP and IgG4-RKD, and examined extracted RCC tissue. [Methods] Typical findings of IgG4-RKD attached with RCC were recognized. Next the evaluation of mRNA expression levels of cytokines in the tissues of this case and other ten ordinary RCC cases was performed. [Results] All cases showed sufficient values of IL-10 and great values of TGFβ. Although prominent differences were not observed in Th1, Th17, and Treg

cytokines in all cases, concerned with Th2 cytokines only this case showed increased productions of IL-4 and IL-5, and which were not detected in ordinary RCC cases. [Conclusion] Although a mechanism for development of IgG4RKD has not been clarified, Th2 and Treg cells are thought to be predominantly involved in the pathogenesis.

P1-232

IgG4-related disease complicated with the hypopituitarism and retroperitoneal fibrosis with hyper-eosinophilia correlated with EGPA

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Conflict of interest: None

A 73-year-old man with a past history of bronchial asthma was admitted with mild fever, anorexia, bilateral parotid swelling and lower back pain. Serum levels of the IgG (3054mg/dl), IgG4 (1040mg/dl), eosinophil (1420/μl) and IgE (3873U/ml) were examined. Whole body CT findings were inguinal lymph node swelling and typical features of retroperitoneal fibrosis. The contract brain MRI finding was swelling of the pituitary stalk. Hypopituitarism was diagnosed by the pituitary function tests. The pathological findings of the right inguinal node revealed infiltration of IgG-positive plasmacytes, and more than 40% of those were IgG4-positive plasmacytes. Oral prednisolone (0.6mg/kg; 50mg/day) was administered, and the swelling of the bilateral parotid was abated promptly. After 4 weeks later with prednisolone treatment, the pituitary stalk was dramatically decreased in size. Also, serum level of IgG4 decreased from 1040 mg/dl to 228 mg/dl and pituitary functions tests was improved. We suggested that IgG4-RD complicated with hypopituitarism and retroperitoneal fibrosis with hyper-eosinophilia and high levels of serum IgE was correlated with EGPA. A few cases of EGPA with high serum level of IgG4 were reported. The IgG4-RD has things in common pathogenesis with EGPA.

P1-233

Skin papules in a patient with IgG4-related disease

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Conflict of interest: None

A 36-year-old male, who had been treated for atopic dermatitis since childhood, presented with itchy papules and generalized lymphadenopathy. He was diagnosed with IgG4 related disease on the basis of a lymph node biopsy and an elevated serum IgG4 level. The papules mainly occurred on his trunk. A skin biopsy revealed IgG4 positive plasmacyte-rich infiltrate in the dermis. The papules were successfully treated with a moderate dose of corticosteroid. With the exception of several case reports and case series, skin lesions in IgG4 related disease have seldom been reported. Considering the fact that a significant number of patients with IgG4 related disease show symptoms of atopic dermatitis, it is quite important to differentiate skin manifestations of IgG4 related disease from those of atopic dermatitis.

P1-234

A case of IgG4-related Mikulicz disease complicated with a variety of allergic diseases

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Conflict of interest: None

A 36-year-old man who has past medical histories ofmany allergic diseases, such as atopic dermatitis, eosinophilic sinusitis, eosinophilic pneumonia, bronchial asthma and eosinophilic dermatitis presented to our hospital with swollen eyelid, diplopia and swelling of bilateral submandibular glands which developed over the course of several months. The serum IgG4 level and IgE level were elevated. Orbital MRI showed the swelling of lacrimal glands andexternal ocular muscle. PET/CT showed uptake in nasal sinus, submandibular glands, lacrimal glands, mediastinal lymph node and hilar lymph node. Pathology specimens from submandibular glands and lacrimal glands showed no malignancy, but failed to show significant increase in IgG4-positive plasma cell/ IgG cell over 50 %. We diagnosed this case as IgG4-related Mikulicz disease-based on guidelines and treated with prednisolone 40 mg/day. All the symptoms disappeared and the serum IgG4 level became normal.

P1-235

A Case of IgG4-related Mikulicz's disease (MD) associated with enlargement of extraocular muscles and lung lesion

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Conflict of interest: None

A 64-year-old man with chronic atrial fibrillation, previously diagnosed with hyperproteinemia (8.8 g/dl), presented with 10-year history of right submandibular mass and one-year history of left ocular proptosis. His ocular movement and visual field was normal. Serum IgG and IgG4 concentration were high as 3113 mg/dl and 1430 mg/dl, respectively. Anti SS-A and SS-B antibody was not detected. Orbital magnetic resonance imaging (MRI) revealed bilateral swelling of lacrimal grands and extraocular muscles. Computed tomography (CT) demonstrated small nodules in both upper lungs, whereas no significant findings was observed in pancreas, biliary tract, kidney, and retroperitoneum. Right submandibular gland biopsy showed lymphocyte and IgG4 positive plasmacell infiltration with fibrosis and ratio of IgG4 positive/IgG positive cells was above 50%. He was treated with prednisolone 40 mg per day. MRI finding of enlarged extraocular muscles resolved rapidly, as with the lung lesions observed in chest CT. Recent reports demonstrate respiratory lesions are associated with up to half of patient with IgG4-related MD, and ocular adnexa other than lacrimal grands can also be involved. The feature of our case was examined by means of refferring to previous reports.

P1-236

Clinical features of seronegative rheumatoid arthritis complicated with interstitial pneumonia

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Conflict of interest: None

[Objectives] Many past papers reported that rheumatoid arthritis (RA) complicated with interstitial pneumonia (IP) was associated with males, high titer of rheumatoid factor (RF), and smoking habit. However, reports on seronegative cases were rare. In this study, we clarify the clinical features of seronegative RA complicated with IP (RA-IP). [Methods] We investigated chest HRCT and serological tests including RF and ACPA levels in 149 RA patients (female, 98; male, 51). [Results] Thirty RA patients had IP (female, 16; male, 14). Seven of the 30 RA-IP patients were seronegative. Seronegative RA-IP patients (female, 6; male, 1) consisted of a significantly higher percentage of females compared with seropositive RA-IP patients. However, other indexes such as age, disease duration, and smoking habit, did not differ between seronegative and seropositive RA-IP patients (age, 72.6±10.3y.o. vs. 69.7±8.3y.o.; disease duration, 7.0±5.0 years vs. 11.3±7.6 years; percentage with smoking habit, 42.9% vs. 56.5%). [Conclusion] Female IP patients who are serologically negative for RF and ACPA, may actually have RA and her IP may be related to RA.

P1-237

Treatment with polymyxin B-immobilized fiber column direct hemoperfusion (PMX-DHP), for acute exacerbation of interstitial pneumonia complicated with rheumatoid arthritis

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Conflict of interest: None

A-77-year-old female, who has been suffered rheumatoid arthritis since 1997. Initially, she was treated with several DMARDs, but they were stopped because of adverse events. Then, she has been treated mainly with low dose prednisolone (PSL). She presented to a local hospital because of general fatigue and worsening dyspnea of 3 days duration. She developed severe hypoxia, and chest CT revealed bilateral diffuse infiltrative shadows and ground glass opacity. She was transferred to the emergency and critical care center of our hospital. She was diagnosed as acute exacerbation of interstitial pneumonia complicated with rheumatoid arthritis. She was treated with 1 g of methyl-PSL for 3 days followed by 60 mg PSL daily. Intravenous cyclophosphamide (IVCY) therapy and oral administration of cyclosporin A were used for co-treatment. She was additionally treated with PMX-DHP for two days. After these treatments, her oxygenation was gradually improved and she was recovered from respiratory failure. PMX-DHP therapy may be effective in improving the acute exacerbation of interstitial pneumonia complicated with rheumatoid arthritis. We will present this case with reference of literature.

P1-238

Association of Combined pulmonary fibrosis and emphysema (CPFE) with Rheumatoid Arthritis

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Conflict of interest: None

[Background] Combined pulmonary fibrosis and emphysema (CPFE) is characterized by the coexistence of emphysema of the upper lung field and fibrosis of the lower lung field in a same patient. [Patients and Methods] Retrospective review of chart was conducted on patients with rheumatoid arthritis (RA). 253 RA patients (male 64, female 189) who visited our hospital in October 2013 were included. [Results] 50 cases (male 21, female 29) was diagnosed with interstitial pneumonitis, 25 cases (male 16, female 9) was diagnosed with emphysema. 11 cases (male 9, female 2) are classified as having CPFE. The disease duration of RA is 10.2 ± 8.6 years and all were smokers. Only two patients complained dyspnea on exertion. A flattened diaphragm was observed in 4 cases and others showed normal level in Chest X rays. In respiratory function tests, 4 out of 6 tested showed obstructive pattern and 4 out of 5 showed decreased DLco. A lung cancer was observed in a patient and pulmonary hypertension was observed in another one. [Discussion] The incidence of CPFE was 15% in male RA patients. Lack of symptoms and normal diaphragm level may make it difficult to detect CPFE in patients with RA. Further studies are required for the longitudinal follow up to see the outcome of CPFE in RA patients.

P1-239

A case of drug-induced interstitial pneumonia occurring after long-term tocilizumab administration

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Conflict of interest: None

The patient was a 71-year-old woman diagnosed with rheumatoid arthritis (RA) in July 2011. She started receiving methotrexate (MTX) treatment, but the treatment was discontinued owing to side effects. From September 2011, tocilizumab (TCZ) treatment was initiated because of high disease activity, and RA went into remission. In June 2013, she developed mild cough accompanied with dyspnea on exertion. Her chest computed tomography (CT) showed interstitial shadows located mainly subpleurally in both lungs, and the KL-6 levels were as high as 1539 U/mL; therefore, interstitial pneumonia was suspected. The patient was hospitalized, and underwent bronchoscopy. The drug lymphocyte stimulation test with the bronchoalveolar lavage fluid was negative, but histopathological findings from lung biopsy specimens showed signs of subacute interstitial pneumonia and were consistent with a drug-induced condition. She diagnosed as drug-induced interstitial pneumonia due to TCZ. In Japan, the reported incidence of drug-induced interstitial pneumonia due to tocilizumab is 0.4% (35/7901 cases). The median onset time is 71.5 days. We report our experience with a case of drug-induced interstitial pneumonia due to TCZ, which developed approximately 2 years after initial treatment.

P1-240

An autopsy case of rheumatoid arthritis complicated by recurrent interstitial pneumonia with prolonged high level of aspergillus antigen

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Conflict of interest: None

On 2008, a 66-year-old man with rheumatoid arthritis was complicated with right interstitial pneumonia (IP) after etanercept therapy for five months. Aspergillus antigen was high level (4.5). By bronchoscopy, he was diagnosed with drug induced IP without evidence of aspergillous infection, then etanercept withdrew. On 2010, he was administered tocilizumab, and tocilizumab withdrew because he became remission after administration for 2years and 2 months. On November 2012, after three months since tocilizumab withdrew, right IP recurred. He was administered mPSL pulse, IVCY, PSL and cyclosporine, however re-exacerbation occurred several times and pneumothorax occurred. He was suspected as chronic necrotizing pulmonary aspergillosis (CNPA) because aspergillus antigen showed prolonged highest level (>5.0) and β-D-glucan was negative, then itraconazole administered. However, left lung deteriorated. In spite of twice mPSL pulse therapy, antibiotics and voriconazole, he died on the 12th day after hospitalization. The findings of lung tissue on autopsy showed extensive old and new non-specific interstitial pneumonia (NSIP). Any bacterial infection was suspected to trigger deteriorating IP finally. Several aspergillus fumigatus were detected in alveolar duct of left S6.

P1-241

Four cases we had difficulty in distinguishing drug-induced pneumonia by MTX or pneumocystis pneumonia

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Conflict of interest: None

[Objective] Examination of the drug-induced pneumonia by MTX and PCP examined four difficult cases. [Method] We examined four patients who presented the ground-glass pattern from April, 2010 to November, 2013. They used MTX because of treating their rheumatoid arthritis or SLE. [Results] Cases: 1) 83y.o. Male. RA, 2) 76 y.o. Male. RA, 3) 79 y.o. female. RA, 4) 56 y.o. female. SLE. MTX dose: 1) 4 mg/w, 2) 6 mg/w, 3) 10 mg/w, 4) 12mg/w. PSL dose: 1) 8 mg/d, 2) 20 mg/d, 3) nothing, 4) 20 mg/d. Biolocs: 3) ETN βD glucan: 1) 46.7pg/ml, 2) 75.6pg/ml, 3) 87.4pg/m, 4) 56.0pg/ml *Pneumocystis jirovecii* PCR positive (by bronchoscopy): 1),3),4). Treatment: 1) 2)discontinue MTX, 3) discontinue MTX and add on Trimethoprim/sulfamethoxazole, 4) discon-

tinue MTX, add on Trimethoprim/sulfamethoxazole and pemtamidine. They all recoverd. [Conclusion] TheirβD glucan was all elevated, even the cases we could not prove *P. jirovecii*. We could not distinguish between drug-induced pneumonia by MTX and PCP. We also could not but discontinue MTX, even the cases we could prove *P. jirovecii*.

P1-242

A case of follicular bronchiolitis associated with RA, which needed to differentiate from HTLV-1 associated bronchiolo-alveolar disorder and pulmonary MTX associated LPD

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Conflict of interest: None

72-year-old male who had been treated by MTX to RA for two years, had suffered from productive cough from three years ago. Because his arthritis was worsen recently, he admitted to our hospital to review the treatment. Disease activity of RA was high and newly bone erosions were detected by X-ray. Chest computed tomography exhibited centrilobular nodules with ground-glass opacities in the left lower lobe, and his pulmonary function exhibited obstructive dysfunction of small airways. Because he was positive for anti HTLV-1 antibody, as differential diagnosis, HTLV-1 associated bronchiolo-alveolar disorder was suspected except for mycobacterial infection, RA lung, and malignancies. Although bronchoscopy was conducted, results between histology of TBLB and cytology of brushing was dissociated as lung infiltration of adult T cell lymphoma and MTX-associated lymphoproliferative disorder. Therefore lung biopsy using video-associated thoracic surgery (VATS) needed. Lung specimens from VATS revealed lymphoid follicules with germinal center. No abnormal cells were detected by flow cytometric analysis and no rearrangement of TCR and IgH by PCR. Follicular bronchitis associated with RA was diagnosed, and MTX and TNF inhibitor treatment was administrated.

P1-243

A case of CNS lupus accompanied by Pneumocystis carinii pneumonia who showed patchy consolidation and ground glass shadow during high dose steroid therapy

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Conflict of interest: None

An 18 year-old female suffered from fever, arthritis, butterfly rash and intellectual disturbance in April 2013. She was admitted to our hospital and was diagnosed as systemic lupus erythematosus (SLE). Prednisolone (PSL: 50mg daily) was started for her neurological symptoms (CNS lupus). As her neurological disorder improved, PSL was tapered to 40 mg daily and she was discharged from the hospital. Three days after the discharge, she noticed to have high fever and dyspnea. Chest CT showed patchy consolidations and ground glass shadows in both lung fields. She was suspected to have lupus pneumonitis or alveolar hemorrhage according to chest CT findings. Methyl PSL pulse therapy was immediately initiated with PIPC/TAZ and trimethoprim- sulfamethoxazole considering the possibility of opportunistic infection as pneumocystis carinii pneumonia (PCP). Her respiratory symptoms improved promptly from the next day. Although β-D-glucan was negative at onset of respiratory symptoms, it was revealed that PCP-DNA was positive in her sputum at a later date. 【Clinical significance】 We reported a SLE patient who complicated PCP during PSL treatment. Chest CT showed atypical shadow considering PCP and it was difficult to reach to correct diagnosis.

P1-244

Immnosuppressive therapy in overlap syndrome of systemic sclerosis and Sjögren's syndrome with pulmonary hypertension

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Conflict of interest: None

[Introduction] Progressive pulmonary arterial hypertension (PAH) associated with systemic sclerosis (SSc) is crucial and a little effective therapy has been reported until now. Diagnosis of limited cutaneous SSc (lc-SSc) is difficult at an early stage, and Sjögren's syndrome (SjS) overlaps with SSc sometimes. We report two cases of PAH with overlap syndrome of lc-SSc and SjS. <Case1> A 70-year-old woman complaining of dyspnea on exertion (DOE) over seven years suffered from PAH three years ago. She could not walk dozens of meters without an oxygen inhaler, though triple vasodilators had been administered. After diagnosed as overlap syndrome of SjS and lc-SSc, steroid therapy and intermittent intravenous cyclophosphamide therapy were begun. The mean pulmonary arterial pressure improved. <Case2> A 67-year-old woman diagnosed as overlap syndrome of lc-SSc with PAH. She had SjS eighteen years ago and complained DOE for eight months. We plan steroid and endothelin receptor antagonist therapy. [Acknowledgement] We thank to the Department of Cardiology, National Cerebral and Cardiovascular Center, Kobe, Japan and the Division of Nephrology, Kobe City General Hospital, Kobe, Japan.

P1-245

Two cases of SLE-related pulmonary arterial hypertension complicated with Sjogren's syndrome

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Conflict of interest: None

Pulmonary arterial hypertension (PAH) is serious complication in patients with CTD. However, systemic lupus erythematosus (SLE) and Sjögren's syndrome (SjS) related PAH is suggested a good prognosis in order to react to immunosuppressive therapy. We report two cases of SLE-related PAH complicated with SjS which were responded to treatment with immunosuppressive agents and vasodilators. Case1: 42-year-old woman, she was diagnosed as SjS and SLE with dry eye, photosensitivity, arthritis, anti-SSA, DNA, nuclear antibodies positive. She showed symptoms of exertional breathlessness (FC II), right heart catheterization (RHC) was performed and pulmonary artery pressure (mPAP) was elevated to 35mmHg. This case was diagnosed as SLE-related PAH complicated with SjS, and was treated with moderate dose PSL and sildenafil, FC was improved from II to I. Case2: 55-year-old woman, she was diagnosed as SjS with dry eye and mouth, anti-SSA/B antibodies positive. She showed symptoms of exertional breathlessness (FC II), RHC was performed and mPAP was elevated to 42mmHg. Furthermore, bicytopenia and anti-DNA antibody were appeared, this case was finally diagnosed the same as case1. This case was treated with high dose PSL, tacrolimus, ambrisentan and sildenafil, FC was improved from II to I.

P1-246

Clinical characteristics of Polymyositis/Dermatomyositis patients who complicated interstitial lung disease in our hospital

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Conflict of interest: None

[Objectives] Polymyositis/Dermatomyositis (PM/DM) patients complicated with interstitial lung disease (ILD) have poor prognosis. Especially, rapid progressive interstitial pneumonitis has high morbidity. But, it is unknown what factor influences the prognosis in other types of ILD.

So, we investigated the clinical characteristics of PM/DM patients complicated with ILD in our hospital. [Methods] Patients who visited our hospital from April 2004 to April 2013 were subjected. We investigated 36 PM/DM patients who had the stable period of ILD retrospectively. [Results] 3 patients were died at the time of May 2013. There were no significant differences in laboratory findings and radiology findings between survivors with non-survivors. But, all non-survivors used only corticosteroid, and 2 patients died by infection. Patients who received combination therapy with immunosuppressant and corticosteroid tended to use less corticosteroid compared with patients who administered only corticosteroid. [Conclusion] ur findings suggest that Patients who treated with combination of immunosuppressant and corticosteroid had well-prognosis in our hospital. Our findings also indicate that combination therapy may be required in PM/DM patients complicated with ILD.

P1-247

Systemic muscle pseudohypertrophy in a patient with amyloidosis mimicking myositis

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Conflict of interest: None

【Case】A 63-year-old male with a past medical history significant for lumbar herniated disk and asthma presented with worsening severe low back pain for 6 months. He was admitted to the previous hospital for difficulty in walking in May 2013. He had high CK enzymes. The whole body CT scan showed generalized muscular hypertrophy. He was transferred to our hospital for further evaluation. The physical examination revealed distended abdomen, right femoral swelling and bilateral lower leg edema. The neurologic findings were within normal. He had hypercalcemia, anemia, hypoalbuminemia and proteinuria. The CK levels returned to normal. The CT scan showed generalized muscle hypertrophy and osteolysis in spine, pelvis and femoral. Immunoelectrophoresis of the serum and urine revealed a monoclonal κ-light chain. Bone marrow biopsy showed proliferation of monoclonal plasma cells. Abdominal skin biopsy and femoral muscle biopsy showed the deposition of eosinophilic amorphous materials positive for Congo red stain. He was diagnosed with Bence-Jones type myeloma with AL amyloidosis.【Conclusion】Muscle pseudohypertrophy is a rare manifestation of amyloid myopathy. It should be considered the possibility of amyloidosis during the evaluation of muscle pseudohypertrophy of unknown cause.

P1-248

A case of Adult Onset Still Disease developing MAS (Macrophage Activating Syndrome) after treatment with Tocilizumab (TCZ)

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Conflict of interest: None

We report a case of Adult Onset Still's Disease developing MAS (Macrophage Activating Syndrome) after Tocilizumab (TCZ) therapy a 22 year-old woman, who was diagnosed with AOSD two years ago, was admitted to the hospital for relapse. mPSL pulse and increased dose of MTX couldn't control the disease activity. Additional Tocilizumab therapy made clinical improvement, and PSL was tapered to 30mg/day. After second administration of TCZ, she presented leukocytopenia, thrombocytopenia, hypofibrinogenemia, hypertriglycemia, and markedly elevated LDH. Bone marrow aspiration reveals nonspecific findings. But MAS was clinically suspected. TCZ was discontinued, then mPSL pulse and IVIG was started. We further added cyclosporine and infliximab, which made a good clinical response. TCZ is reported to be an effective treatment for refractory AOSD in some literature. On the other hand, MAS after TCZ therapy has been reported suggesting the relation between TCZ and MAS. There are few reports about its mechanism, which remains indistinct. MAS with the treatment of TCZ seems to have milder symptoms compared to that without TCZ. With notice of marked reduction of CRP in TCZ therapy, attention should be kept on diagnosis of MAS.

P1-249

Effectiveness of tocilizumab for adult onset Still disease

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Conflict of interest: None

[Background] Recently, reports about the effectiveness of tocilizumab (TCZ) for adult onset Still disease (AOSD) are increasing. [Purpose] To examine the effectiveness of TCZ for AOSD. [Object and Method] Investigate the medical record of 20 (woman 13, man 7) AOSD patients from May, 2002 by July, 2013 retrospectively to compare the patients background and the effect of treatment, the adverse effect of ten TCZ administrated group and ten non-TCZ administrated group. Remission was defined as disappearance of the clinical manifestation and the CRP normalization. [Result] In the TCZ administrated group and the non-administrated group, CRP at the start of treatment is 16.5 and 12.7 mg/dl respectively, the serum ferritin level are 16340 and 15219 ng/ml. The mean PSL starting dose was 30.5 mg in the TCZ administrated group and lower than 50.0 mg of non-TCZ administrated group and, total PSL dose of one year after the start of treatment were 4474 and 6953 mg respectively. Eight TCZ group (80%) and six non-administrated group (60%) achieved remission. One cellulitis was reported as the serious adverse effect in the TCZ administrated group. [Conclusion] TCZ was suggested to have a possible beneficial effect for AOSD.

P1-250

A refractory case of adult onset still disease treated with abatacept

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Conflict of interest: None

A 66-year-old woman diagnosed as adult onset still disease (AOSD) in January 2010. Initially she was treated with high dose steroids (1mg/kg/day, prednisone 50mg), slowly tapered and received maintenance therapy with prednisone 5mg from September 2011. She had low grade fever for 14 days accompanied by wrist pain and generalized erythema from late July 2012. Skin biopsy at an erythema revealed the mild infiltration of inflammatory cells in the epidermis, which was a corresponding finding of AOSD. Serum ferritin concentration was elevated (292.4 ng/ml, normal value 4.6-204 ng/ml), we diagnosed as AOSD recurrence rule out infection and malignancy. The high dose steroids were effective, but her disease got worse with tapering. Methotrexate (MTX) was started and increased to 14mg per week, but could not decrease the dose of prednisone to 30mg, and then switched to abatacept 500mg with prednisone 30mg tapered to 3mg. This case is refractory AOSD predonisolone-resistant, which dose not improves by combination therapy of MTX. Cytokines, such as IL-6, IFN-gamma, TNF-alpha, have been found at high levels in patients of AOSD, as well as IL-4 and IL-18, reflecting T-cell activation. Abatacept is effective in our cases; we think T-cell activation because of non-responsive MTX.

P1-251

A case of adult onset Still disease of no activity presenting recurrent pericarditis

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Conflict of interest: None

The patient was a 62-year-old female. In January 2013, she was admitted to our hospital for fever and arthralgia lasting a week. For the

presence of rash, arthritis, spiking fever, sore throat, leukocytosis, liver dysfunction and hyperferritinemia, her illness was diagnosed as adult onset Still disease (AOSD). In addition, anterior chest pain worsened by body motion and respiration appeared. From electrocardiogram (ECG) and echocardiogram acute pericarditis due to AOSD was revealed. High-dose corticosteroid therapy was started, and her symptoms were reduced immediately, and then she was discharged. Disease activity was low during decreasing corticosteroid treatment. In September 2013, she felt anterior chest pain similar to the past episode. She was re-admitted and revealed to have pericarditis from blood tests, ECG and echocardiogram. But she had no other symptoms of AOSD, and ferritin level was normal. Symptomatic treatment with acetaminophen ameliorated her pericarditis. We concluded that she had recurrent pericarditis maybe due to autoimmune mechanisms following the first pericarditis. There is no report of cases of AOSD of no activity presenting recurrent pericarditis. Recognition of recurrent pericarditis is important in determining the treatment strategy.

P1-252

Tocilizumab was effective in the treatment of steroid-resistant macrophage activation syndrome in a patient with adult onset Still's disease

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Conflict of interest: None

[Introduction] There have been an increasing number of reports that tocilizumab (TCZ) was effective in the treatment of patients with adult onset Still's disease (AOSD). This is a case report on an AOSD patient whose macrophage activation syndrome (MAS) was resistant to steroid but well-treated by TCZ. [A case report] A 29-year-old man complained of fever and arthritis. We diagnosed AOSD because of sore throat, rash during the fever, lymph node and spleen enlargement and the markedly-elevated serum ferritin concentration (27,564 ng/mL). His symptoms were not alleviated by high dose steroid including pulse therapies. And then he developed MAS and disseminated intravascular coagulation (DIC). TCZ besides steroid cured fever after its 1st administration. Two weeks later, MAS and DIC improved at the 2nd TCZ administration. The serum IL-18 concentration, which had risen to 111,000 (pg/mL), went down but was still at a high value 21,100 (pg/mL) after the 4th biweekly TCZ. Thereafter, continuing monthly TCZ and monitoring serum IL-18 concentrations, we reduce the steroid dosage. [Discussion] TCZ was effective to steroid-resistant MAS in AOSD. The serum IL-18 concentration, which reportedly reflects the disease flare-up potential, is a good biomarker for the treatment of AOSD with MAS.

P1-253

Clinical characteristics in arthritis-type of patients with adult-onset Still's disease

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Conflict of interest: None

[Objectives] Adult-onset Still's disease (AOSD) is an acute inflammatory disorder of unknown origin that characterized by high spiking fever, polyarthralgia, a salmon-pink skin rash, liver dysfunction and lymphoadenopathy. It is well known that a number of patients with AOSD have RA-like clinical courses. In the present study, we examined the distribution of the joints with tenderness and/or swelling and radiographic findings of RA-like patients with AOSD. [Methods] Ninty patients with AOSD who were treated in Institute of Rheumatology, Tokyo Women's Medical University enrolled in this study. The patients group consisted of 30 men and 60 women. We classified the patients with AOSD into 2 groups; RA-subtype (n = 20) who met the revised criteria of American College of Rheumatology clinical diagnostic criteria for RA and nonRA-subtype (n = 70) who didn't met it. [Results] Our result indicated that serum levels of ferritin and IL-18 were high in AOSD. ANA, RF and anti-CCP antibody were not detected in most patients with either nonRA-subtype and RA-subtype. Wrist, MCP, MTP joint arthralgia were more frequently observed and DIP joint arthralgia and radiographic findings were more frequently observed than RA and were accompanied by an osteosclerosis lesion to a high rate.

P1-254

Clinical features of elderly patients with adult Still's disease

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Conflict of interest: None

[Objective] To examine the clinical features of elderly patients with adult Still's disease (ASD). [Methods] We retrospectively examined symptoms, laboratory findings, treatments and the clinical course after treatment of 9 elderly patients with ASD (age 60-80 years), and compared those in 10 young patients with ASD (age 16-37 years). [Results] Spiking fever, rash, and arthralgia were found in almost all patients in both groups. Serositis (n=2) and hemophagocytic syndrome (n=3) were only shown in elderly patients. Although serum ferritin concentrations were markedly elevated in all patients, the levels were significantly higher in elderly patients. All patients were treated with corticosteroid and all young patients achieved remission with steroid therapy alone. In elderly group, additional immunosuppressants and/or biologic agents became necessary for remission in 3 patients. Relapse within 1 year was shown in only elderly group (n=4). [Conclusion] In patients with ASD, severe inflammatory conditions and difficulty in achieving and keeping remission were observed more frequently in elderly group.

P1-255

Trimethoprim-sulfamethoxazole (ST) should not be used for Pneumocystis jirovecii pneumonia (PJP) prophylaxis in Adult onset Still's disease (AOSD). Suggestive two cases report

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Conflict of interest: None

【introduction】PJP is an important opportunistic infection, and prevention is recommended. On the other hand, ST is easily induced drug allergy. In addition, hypersensitivity to drugs of AOSD is well known. Here, we had two cases of AOSD, which had drug allergy to ST, and exacerbation of disease activity itself at the same time and difficult to distinguish.【Case 1】48-year-old, Female was treated with PSL, MTX, and CsA as steroid resistant AOSD. She had PJP during the treatment and ST was administered. After 8 days, she had fever. Another infection, AOSD flare, and drug allergy were suspected. Antibiotics and antifungal agent were started and ST was stopped. she had eruption and increasing of ferritin. mPSL pulse therapy started.【Case 2】74-years-old female was treated with PSL30mg for AOSD. At the same time, ST had started. After tapering PSL to 20mg, fever relapse. Even though revert PSL to 25 mg, she had high fever, liver dysfunction and increasing of ferritin. After stopping ST, fever and laboratory data improved without dose escalation of PSL.【Discussion/Conclusion】we experienced two cases potentially exacerbated diseases such as fever, increasing ferritin after administration of ST in AOSD. ST should not be used as first line for PCP prophylaxis in AOSD.

P1-256

Two case of Adult-onset Still's disease with persistent skin rashes

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Conflict of interest: None

The typical skin presentation of Adult-onset Still's disease (AOSD) is an evanescent salmon-pink skin rash. We report two cases with atypical skin eruptions. [Case 1] A 64-year-old woman was admitted to our hospital because of itching skin eruption and high fever. She also complained of sore throat and arthralgia. Leukocytosis, liver dysfunction and elevated ferritin (15800 ng/ml) were noted. She was diagnosed as AOSD. A skin biopsy from right thigh revealed perivascular infiltrations composed of lymphocytes. Oral prednisolone (PSL) 1mg/kg/day improved skin eruptions. But liver dysfunction deteriorated. Pulse methylprednisolone treatment was done. Cyclosporine 150mg was added. Liver dysfunction improved gradually. [Case 2] A 27-year-old man presented with fever, sore throat, arthralgia and itching skin eruptions for more than 2 weeks. Leukocytosis and elevated ferritin (7300ng/ml) were noted. AOSD was diagnosed. A skin biopsy from red rash on his hip revealed perivascular infiltrations composed of lymphocytes. Fever and skin eruptions were improved by acetylsalicylic acid. However, PSL 20mg/day was requisite to treat arthralgia. [Conclusion] It is important to understand various cutaneous manifestations of AOSD for early and correct diagnosis.

P1-257

Clinical features and prognosis of adult-onset Still's disease: retrospective analysis

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Conflict of interest: None

[Objectives] To describe the clinical features, treatment, and prognosis of patients with adult onset Still's disease (AOSD). [Methods] Twelve patients with AOSD were analyzed retrospectively. [Results] The patients were 6 men and 6 women with an average age of 37.5 years (range 19-64). Common clinical features were fever (100%), arthritis (100%), lymphadenopathy or splenomegaly (66.7%), rash (58.3%), and sore throat (58.3%). The laboratory findings were as follows: leukocytosis (75.0%), elevated transaminase levels (66.7%), and elevated ferritin levels (50.0%). An initial average prednisolone (PSL) dose was 42.5mg/day, and other immunosuppressants were added in 4 patients. Average 1.9 recurrences after initial treatment were observed with an average PSL dose at recurrence being 9.4mg/day. After recurrence, increase in PSL dosage was performed in 10 patients, and addition of other immunosuppressants in 9 patients. An average PSL dose at the last review was 7.1mg/day in 8 patients with remission state for more than one year, 7 of whom received other immunosuppressants. [Conclusions] Our data suggests the effectiveness of immunosuppressants for the induction and maintenance of remission and the reduction of PSL dosage in the treatment of AOSD.

P1-258

A case of refractory hemophagocytic syndrome (HPS) associated with systemic lupus erythematosus (SLE) successfully treated with etoposide (VP-16)

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Conflict of interest: None

A 36-year-old woman was diagnosed SLE because of fever, oral ulceration, leukocytosis, ANA 320 and double-strand-DNA>300 IU/l. The serum ferritin was elevated and pancytopenia and her bone marrow smear showed hemopagocytosis. We ruled out other disease and made a diagnosed of HPS associated with SLE. Therfore we started steroid pulse therapy and intervenous immunogloblin, which was inefective.

P1-259

A case report of macrophage activation syndrome (MAS) by Weber-Christian (W-C) disease that periodic assessment of cytokine profile was useful in therapy evaluation

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Conflict of interest: None

A 29-year-old man was admitted to a local hospital showing signs of a fever and erythema of his face and upper body, hepatic dysfunction. He was diagnosed with lobular panniculitis by the skin biopsy. He took prednisolone (PSL) 20mg/day, but his disease was resistant. He was introduced to our hospital. We diagnosed W-C disease caused by unkouwn unexplained lobular panniculitis. He had MAS for hepatic dysfunction and cytopenia, evidenced by elevated sIL-2R 3474U/ml and ferritin 3510ng/ml. He took steroid pulse therapy and PSL60mg/day. He cured a fever and erythema, but continued to get worse hepatic dysfunction and cytopenia. We did not get the specific findings by the liver biopsy. We thought exacerbation of MAS for sIL-2R 5370U/ml, ferritin 64500ng/ml, neopterin 56nmol /L (reference value less than 5), IL-18 25500pg/ml (reference value less than 500). 2nd steroid pulse therapy is invalid. We got the effect in combination of Tac, ICVY and plasma exchange. After these treatment, sIL-2R and ferritin was normalized and he was gradually recoveried and administered the PSL to 10mg/day. He discharged without relapse. His disease activity shows the cytokine profile, such as IL-18 (530 at discharge) and neopterin (5.3) that described no report previously. His case is very rare of W-C disease complicated MAS.

P1-260

Renal pathology in patients with Crystal storing histiocytosis

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Conflict of interest: None

[Objectives] To evaluate the factor determinating the distribution of renal lesions in crystal storing histiocytosis (CSH) [Methods] Case presentation with literature review [Results] 69yr women, who were reffered to our department for the investigation of leukocytopenia, hypocomplementemia, and nephrotic syndrome, exhibited CSH with no findings featuring lupus nephritis. The crystals were shown mainly in the glomerulus rather than tubules. [Conclusion] The present case with CSH was the first to exhibit the crystals mainly in the glomerulus. Most of the patients were accompanied by monoclonal hypergammopathy with kappa-light chains. Patients with Fanconi syndrome demonstrated the proximal tubular lesions of various distributions. Patients with multiple myelome and Fanconi syndrome were reported to have diamond-shaped crystals, whereas those with CSH demonstrated needle-shaped crystals. The difference in the ultrastructural patterns of inclusions in multiple myeloma and CSH are attributed to the difference in the structures of monoclonal kappa-light chains. Crystals were noted mainly in the plasma cells in patients with multiple myeloma, whereas in macrophages with CSH. Further study is needed to evaluate whether the crystals were present predominantly in the glomerulus or tubules.

P1-261

Two cases of relapsing polychondritis with airway involvement

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Conflict of interest: None

Case1: 47-year-old female was admitted to our hospital because of subglottic laryngitis. Two weeks after admission, she presented with arthritis and dyspnea. CT showed diffuse airway-wall thickening and luminal narrowing and costocondritis. She was diagnosed as relapsing polychondritis (RP). She improved with intravenous methylprednisolone pulse, she was consecutively treated with oral prednisolone and methotrexate up to 16mg weekly. When she was treated with PSL 20mg/day, follow-up CT showed progression of airway luminal narrowing and CRP remained high (1-3mg/dl). Although cyclosporine and colchicine were added, they were not effective. Then she was finally treated with infliximab (IFX) 3mg/kg every 8 weeks, resulting in improvement. Case2: 75-year-old female, who had been treated as asthma, was admitted to our hospital because of severe subglottic stenosis. Then she urgently underwent tracheostomy. As she also had auricular, nasal chondritis, she was diagnosed as RP and subsequently treated with PSL 30mg/day. She sometimes relapsed as PSL was tapered. [conclusion] Out of our 9 cases with RP, there are two cases (22%) with airway involvement. Our cases suggested that IFX may be one of the effective therapies for patients who are refractory to PSL and other immunosuppressive agent.

P1-262

5 cases of juvenile idiopathic arthritis possibly induced by Human Papillomavirus vaccines

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Conflict of interest: Yes

We present 5 cases of juvenile idiopathic arthritis after Human Papillomavirus vaccines Case 1, A-15 year old female developed high fever and polyarthritis at 1 week after second time vaccines. She was medicated with salazosulfapyridine (SASP) 1000 mg/day and methotrexate (MTX) 11mg/w, but artithitis of the left wrist was persisted. Case 2, A-17 year old female developed high fever and polyarthritis at 5 months after second time vaccines. She was medicated with MTX 10mg/w and Tocilizumab (TCZ). Case 3, A-13 year old female developed polyarthritis at 2 months after second time vaccines. She was medicated with MTX 12mg/w and TCZ. Case 4, A-13 year old female developed oligoarthritis at 1 months after third time vaccines. She was medicated with SASP 1000mg/day. Case 5, A-17 year old female developed oligoarthritis at 1 months after second time vaccines. She was medicated with SASP 1000mg/day. After treatment with TCZ, case 2 and case3 achieved clinical remission. In Case 4 and Case 5, their condition was good after stopping administering SASP, they have been followed carefully with no medication. Only case 2, blood test showed positive rheumatoid factor, all cases showed negative aint-CCP antibody. Case 1.2.3.5 were administered Cervarx ®, only Case 4 was administered Gardasil ®.

P1-263

Continuous change from systemic juvenile idiopathic arthritis to macrophage activation syndrome

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Conflict of interest: None

We have believed that macrophage activation syndrome (MAS) is a complication of systemic juvenile idiopathic arthritis (S-JIA). But MAS is not a complication, it might be a continuous change from S-JIA. We report a case of S-JIA prevented a development of MAS. A 7-year-old boy presented with fever, polyarthralgia, and rash. A diagnosis of s-JIA was made. His disease frequently relapsed. A disease flare-up characterized by arthralgia and fever and serum CRP concentrations elevated occurred. He treated with the mPSL pulse therapy administered. This therapy resolved fever. But laboratory findings LDH elevated, though no leukocytosis was observed. He treated with dexamethasone palmitate like a MAS. And then, he prevented a development of MAS. The diagnosis of MAS is frequently difficult to make, and there is no gold standard to identify the condition. We have evaluated his serum IL-18, and compared the other cases of MAS. We considered his condition was an intermediated state of S-JIA and MAS. Perhaps, S-JIA and MAS represent the two ends of a clinical spectrum of disease caused by the activity of macrophage.

P1-264

Knee synovectomy and open biopsy of the lymph nodes in a child with juvenile idiopathic arthritis; a case report

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Conflict of interest: None

[Objectives] We report a case of oligoarticular juvenile idiopathic arthritis (JIA) with hyperplasia of the popliteal lymph nodes, of which open biopsy demonstrated the microscopic findings similar to the Castleman disease. [Case presentation] Two years and three months girl visited our hospital with bilateral knee pain. Laboratory findings was as follows: WBC 11790/μl, RBC 457万/μl, Hb 9.1g/dl, Hct 29.8%, Plt 63.9万/μl, CRP 5.99mg/dl, ferritin 38.5ng/dl, Fe 8μg/dl, RA (-), MMP-3 483ng/ml, anti-CCP Ab (-), IL-6 19.7pg/ml. MRI showed fluid collection in the bilateral knee joint with thickness of synovium, and hyperplasia of the popliteal lymph nodes. Arthroscopic synovectomy and open biopsy of the popliteal lymph nodes was undergone for the purpose of diagnosis and treatment of worsen synovitis. Pathological findings of the synovium showed synovitis compatible with rheumatoid arthritis, and that of lymph nodes showed hyperplasia with follicle formation and infiltration with plasma cells which was similar to the Castleman disease. Patient was administered steroid (2mg/kg/day) per os and her symptoms were improved. [Conclusion] JIA with hyperplasia of the lymph nodes may have a pathophysiology similar to the Castleman disease.

P1-265

Two cases of childhood-onset granulomatosis with polyangiitis

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Conflict of interest: None

We report two girls with granulomatosis with polyangiitis who developed nasal septum inflammatory granuloma. One patient is 5-year-old girl who was suffering from fever, nasopharyngitis, and oral ulcer for a few months before administration. The CT scan showed retropharyngeal mass and hypertrophy of nasal septum. Histological findings of nasal and pharyngeal mucosal biopsy demonstrated granulomatous inflammation. She was diagnosed as having limited granulomatosis with polyangiitis. She was treated with corticosteroid and monthly intravenous cyclophosphamide and achieved remission. Another patient is 12-year-old girl who was suffering from fever, nasopharyngitis, and headache for few days before administration. She developed ophthalmalgia, congestion, and photophobia, and diagnosed as having bilateral scleritis. Nasal fibroscopy showed nasal mass and histological findings demonstrated granulomatous inflammation with necrotizing vasculitis. She was diagnosed as having granulomatosis with polyangiitis and treated with corticosteroid and intravenous cyclophosphamide and achieved remission. Although granulomatosis with polyangiitis is rare in children, in case of patient with chronic systemic inflammation and paranasal sinuses involvement, we should rule out this disease.

P1-266

three cases report: Patients complicated with interstitual pneumonitis who had refractory systemic juvenile idiopathic arthritis

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Conflict of interest: None

Lung diseases complicated with collagen diseases are common and sometimes serious in adult patients with RA, however, it is rare in children with rheumatic diseases especially in systemic JIA. Therefore, we present 3 patients with systemic JIA, age at onset was 2, 3 and 4 years respectively, who complicated with interstitial pneumonitis (IP). IP was clinically diagnosed by CT findings in all patients, and no pathological findings were obtained by peribronchial examination. IP finding were gradually resolved in accordance with clinical remission after initiating tocilizumb (TCZ) in 2 of 3 patients. The rest of one patient who had repeated episodes of macrophage activating syndrome, however, her clinical and laboratory findings of IP such as dry cough and increase in serum KL-6 level gradually emerged after initiating TCZ therapy. Biologic agent was switched to infliximab by considering the possibility of TCZ induced IP, however, IP became worse in CT findings and elevated KL-6 levels after the switching. Therefore, biologic agent was re-switched to TCZ, and intravenous cyclophosphamide (IVCY) was initiated after excluding possible infectious pathogens. One year after initiating IVCY, she was discharged without oxygen therapy though her serum KL-6 level remained still high.

P1-267

Clinical courses in 5 children with systemic juvenile idiopathic arthritis complicated with macrophage activation syndrome at primary onset

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Conflict of interest: None

[Objectives] Macrophage activation syndrome (MAS) is a critical complication of sJIA. MAS causes coagulation abnormality, hemophagocytosis, tissue injury and multiple organ failure originating in excessive IFN-γ, TNF-α and IL-18. However, it is not well clarified if MAS at onset influences the prognosis. [Methods] Five children with sJIA with MAS at onset referred to our hospital between Apr 2010 and Oct 2013 were investigated regarding to their clinical course and laboratory examinations. [Results] Laboratory examinations at onset were; AST 173±87.3 IU/L, LDH 1060±741.8 IU/L, ferritin 22250.6±11811.2 mg/dl, WBC 8828±8554 /μL, PLT 15.9±11.8×10^4/μL, IL-6 126.8±112.7pg/ml and IL-18>5000 pg/ml. Methyl prednisolone pulse therapy (n=5), i.v. cyclosporine (n=5), plasma pheresis (n=3) and leuklocytapheresis (n=1) were performed and all patients survived. Two patients had relapse of sJIA, but no patient developed MAS. On last observation, IL-6 (7.3±9.4 pg/ml), IL-18 (693.8±619.0 pg/ml) and MMP-3 (31.6±35.1 ng/ml) were normal or slightly elevated. No patients showed chronic arthritis. [Conclusion] After the resolution of MAS, all patients showed neither chronic arthritis nor persistent elevation of IL-6, IL-18 and MMP-3. MAS at onset would not always suggest long-term poor prognosis of sJIA.

P1-268

Pharmacokinetic of mycophenolate mofetil in children with autoimmune disease

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Conflict of interest: None

[Objectives] The suitable dose of mycophenolate mofetil (MMF) and pharmacokinetic (PK) in pediatric autoimmune disease are not available in Japan. There are several reports about PK of MMF in adult renal transplant recipients. In these reports, calculate the area under curve (AUC) of mycophenolic acid (MPA) range should be 30-60μg·h/ml, however, MMF was often used in combination with calcineurin inhibitor. The purpose of this study is to describe the PK of MMF in 7 pediatric patients with autoimmune disease. [Methods] Blood samples were taken for measurements of MPA concentration at 0, 1, 2, 3, 4, 6, and 8hour, and calculate the AUC. [Results] Patients were all females, and included 5 with systemic lupus erythematosus and 2 with mixed connective tissue disease. Mean age at time of diagnosis was 9.4±1.0years, and at this study 12.4±2.1years. They were treated with prednisolone 5.9±2.1mg (0.1-0.3mg/kg/day) and MMF without concomitant immunosuppression. The MMF doses were 1000mg±264mg/day (902±216mg/m^2/day, 31.0±8.4mg/kg/day). Mean $AUC_{0\text{-}12h}$ was 52.5±22.6μg·h/ml. There was a positive correlation between MPA-AUC and MMF-doses per body surface area or body weight. [Conclusion] Our mean MPA-AUC was generally the same as that proposed to be sufficient for immunosuppression in past report.

P1-269

Eight Japanese cases with Adult Still's Disease developed from systemic-onset Juvenile idiopathic arthritis

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Conflict of interest: None

[Objectives] Long-term outcome of systemic-onset JIA beyond adolescence has not been described. [Methods] Clinical Characteristics of eight patients with Adult Still's Disease (ASD) developed from systemic-onset Juvenile idiopathic arthritis (sJIA) were evaluated. [Results] Eight patients (5 male and 3 female) were 43.4±9.0 years of age. Their sJIA onset were at the age of 2 (2 cases), 3 (1case), 4 (1 case), 11 (3 cases), and 13 (1 case). The clinical course of sJIA was "continuously active" in 5 cases and "recurrently active" in 3 cases. In seven cases, ASD developed after 13.4±4.5 years of clinical remission of sJIA off medication (CR) (age of ASD onset: 27.1±5.1 years). Four "continuously active" sJIA cases eventually obtained CR required 9.0±1.0 years of active phase until CR. The clinical course of ASD were "continuously active" in 3 cases and 2 of the three were also in "continuously active" in sJIA. [Conclusion] Further investigations are required to figure out prognostic factors over adolescence in sJIA.

P1-270

Blood purification for pediatric collagen diseases

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Conflict of interest: None

Objective Due to recent advances in equipment size and materials, blood purification can be performed safely for the severe condition of multiple organ failure and infectious disease in children. Depending on the target substances to be eliminated, different procedures, such as adsorption, filtration and plasma separation, are possible, and partial plasma exchange with continuous hemodialysis (PDF: Plasma-Dia-Filtration) has been performed for pediatric collagen disease including macrophage activation syndrome. Methods The patient background and method of blood purification from 2000 to 2012 in our hospital were investigated. Results PDF is effective for removing substances with medium molecular weights, such as inflammatory cytokines including IL-6 and TNF-a, and minimally invasive for patients because of the amount of FFP required was one-fifth the normal amount. Conclusion Blood purification therapy is one of useful choice of the combination therapy for secure remission by immunosuppressive drugs in children collagen disease. In particular, PDF is useful to regulate of inflammation and increased recently.

P1-271

High serum IL-6 and IL-18 in children with systemic juvenile idiopathic arthritis accompanying persistent elevation of serum MMP-3 under tocilizumab treatment

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Conflict of interest: None

[Objectives] Long-term prognosis of systemic juvenile idiopathic arthritis (sJIA) has been improved by tocilizumab (TCZ). However, patients who initially developed systemic type but later changed to polyarticular type are likely to take chronic and refractory courses, and thier articular prognosis is poor. We examined serum IL-6 and IL-18 in two boys with sJIA accompanying persistently high MMP-3. [Cases] Patient 1 (5 y, boy) and 2 (5 y, boy) developed sJIA at 4- and 3-year-old, respectively. They were successfully treated with steroid pulse therapy followed by prednisolone, but both patients experienced relapse one year after the onset. Thereafter, they have been well treated with TCZ, but they developed arthritis or synovial cyst even under TCZ treatment. Arthritis and synovial cyst were successfully treated with additional steroid and methotrexate in both, but MMP-3 has been keeping abnormally high values. Additionally, IL-6 and IL-18 had also rebounded to abnormally high values and the elevaton has been persistent. [Conclusion] Persistent elevation of IL-6 and IL-18 may suggests pathophysiology of refractory sJIA patients who change from systemic type to polyarticular type. For such TCZ resistant patients, new therapy such as IL-18 blockade should be developed.

P1-272

2 cases of children with cryofibrinogenaemia

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Conflict of interest: None

[Objectives] Cryofibrinogenaemia may be primary or secondary, and itself is often asymptomatic. The mechanism or pathogenesis is unclear. we report 2 child cases of transient cryofibrinogenaemia. [Methods] Case1: 3-year-old boy complained annular erythema. Erythema appeared on his cheeks that had been resistant to corticosteroid ointment 4 months before. Common values of blood test were normal and autoantibodies were negative. Cryofibrinogen was slightly high level, 84 (<80)μg/ml. We diagnosed him as cryofibrinogenaemia and treated with dipyridamole. Erythema disappeared 3 months later and cryofibrinogen decreased to normal level after having increased to 268μg/ml once. Case 2: 13-year-old girl complained livedo reticularis. Erythema and edema appeared on her lower limbs10 days before her visit. On 5th day, livedo reticularis occurred on dorsum pedis. Index of inflammatory including white blood cell count, erythrocyte sedimentation rate and CRP was increased. Autoantibodies were negative and cryofibrinogen was remarkably increased, 840μg/ml. We treated her with aspirin and skin manifestation disappeared quickly. Cryofibrinogen decreased 3 months later. [Results] Both 2 cases were transient. [Conclusion] We report 2 child cases of cryofibrinogenaemia treated with antithrombotic therapy.

P1-273

A case of polyarticular juvenile idiopathic arthritis with prolonged refractory rash

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Conflict of interest: None

[BACKGROUND]: Only few among polyarticular JIA (pJIA) show significant rash. We present a case diagnosed as pJIA with prolonged rash. [Case]: The subject is 8-years-old girl, had a minor arthralgia, erythema charaterized by pruritus on the whole body. Her symptoms were prominent pain in both hands, knees, and ankles. Active synovitis was recognized by MRI. The pathology of skin showed an infiltration of neutrophils, eosinophils around vessels in the dermis. Diagnosed as RF-Negative pJIA, the MTX, NSAID, PSL treatment was introduced. Adalimumab was injected 2 months after, and rash and joint symptoms ameliorated. [DISCUSSION]: Although the pathogenesis of pJIA is distinct from systemic JIA (sJIA), it is of interest our pJIA case with rheumatoid rashes which usually seen in sJIA.

P1-274

A case of oligoarticular JIA with rice bodies which disappeared by weekly oral methotrexate therapy

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Conflict of interest: None

[Introduction] Rice bodies are rare feature of Rheumatoid arthritis or juvenile idiopathic arthritis (JIA). We report a girl of oligoarticular JIA with rice bodies in bilateral knee joints at an early phase, and they disappeared by weekly oral methotrexate (MTX) therapy. [Case] A case is a two-years-old girl. She had got dysbasia. After two months, she had developed pain, swelling, and limitations range of bilateral knee and right elbow joints motion. Many rice bodies was collected from synovial fluid of right knee joint, which that was also revealed that there was synovium hyperplasia with rice bodies by MRI exam. In blood exam, RF, anti-CCP-Ab and ANA are negative. A culture test of joint fluid including tuberculous is negative. She was diagnosed as oligoarticular JIA and treated with NSAID and weekly oral MTX. Thereafter, arthritis had improved. After three months, MRI exam of knee joints showed that rice bodies disappeared. Currently, she is administrated tocilizumab because of remained active arthritis. [Discussion] Rice bodies may contain coarse collagenous fibers, fibrin, or elastin. They frequently are perfomed surgical resection, but in this case, they vanished by only methotrexate. Particularly, in children, rice bodies may disappeared by drug therapy.

P1-275

Autoimmune lymphoproliferative syndrome infant with mimic Hemophagocytic lymphohistiocytosis like syndrome

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Conflict of interest: None

Autoimmune lymphoproliferative syndrome (ALPS) represents a failure of apoptotic mechanisms to maintain lymphocyte homeostasis. Chronic lymphadenopathy, splenomegaly, multiple autoantibody are the major symptoms due to FAS (TNFRSF6) gene mutation, This report describes a 1-year-old case suspected familial hemophagocytic lymphohistiocytosis like symptoms during onset. Prolonged low complement, positive ds/ss/DNA, SS-A/B Ab, hyper IgG, high sIL-2R were consistence with ALPS. Long term observation is required to pursue the complication, such as lymphoma, JMML and autoimmune disease. Genetic analysis is ongoing.

P1-276

Somatic *NLRP3* mosaicism in Muckle-Wells syndrome

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Conflict of interest: None

[Objectives] Familial cold autoinflammatory syndrome, Muckle-Wells syndrome (MWS), and chronic infantile neurologic, cutaneous and articular (CINCA) syndrome are dominantly-inherited autoinflammatory diseases associated to gain-of-function *NLRP3* mutations and included in the cryopyrin-associated periodic syndromes (CAPS). Although somatic *NLRP3* mosaicism has been detected in -35% of patients with CINCA, no data are currently available regarding the relevance of this mechanism in other CAPS phenotypes. In this study, we evaluated somatic *NLRP3* mosaicism as the disease-causing mechanism in patients with clinical MWS phenotypes and *NLRP3* mutation-negative. [Methods] *NLRP3* analyses were performed by Sanger's sequencing and by massively parallel sequencing. Two different assays determined the functional consequences of the detected variants. [Results] A variable degree of somatic

NLRP3 mosaicism was detected in 12.5% of enrolled patients. Six different missense variants, three novel (p.D303A, p.K355T, and p.L411F), were identified. Functional analyses confirmed that they were disease-causing, gain-of-function *NLRP3* mutations. [Conclusion] We showed somatic *NLRP3* mosaicism underlying MWS, probably representing a shared genetic mechanism in CAPS not restricted to CINCA syndrome.

P1-277

Chronic recurrent multifocal osteomyelitis; a case report

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Conflict of interest: None

Chronic recurrent multifocal osteomyelitis (CRMO) is a rare autoinflammatory disorder that mostly affects children. A 10-year-old girl presented with the right ankle pain during the footrace. The pain once subsided with NSAIDs and rest, however she again complained the pain without any injury. Radiographs and MRI showed an osteolytic and sclerotic lesion in the right distal fibula. Blood test revealed nonspecific evidence of inflammation. Her symptom repeatedly improved and worsened. Eight months after the initial symptom, she presented with the left ankle pain and the subsequent imaging demonstrated the same lesions as the right ankle. Iliac bone biopsy was performed and showed no evidence of malignant findings. Consequently, the diagnosis of CRMO was made based on the combination of the clinical, radiological and histopathological findings. The lesions have not progressed and the patient is symptomatically improving. The natural history of CRMO is unpredictable course of acute exacerbations and spontaneous remission. The diagnosis is made by exclusion based on the clinical, radiological and pathological criteria, therefore it is difficult to diagnose in the acute stage. The awareness of the corresponding feature can help avoid of unnecessary diagnostic procedures.

P1-278

A case of Castleman's disease which was diagnosed as prulent arthritis of the hip following total hip arthroplasty

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Conflict of interest: None

[Objectives] A case report of Castleman's disease. [Methods] A 46 years-old Female. Two years later of left THA, swelling of left lower leg and left inguinal lymph node were indicated. Low grade fever, white blood cell; 8,400, C reactive protein; 2mg/dl, effusion surrounding of the THA and in the same side of the iliac muscle suggested the development of purulent arthritis of the hip. Then debriedment surgery was performed. But bacterial culture of the effusion was negative. Hypoproteinemia and pleural effusion were gradually aggravated. The size of abdominal lymph nodes were increasing in CT. Histological findings of debriedment tissue showed distinct feature of prolifilation of plasma cells around the folicles. On the basis of these findings, anew diagnosis as Castleman's disease (CD) was carried out. CD has no characteristic clinical and pathological findings. CD is diagnoised on the basis of non-distinctive symptoms such as fever, general fatigue, anemia, lymph node swelling and characteristic histological findings. Although a better prognosis is expected by steroid or biologics therapy, fundamentally CD is an unknown pathogensis, poor prognosis disease. [Conclusion] As a differential diagnosis, CD should be consider for the patient with hypoproteinemia and aseptic abscess.

P1-279

Case report of familial Mediterranean fever complicated by tuberculous lymphadenitis

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Conflict of interest: None

[Case] A 54-year -old female [Present Illness] The patient was admitted to a hospital because of fever, abdominal pain and chest pain. various examinations did not establish diagnosis. [Clinical course] There was past history suggesitive of tuberculosis. CTscans of the chest and abdomen revealed multiple enlarged calcified hilar, intraperitoneal and axillar lymph nodes. Tuberculin test proved to be strong positive. A biopsy of the left axillary lymph node revealed tubercular bacilli. These findings lead to the diagnosis of tuberculous lymphadenitis. Antituberculosis drugs were started but there was little changes in symptoms. Symptoms building in waves periodically gave me a hint on the possibility of familial Mediterranean fever. Genetic analysis of the MEFV gene revealed MEFV mutation: a variant of familiar Mediterranean fever. After the medication with colchicine, the symptoms subsided. [Conclusion] I have experienced one case suggestive of familial Mediterranean fever complicated by tuberulous lymphadenitis.

P1-280

A Long-term Follow-up of Japanese Mother and Daughter with Blau Syndrome: Significance of Anti-cytokine Biologicals and Ultrasound Study of the Joints

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Conflict of interest: None

[Objectives] Blau syndrome (BS) is an autosomal dominant autoinflammatory disease associated with *NOD2* gene mutations. It is characterized by arthritis, skin rash and uveitis. We here report contrasting outcomes of a daughter and her mother with EOS/BS. The daughter developed exanthema at 8 months of age, arthritis and uveitis at 10 years. Although she was initially diagnosed with juvenile idiopathic arthritis (JIA), genetic investigation at 15 years revealed an E383G mutation in the *NOD2* gene. She was treated with infliximab, which was switched to adalimumab later. Since then, her clinical condition has been well-controlled. Her 48-year-old mother with joint deformity and blindness under the diagnosis of rheumatoid arthritis (RA) and Behcet's disease carried the identical gene mutation. Although she had been treated with prednisolone and methotrexate, their efficacy was not sufficient. Upon ultrasound studies of their joints, findings of tenosynovitis overwhelmed those of articular synovitis. [Conclusion] BS must be considered for differential diagnosis of JIA and RA. Ultrasound studies of the joints are of diagnostic value. Anti-cytokine biologicals may be beneficial for those patients.

P1-281

A case of familial Mediterranean fever associated with IgA vasculitis symptoms

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Conflict of interest: None

[Introduction] Familial Mediterranean fever (FMF) is a hereditary autoinflammatory disease characterized by periodic fever and serositis. It is caused by mutations in *MEFV* genes. This is a case of FMF associated with IgA vasculitis (IgAV) symptoms. [A case report] A 49-year-old man complained of fever and abdominal pain. At the age of 41 in 2004, we di-

agnosed his illness as IgAV because of leg purpura, knee arthritis, abdominal pain, skin leukocytoclastic vasculitis and IgA nephropathy. He was treated with steroid and immunosuppressive drugs. Nevertheless he had periodic attacks of fever and abdominal pain and serum inflammatory response. In September 2012, the attack cycle shortened and serum response got striking. We suspected FMF and analyzed *MEFV* genes of his and his parents after informed consent. His *MEFV* genes had paternal heterozygous mutation M694I in exon 10 and maternal heterozygous mutation E148Q in exon 2. Since the treatment with colchicine (1mg/day) was started, he has been free from symptoms. [Discussion] Recently, several cases of FMF associated with systemic vasculitis including IgAV have been reported in Southwest Asia. Similarly this case suggests *MEFV* mutations is not only genetic predispositions to FMF but also may contribute the pathogenesis of vasculitis.

P1-282

Familial Mediterranean fever in siblings: analysis of three families

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Conflict of interest: None

[Objectives] Familial Mediterranean fever (FMF) is an autosomal recessive disorder characterized by recurrent self-limited attacks of fever and serositis. We analysed clinical findings and MEFV mutations of three families with FMF. [Methods] Six patients with FMF from three different families were enrolled. Clinical characteristics and MEFV mutations were analysed. [Results] Two patients had typical clinical manifestation with FMF and four patients had atypical manifestation. Age at disease onset, duration of fever and accessory symptom indicated nonsimilarity within siblings. In genetic analysis of MEFV gene, all patients had polymorphisms of exon 2, 3 (P369S/R408Q, E148Q/L110P, R202Q, E148Q), but no paritents had mutation of exon 10. The polymorphisms were different in siblings. [Conclusion] It was described that MEFV mutations were the same in 55% families and age at disease onset, age at onset of therapy and presence of amyloidosis were similar within siblings with FMF in Turkey. In this study, sliblings with FMF had different phenotype and genotype.

P1-283

A case of Familial Mediterranean Fever (FMF) who required bilateral total hip arthroplasty and gave birth to a healthy male infant while continuing colchicine treatment during the course of pregnancy

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Conflict of interest: None

The case is a female patient who underwent bilateral THA when she was 20 years old due to severe coxalgia. Simultaneously she had repetitive attack of abdominal pain and fever of unknown etiology several times a year, therefore only symptomatic treatment could be done. No abnormal findings were found even on detailed examination and the patient was referred to our hospital at 24 years old. Contrast enhanced CT during her abdominal attack with elevation of WBC, CRP, neutrophil CD64 showed a sign of perihepatitis, but chlamydial infection was negative. M694I/E148Q/E148Q gene mutation was found in the MEFV gene; we diagnosed the patient as FMF and started 0.5mg/day of colchicine. After that, the frequency of abdominal attack and fever improved dramatically. To respond to the patient's expectation to bear children; we continued the use of colchicine which was suggested globally. After 5months of treatment she got pregnant and we continued the use of colchicine. During pregnancy there were 3 times of abdominal attack and fever, however she gave birth to a healthy 3354g male infant after 39 weeks and 2 days of gestation. We here report this case of FMF which is rare in terms of required THA due to complication of arthritis, and continued use of colchicine during pregnancy.

P1-284

Genetic polymorphisms of inflammasome factors in Japanese patients with Palindromic rheumatism

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Conflict of interest: None

【Objectives】Palindromic rheumatism (PR) is an autoinflammatory syndrome characterized by periodic acute arthritis. *MEFV* and *NLRP3* genes encode the proteins that constitute inflammasome, associated with inflammation signaling and are thought as genetic risk factors of PR. We here performed a genetic analysis in the Japanese patients with PR. 【Methods】The subjects were three Japanese patients with PR. Two of them are mother and daughter, 60 and 27 years old. We obtained genomic DNA and total RNA from peripheral blood, and performed sequence analysis of *MEFV* and *NLRP3*. We also analyzed pyrin (*MEFV* transcript) in lymphocytes by using Western blotting.【Results】We identified several SNPs including rs224204 and novel polymorphisms in *MEFV* genomic DNA and exon2 skipping in *MEFV* mRNA and protein. We also found rs3806265, rs3806268 and 2 novel polymorphisms in *NLRP3*.【Conclusion】Among the polymorphisms we identified, rs3743930 is reported in the Spanish patients with PR. Furthermore, rs224204 and rs3806265 are reported as related risk factors of Juvenile Rheumatoid arthritis. It is also reported the inflammasome inhibitory activity of pyrin decreases in the case with exon2 lacking. These indicate these polymorphisms are associated with the pathogenesis of Japanese patients with PR.

P1-285

Colchicine effective for CPPD crystal deposition disease with MEFV mutation

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Conflict of interest: None

[Objective] A patient who has calcium pyrophosphate dihydrate (CPPD) crystal deposition disease carries Mediterranean fever (MEFV) gene mutation and colchicine was effective. We discussed the effect of this therapy and the association between MEFV mutation and CPPD crystal deposition disease. [Description of the Case] A 89 y/o female suffered from episodes of left wrist joint pain in August 2012. Treatment with 15mg/day prednisolone (PSL) was effective; however the symptom relapsed when PSL therapy was stopped. In October 2013, she was referred to our hospital with right knee pain. Laboratory data revealed elevated levels of C-reactive protein (13.77 mg/dL). Her synovial fluid contained CPPD crystal. Genetic analysis disclosed MEFV mutation (E148Q/L110P), and treatment with 0.5mg/day colchicine therapy was started. Her symptom disappeared promptly and levels of C-reactive protein falled. However, the diagnostic criteria for FMF did not fulfilled. [Conclusion] CPPD crystal might trigger the activation of NLRP3 inflammasome, and pyrin encoded by MEFV mutation cannot regulate the activation of NLRP3 inflammasome. Colchicine suppressed the activation of NLRP3 inflammasome, so it was suggested that colchicine therapy might be effective for patients with CPPD crystal deposition disease.

P1-286

a patient with familial Mediterranean fever

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Conflict of interest: None

The patient was a 54 -year-old man. Pointing out proteinuria in physical examination since 2010. He had diarrhea and fever in January 2011, and diagnosed with AA amyloidosis by biopsy of the kidney and upper and lower gastrointestinal tract. He was also pointed out the renal damage (Cre2.8 mg / dL). Infliximab and colchicine are also administered, but the effect was insufficient, and progression of renal failure, diarrhea and fever were continued to start hemodialysis in September 2013. At the time, CRP and SAA were 7.0mg/dL, 587 μg / ml ewspectively. Symptoms improved in Tocilizumab administration, but not yet in dialysis withdrawal. The mutation on Exon2 E148Q and R202Q, Exon3 P369S, R408Q of MEFV gene were confirmed. These mutations were rare in Japan. And the mutation on exon10 M694I, pecific to FMF with amyloidosis in Japan, was neagtive. Missense mutations in the TNFRSF1A of TNFR1 gene is reaserched, because we suspected the possibility TNF receptor-associated periodic syndrome (TRAPS). But, the mutation was negative. The patient has amyloid risk factors (C-13T and SAA1 1.3) in the SAA1 gene analysis, resistant to colchicine, and his two daughter had two weeks or more period of fever. So we diagnosed the patient FMF variant.

P1-287

Expression of TLR2 and TLR6 of macrophages after stimulating by lipoteichoic acid

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Conflict of interest: None

[Objectives] Septic arthritis due to gram positive cocci is a very harmful against joint, and may occur in the patients with rheumatoid arthritis under immune-suppressive status. Macrophage could recognize Lipoteichoic acid (LTA) by TLR2/TLR6 heterodimer and produce some inflammatory cytokines and enhance the immune reactivity. This study was designed to clarify the expression of TLR2 and TLR6 in LTA-mediated response of macrophages. [Methods] Mouse primary macrophages derived from bone marrow (PMDM) were stimulated by soluble LTA (sLTA) (100 ng/ml). mRNA levels of TNF-α, IL-1β, TLR2 and TLR6 were quantified by quantitative real-time PCR and expression of TLR2 and TLR6 on cell surface were analyzed by flow cytometry. [Results] sLTA increased significantly mRNA levels of TNF-α, IL-1β and TLR2 ($p<0.05$). Otherwise, expression of TLR2 was decreased on PMDMs stimulated by sLTA compared to non-stimulated PMDMs. [Conclusion] It was indicated that pathogen-associated molecular patterns possible prolonged inflammation of septic arthritis. Additionally, discrepant of TLR2 between increased mRNA levels and decreased expression on cell surface seemed to reflect the possibility of self-protective systems in macrophage to escape from overshooting against the PAMPs.

P1-288

Rheumatoid arthritis complicated by synovitis due to propionibacterium acnes

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Conflict of interest: None

<Introduction> Propionibacterium Acnes (P.acnes) is known as a kind of bacterium causing acne. We experienced a case of rheumatoid arthritis (RA) complicated by synovitis due to P. acnes which was difficult to distinguish from SAPHO syndrome. <Case> A 69-year-old man was diagnosed RA 2 years ago. Anti-rheumatic drugs such as methotrexate and bucillamine and predonisolone (PSL) were started, arthralgia and elevation of C-reactive protein were gradually ameriolated. However, one year before, arthralgia focusing on right hip joint were deteriorated. Addition of gold sodium tiosulfate was effective for a limited time only. CT scans and MRI of pelvis showed well defined mass suspected as abscess near right hip joint. Stab cultures were performed, however, no bacteria were detected. Finally, Open biopsy of right hip joint was administered. Pathologically, hyperplasia of synovial membrane was seen. In tissue culture, P.acnes was detected as slow grower. At present, we administered PSL and tacrolimus to RA, amoxicillin to infection. <Discussion> In this patient, it's difficult to distinguish RA with P. acnes infection from SAPHO syndrome because he didn't have palmoplantar pustulosis and had hyperostosis of lumbar vertebrae. We report the unusual case with a review of the literature.

P1-289

A case of rheumatoid arthritis with Listeria monocytogenes sepsis combined with fungal endophthalmitis

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Conflict of interest: None

We report a case of a 71-year-old woman, who developed Listeria monocytogenesis sepsis and fungal endophthalmitis under therapy with 6mg/w of methotrexate and 3mg/d of prednisone. She had been complicated with rheumatoid arthritis for 21 years, and she was in remission. On September 2013, she felt dyspnea and visited our hospital by ambulance. She showed hypoxia and hypotension (60/34 mmHg). Laboratory findings were pancytopenia (WBC 900, neutrophil 513, Hb 7.8bg/dl, platelet $7.7X10^4$ /mm^3) and CRP 10.83 mg/dl. She immediately admitted in suspicious of septic shock. Septic Listeria monocytogenes was evident by blood culture. β-D-glucan was high (107 pg/ml). Fundus examination revealed white spots on macula. She was suspected with fungal endophthalmitis and administered with MCF for two weeks. However, her eyes showed deterioration, and antifungal therapy was switched to AMPH. Due to leukocytopenia, AMPH was switched to FLCZ, then her eye became good control and β-D-glucan decreased to 8.9 pg/ml. Antifungal therapy discontinued after total 4 weeks administration. Physicians should be aware of the possibility of Listeria monocytogenes sepsis and fungal endophthalmitis in immunocompromised host even without receiving biologics agents.

P1-290

Listeria infection in rheumatic diseases: two case reports and review of literature

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Conflict of interest: None

Listeriosis is known as fatal disease, and we think it is important disease for patients with rheumatic disease. We report 2 Listeria infection cases in our hospital with rewiew of literature. (case1) 62-year-old man with dermatomyositis and type 2 diabetes. He had a fever with chills 2days ago. He got a check-up at our hospital and was diagnosed a cold. But his symptoms didn't get well, and was admitted. CT scan didn't find

anything, but blood culture was positive and diagnosed Listeriosis. He was cured. (case2) 66-year-old woman with rheumatoid arthritis treated with 5mg PSL, 6mg MTX and IFX. She had a fever with chills a few days ago. She got numbness in a limb, and was losing her consciousness. She was admitted in our hospital. CSF analysis revaealed CNS infection, blood culture was positive, and she was diagnosed Listeriosis. She was dead.

P1-291

The investigation of the Listeria monocytogenes infection and rheumatic disease in our hospital

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Conflict of interest: None

[Objectives] The *Listeria monocytogenes* (LM) infection is observed in patients receiving the immunosuppressant such as TNF α inhibitor. We searched the tendency of the LM positive case and rheumatic disase in our hospital. [Methods] We searched the LM postive cases among the bacterial cultures in our hospital from April 2007 to September 2013. [Results] The LM positive is confirmed on 18 samples, 9 patients, during 88426 samples (2.6 samples of 12700, 0.02%, and 1.3 patients per a year). The 2 of 9 patients are malignant rheumatoid arthritis, which was identified LM by blood culture at the initial visit to hospital and the appropriate treatment was performed at early stage. The first case is 64-year-old male, treated with methotrexate, prednisolone (PSL) and infliximab. The patient visited ER due to diarrhea, abdominal pain and fever and treated with ABPC and GM. The second case is 64-year-old male with past history of lung tuberculosis and chronic bronchitis, treated with PSL and tacrolimus. He was hospitalized due to fever, cough and conscious disturbance and was treated with SBT/ABPC. [Conclusion] It is important to perform the blood culture of patient at risk of LM infection such as receiving immunosuppresant.

P1-292

purulent arthritis due to Nocargia infection in a patient with rheumatoid Arthritis and systematic lupus erythematosus

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Conflict of interest: None

A 44-year-old femail was diagnosed as rheumatoid arthritis (RA) in 1990 and as systematic lupus erythematosus (SLE) in 2001. She was treated with 13mg/day of prednisolone, 1mg/day of tacrolimus, 8mg/day of methotrexate, and 600mg/week mizoribin. In May 2013, her right knee joint was swollen with tenderness. we assessd exacerbation of RA because of negative bacterial culture of synovial fluids and inactive disease of SLE. We injected steroid into her knee joint and initiated abatacept. However, her right knee joint was worse and serum level of CRP was elevated from 3.96mg/dl to 21.19mg/dl. Repeated bacterial culture of synovial fluids showed *Nocardia elegans.* Meropenem and sulfamethoxazole/trimethoprim (ST mixture) were initiated, and arthroxesis was performed. Based on the result of drug sensitivity test, ST mixture was discontinued. She was treated with meropenem and clarithromycin for 6 weeks with favorable response.

P1-293

Adult-onset acute rheumatic fever; A case report

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Conflict of interest: None

[Case report] A 69-year-old man was hospitalized for acute rheumatic fever. He had not suffered from rheumatic fever. The incidence of rheumatic fever has decreased in most developed countries with improvements in sanitary conditions. The low incidence of this disease makes a accurate diagnosis difficult. Due to the fact that acute rheumatic fever can occur in the elderly and adults, this disease should not be overlooked when making a differential diagnosis.

P1-294

Predictors of in-hospital mortality for pneumocystis jirovecii pneumonia in immunosuppressed patients with connective tissue disease

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Conflict of interest: None

[Objectives] Pneumocystis jiroveci pneumonia (PCP) is a life-threatening disease in immunocompromised patients. The purpose of our study was to describe the outcome and prognostic factors of in-hospital mortality in PCP patients using biologics or immunosuppressive agents. [Methods] We evaluated retrospectively the clinical characteristics, management, and outcomes of PCP patients with connective tissue disease at our hospital from 2004 to 2013. PCP was diagnosed by polymerase chain reaction (PCR) for respiratory samples or elevation of serum βD-glucan with chest computed tomography (CT) findings. [Results] 30 patients (e.g., Rheumatoid arthritis (63%) and Microscopic polyangitis (13%)) were included in the study. 20 patients had concomitant with some underlying pulmonary diseases. In-hospital mortality rate was 23% (7 patients). Hospital mortality was associated with hypoxemia, hypoalbuminemia, high lactate dehydrogenase levels at day 1, progressive hypoxemia, and increase of lactate dehydrogenase levels at day 5 by the Kaplan-Meier method. [Conclusion] We conclude that predictive factors of in-hospital mortality in PCP patients with connective tissue disease were related with the patients' clinical severity at diagnosis and the response to PCP therapy.

P1-295

Tacrolimus-related cardiomyopathy in a patient with dermatomyositis

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Conflict of interest: None

We report the case of a 61-year-old female patient with dermatomyositis who developed tacrolimus (TAC)-related cardiomyopathy. The patient was diagnosed with dermatomyositis in 2008 and was treated with prednisolone (PSL). In 2010, she developed interstitial pneumonia; TAC therapy was therefore initiated. In December 2012, she was admitted to our hospital with exacerbation of interstitial pneumonia, which responded well to increased PSL and TAC doses. In March 2013, she began to notice exertional palpitations. ECG revealed ST-segment depression and T-segments in I, aVL, V2–V5. Furthermore, her serum tested positive for troponin T, and her plasma brain natriuretic peptide levels were increased to 364.6 pg/ml. Acute coronary syndrome was suspected and she was readmitted. Although cardiac catheterization revealed no abnormal findings, echocardiography findings were consistent with the diagnosis of hypertrophic cardiomyopathy. TAC-related cardiomyopathy was suspected; therefore, TAC was discontinued and cyclosporine was initiated. Her symptoms have gradually ameliorated since then, with a gradual improvement in ECG findings. To the best of our knowledge, this is the first case of TAC-related cardiomyopathy in a patient with dermatomyositis.

P1-296

Palisaded neutrophilic granulomatous dermatitis with intraorbital tumor in a patient with temporal arteritis

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Conflict of interest: None

A 71-year-old woman complained of papules on her trunk and limbs since July 2012. The papules improved with oral glucocorticoid (GC) therapy but flared again with the withdrawal of GC. She was admitted to another hospital in April and presented with headache and remittent fever. Laboratory tests showed an elevated acute phase reactants level and antinuclear antibodies, rheumatoid factor, PR3 - ANCA, and MPO - ANCA were all negative. Histopathological examination of the skin showed palisaded neutrophilic granulomatous dermatitis (PNGD). From early June, she complained of diplopia, and her left eye became blind which was diagnosed as left central retinal artery occlusion. She also suffered from right ischemic optic neuritis and was adimitted to our hospital. Color duplex ultrasonography showed a dark halo around the lumen of bilateral temporal arteries and superior mesenteric artery. MRI also showed a left intraorbital tumor. She was diagnosed as temporal arteritis (TA) complicated with PNGD and intraorbital tumor. Her symptoms including right visual acuity, skin lesion, and tumor were improved with high dose GC therapy. Since this is the first report of TA with PNGD, the significance of PNGD complicated with systemic autoimmune diseases will be discussed.

P1-297

A case of anti-CADM-140/MDA5 antibody-positive dermatomyositis complicated by refractory interstitial pneumonia for which plasma exchange was effective

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Conflict of interest: None

The patient was a 49-year-old female. The patient had visited a physician one month before. Fever, reduced Gottron's sign, heliotrope rash, CK elevation, and myogenic changes on electromyography were observed, and the patient was diagnosed with dermatomyositis. The chest CT showed complication by acute interstitial pneumonia. Steroid pulse therapy was performed for interstitial pneumonia, but it was ineffective, and the patient was transferred to our hospital. In addition to high-dose steroid, CPA and CsA were immediately initiated, but respiratory failure aggravated and mediastinal emphysema developed. In the same period, renal dysfunction, thrombocytopenia, and hemolytic anemia developed appeared. The patient was diagnosed with TMA, and plasma exchange was initiated. Disturbance of consciousness and convulsion occurred, and a high-intensity region was observed in the occipital white matter on head MRI, based on which PRES was diagnosed. CsA was discontinued because it was assumed to be the cause, and the consciousness and head MRI slowly improved. Plasma exchange was continued thereafter. Mycophenolate mofetil was concomitantly administered, and interstitial pneumonia and respiratory failure were improved. Later, the patient was confirmed to be anti-MDA5 antibody-positive.

P1-298

Two cases of rheumatoid arthritis with maintaining remission, low disease activity only having MTX five years after LCAP

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Conflict of interest: None

[Objectives] As recent RA treatment, early intervention by biological agents (Bio) is basic, but there are many cases having difficulty with the Bio introduction because of complications and long-term much medical expenses. We report 50s woman cases with LCAP first instead of Bio. [Case 1] Her RA became worse despite having MTX4mg/ week and LCAP was performed. Disease Activity Score (DAS) 28CRP was estimated before LCAP, a month, 6 months, and one and half year after was 4.78, 5.70, 2.54, 1.65, respectively. Simplified Disease Activity Index (SDAI) was also estimated 25.5, 34.0, 3.75, 0.58, respectively. Although 6 mg/week of MTX needs, her condition has kept remission for 4.5 years and maintained low disease activity. [Case 2] Her RA became worse despite having maintained with MTX6mg/ week. DAS28CRP was 5.84, 3.99, 3.69, 3.22, respectively. SDAI was 39.0, 19.5, 14.4, 10.2, respectively. Her disease activity has maintained low during approximately five years. [Conclusion] LCAP may induce low disease activity and remission. LCAP is much cheaper comparing with medical expenses of Bio, if LCAP can maintain low disease activity without Bio. LCAP is available to various cases unless severe anemia and thrombocytopenia. LCAP might be as one choice and contribute to medical economy.

P1-299

Development of a leukocytapheresis experiment system in the rat collagen-induced arthritis model and evaluation of therapeutic efficacy

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Conflict of interest: None

[Objectives] While rheumatoid arthritis (RA) treatment including biological drugs has been greatly advanced, many patients are treated inadequately due to underlying disorders such as lung disease and adverse reactions to RA medications. Recently the effectiveness of leukocytapheresis (LCAP), one of the extracorporeal plasmapheresis methods, for the treatment of RA has been reported. However, how the LCAP works for RA patients is mostly unknown. Since clarifying the mechanism of LCAP is crucial for further advancement of RA treatment, we attempted to develop an LCAP system using the rat collagen-induced arthritis (CIA) model and evaluated its therapeutic efficacy. [Methods] An LCAP column with 1/440 of the fiber surface area of the LCAP column for human use was developed for rats. Carotid venous blood was drawn at 0.2 mL/minute using a peristaltic pump, mixed with anticoagulant using a microsyringe, and returned to the caudal vein through the LCAP column for rats. [Results] The LCAP performed 3 times a week after the secondary immune response significantly improved the joint score, joint tissue findings, and T-cell proliferation potential compared with the control rats [Conclusion] The LCAP performed in the CIA rat model during the induction phase significantly improved arthritis.

P1-300

Analysis of clinical aspects of pneumatosis cystoides intestinalis (PCI) in connective tissue disease (CTD) patients

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Conflict of interest: None

[Purpose] To clarify the clinical difference of PCI in patients with or without CTD. [Methods] Analysis patients whose CT scan reports contained the word "pneumatosis cystoides intestinalis." [Subjects] 16 patients 33 reports were detected. Underlying disease ware malignancy 7 (43%), CTD 6 (38%), intestinal pneumonia 3 (19%). Mean Age was 73+/−13 years old. [Results] 1) Patients with CTD were systemic sclerosis 2, dermatomyositis 2, sjogren syndrome 1, rheumatoid arthritis 1. The mean age, disease duration, average prednisolone dosage were 67+/−13 years old, 9+/−13 years 13+/−6mg, respectively. 2) Surgical operations were done in 2 patients who without CTD. One was proved a perforation, the other was a PCI. 3) Patients with conservative therapy were nothing by mouth (NBM) 11, elemental diet1, no limitation on food 2. The average days while PI were disappeared were 18+/−38 days, no significant difference were detected compared with patients with and without NBM. 4) Recurrence was seen in one patient with CTD. [Conclusion] PCI were

found more frequently patients with CTD. The mean age was lower and disease duration was longer. We need to choose appropriate therapy for each patient considering their background.

P1-301

Treatment of arthritis of collagen vascular diseases other than rheumatoid arthritis (RA)

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Conflict of interest: None

[Objectives] The effect of biologics on the arthritis of rheumatoid arthritis is broadly accepted. However, arthritis can be seen in the collagen vascular diseases other than RA. Usually, small amount of steroid resolve arthritis. If the amount of steroid become large and if the administration term become long, the side effect such as osteoporosis could occur in the future. We have to establish the therapy in those cases. [Methods] We determined the effect of biologics on the arthritis in collagen vascular diseases. We carefully observed the effect on arthritis, and also side effect such as lupus-like symptoms. We administered etanercept, adalimumab or tocilizumab to two SLE patients, four MCTD patients, two SSc patients and one dermatomyositis patient. [Results] Biologics improved arthritis in every patient, and there is no serious events. We did not observe lupus-like symptoms, however, one SSc patient who was treated with etanercept, developed skin ulcer. We quit administration of etanercept in order to prevent further aggravation of skin ulcer. [Conclusion] Biologics are quite effective on the arthritis of collagen vascular diseases. In order to prevent unpredictable event, we have to be cautious the control of the collagen vascular diseases.

P1-302

A case of SAPHO (synovitis, acne, pustulosis, hyperostosis, osteitis) syndrome associated with bamboo spine

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Conflict of interest: None

[Case] A man, now in his seventies, had palmoplantar pustulosis (PPP) and subsequently pain in the back and sternoclavicular joint 50 years ago. Acne developed during his thirties. However, PPP and acne had subsided since his forties. He was diagnosed with ankylosing spondylitis (AS) by an orthopedician 10 years ago and NSAIDs were prescribed. Salazosulfapyridine was initiated a year ago but showed no benefit. Inflammation in his left sternoclavicular joint deteriorated a month ago. He also had fever and referred to our hospital. He was diagnosed with phlegmone and it ameliorated by an antibiotic. He became afebrile. Meanwhile, because a SAPHO syndrome was suspected by his history and typical sternocostoclavicular hyperostosis, he was examined by imaging studies simultaneously. In spite of bamboo spine, the trolley-track sign, which is usually seen in established AS, was absent. Furthermore, the bilateral sacroiliitis were not symmetric, which is atypical for established AS. Ultimately, he was re-diagnosed as SAPHO syndrome, instead of AS. **[Clinical significance]** Differentiating spondylitis of SAPHO syndrome from other spondyloarthritis such as AS could be difficult in cases without skin manifestations. Detailed interpretation of imaging studies is useful in such cases.

P1-303

The effects of febuxostat on gout and renal function in subjects with gout or hyperuricemia

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Conflict of interest: Yes

[Purpose] The effects of febuxostat on gout and renal function in subjects with gout were examined in this study. [Objects] 88 patients (47 ± 10 y.o.) taking febuxostat for 12 months were recruited in our clinic. The starting dose was 10 mg/day and the maintenance dose was adjusted to achieve a serum uric acid of less than 6.0 mg/dL. 79 patients were concomitantly medicated 0.5 mg/day colchicine in the prevention of gouty arthritis. [Results] The serum uric acid levels were 8.4±1.2 mg/dL before administration, and then significantly decreased to 5.8±1.1 mg/dL after 12 months medication ($p<0.0001$). 83% of patients were achieved a serum uric acid of less than 6.0 mg/dL. Gouty arthritis was observed in 16% of patients. The lowering of eGFR levels by aging was -0.90 ml/min/1.73m^2/year before treatment and it showed severe decrease of renal function with aging compared with -0.36 ml/min/1.73m^2/year in healthy volunteer. However, eGFR lowering rate were improved to -0.81 ml/min/1.73m^2/year after 12 months treatment. Moreover, eGFR levels in patients with less than 70 ml/min/1.73m^2 of eGFR before treatment were significantly improved from 58±8 to 62±9 ml/min/1.73m^2 ($p<0.005$). [Conclusion] Febuxostat remarkably decreased serum uric acid levels and improved renal function.

P1-304

A Case of SAPHO syndrome with intestinal ulcers following intravesical bacillus Calmette-Guérin (BCG) therapy for bladder cancer

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Conflict of interest: None

A 72-year-old male with a history of SAPHO syndrome was treated with intravesical instillation of bacillus Calmette-Guérin (BCG) for bladder cancer. After seven times of BCG therapy, polyarthritis, oral aphtha and erythema nodosum had developed, followed by colitis. There were no signs of genital ulcers nor ocular manifestations. Colonoscopy revealed multiple ulcers, diffusely distributed throughout ileocecal junction and the entire colon, which were not considered as a typical finding of Crohn's disease or ulcerative colitis. Tissue biopsy revealed a marked inflammatory cell infiltration, tissue granulation, and crypt abscess. Neither vasculitis nor infection (i.e, cytomegalovirus, ameba, mycobacterium) was evident in biopsy specimens. Pathogenic microorganism was not detected by tissue cultures, and T-SPOT was negative. His HLA-B haplotypes were B71, B60. Clinical course and manifestations of this case were unusual for Behcet's disease. All symptoms, including intestinal ulcers, were improved after initiation of methylprednisolone (60 mg daily). Although there were several reports describing reactive arthritis after intravesical BCG therapy, colitis is a rare manifestation. We discuss a possible influence of BCG therapy on colitis by reviewing the previous reports.

P1-305

Cooperative system among experts of rheumatic arthiritis in community medicine

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Conflict of interest: None

[Objectives] This hospital plays an important role on community medicine. In fact, patients of rheumatoid arthritis are mainly taken therapy by orthopedist. Then, the significance of existence in internal physical specialist was evaluated about in-hospital cooperation. [Methods] Since 2009, out of 127 outpatients of rheumatoid arthritis medicated by orthopedists using anti-rheumatic drugs, patients sent to internal medicine were researched in detail. [Results] About 20% patients were sent to in-

ternal medicine. The main reasons for consultation were therapy for infectious diseases, lifestyle-related diseases like diabetes and hypertension, malignant tumors and few others. After then, all patients were included in internal medicine, and were fully taken satisfied therapy. [Conclusion] At the same day, these patients were systematically taken medication by orthopedist and internal physician. Closer cooperation between these two clinical departments contributes to smooth and safety community medicine, highlighting and respecting each other.

P2-001

Patient's global assessment of disease activity of rheumatoid arthritis is influenced by seasonal change, as analyzed based on a nationwide Japanese cohort database (NinJa)

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Conflict of interest: None

[Objectives] Previous studies have suggested that environmental factors, such as weather, humidity and seasonal change, may affect RA. In the present study, we aimed to determine whether patient's global assessment (PtGA) is influenced by seasonal variation, using a NinJa databse. [Methods] RA patients, who were registered in NinJa, are evaluated at any point during the indicated year. We analyzed data from RA patients (n=8,733), whose PtGA, pain VAS and physician's global assessment data were available in NinJa 2011. Spring was defined as from March to May, summer as from June to November, Fall as from September to November and winter as from December to February. [Results] Univariable analysis using NinJa 2011 revealed that PtGA, pain VAS and DAS28 were lowest during fall with statistical significance, which was reproducible in NinJa 2012. On the other hand, multivariate analysis revealed that pain VAS, mHAQ and the swollen joints were the main determinants of PtGA, and seasonal variation was not identified as significant. [Conclusion] We have demonstrated that PtGA was lowest in fall. Seasonal changes can affect RA, although to a lesser degree than pain and activity of daily living, which should be taken into account when examining RA patients to better understand their symptoms.

P2-002

Patient satisfaction and communication regarding treatment goal between rheumatologists and patients

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Conflict of interest: None

【Objectives】To examine the influences of rheumatologist-patient communication on patient satisfaction.【Methods】We conducted a questionnaire survey to 110 rheumatologists and their patients with rheumatoid arthritis (RA) fulfilling the criteria of ACR.【Results】Total of 101 rheumatologists, mean age 49.7±8.9 years and 798 patients, mean age 59.4±11.9 years, returned the questionnaires. Of these, 41.6% rheumatologists answered that they explained about treatment goals to all patients, 51.5% did to the most patients, and 6.9% answered that they sometimes or mostly failed to explain. As for patients, 22.3% answered that they had discussed about treatment goals with their doctors, 42.5% had been just given explanations, 28.8 % had both, and 5.5% had neither. Rheumatologists who explained treatment goals to every patient were more likely to make their patients feel having discussed with doctors and to satisfy them than those who did not explain to all patients.【Conclusion】Rheumatologists' attitudes toward communication regarding treatment goals have significant influences on patient satisfaction.

P2-003

Profiles of elderly patients aged ≧ 75 years with rheumatoid arthritis in our department

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Conflict of interest: None

[Objectives] We investigated and reported the profiles of elderly patients with RA in our department because only few such reports exist. [Methods] Of 295 patients with RA (mean age, 63 years) in our department, we examined 63 patients (10 men and 52 women) aged ≧75 years (mean age, 80 years; range, 75-89 years). [Results] The mean disease period was 14 years (range, 4 months-64years). The Steinbrocker classification of the study patients was as follows: stage I, 21 patients; stage II, 13 patients; stage III, 16 patients; stage IV, 12 patients; class 1, 23 patients; class 2, 23 patients; class 3, 13 patients; class 4, 3 patients. MTX was administered in 19 patients (mean, 6mg/week; range, 4-10 mg/week), and PSL was administered in 44 patients (mean, 4mg/day; range, 1-10mg/day). The DMARD use was as follows: BUC in 16 patients, SASP in 15 patients, TAC in 3 patients, GST in 3 patients, MZR in 3 patients, and ACT in 1 patient. Biologics were administered in 7 patients (ETN in 4, TCZ in 2, and CZP in 1). According to DAS28CRP, remission was observed in 39 patients, low disease activity in 8 patients, and moderate disease activity in 13 patients. [Conclusion] Few cases had high disease activity and worsened function. Thus, RA was appropriately controlled in our department.

P2-004

Prevalence of CKD in RA patients treated with biological agents

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Conflict of interest: None

[Objectives] We examined the prevalence of CKD in RA patients treated biological agents. [Methods] 287 RA patients treated with biological agents were enrolled in this study. The prevalence of each CKD was examined and compared with that of other diseases including Psoriasis, Bechet's disease, and inflammatory bowel disease patients. [Results] The average age of 287 RA patients (47 male, 240 female) was 62.6±14.2 years and mean eGFR was 84.8±30.7ml/min/1.73m^2. The total number of the patients with CKD stage G3~5 were 45 (15.67%), including 22 (7.66%) in G3a, 13 (4.53%) in G3b, 7 (2.44%) in G4, and 3 (1.04%) in G5D. In contrast, there were only 2 CKD patients (stage G3a) in psoriasis patients, 2 CKD patients (stage G3b) in 21 Behcet's disease and 2 CKD (1 in stage G3a, 1 in stage G5D) in 62 patients with inflammatory bowel disease patients. [Conclusion] Our results showed relatively high prevalence of advanded CKD in RA patients using biological agents. We should evaluate the CKD stage and its risk factor when treating RA patients, especially those using biological agents.

P2-005

An era effects of renal pathology in patients with RA

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Conflict of interest: None

[Objectives] As for Rheumatoid Arthritis (RA) treatment method, the revolutionary change in recent years has been brought. Therefore, how the pattern of the renal histological damage changed in RA patients is verified. [Methods] 41 consecutive RA patients to which kidney biopsy was performed from 2001 to 2013 in our hospital were enrolled. We defined the period from 2001 to 2007 as the first term, and the period from 2008 to 2013 as latter term. The differences of the patient backgrounds

and the kidney pathology were examined in each term. [Results] Ratios of RA patients in all kidney biopsies were 18/515 cases at first term (3.5%), and 23/785 cases at latter term (2.9%). As for the ratio of membranous nephropathy (MN), a decrease was intentionally admitted 7/23 at latter term (30.4%) for 14/18 at first term (77.8%). The MN caused by the bucillamine were remarkably decreased. The Ratio of amyloidosis were 2/18 at first term (11.1%), and 5/23 at latter term (21.7%). [Conclusion] A decreased use of DMARDs such as the bucillamine and the gold that caused MN would have brought a decrease of the frequency of MN in patients with RA. It was expected that the Amyloidosis of the patient with long RA duration would become a problem as a cause of the renal damage in the future.

P2-006

Analysis of clinical features and clinical courses in RA patients with lymphadenopathy during methotrexate use

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Conflict of interest: None

[Objective] To investigate the clinical features in RA patients with lymphadenopathy during MTX use. [Methods] Among RA patients who self-reported lymphadenopathy in the IORRA study in October 2012, patients who developed lymphadenopathy during MTX treatment confirmed by their medical records were extracted. Patients were divided into 3 groups; malignant lymphoma (ML) group and benign lymphoadenopathy (BL) group defined by biopsy, and non-biopsy group in which lymphoadenopathy improved after discontinuation of MTX before biopsy. Clinical features of the ML group were assessed and clinical features were compared between ML group and BL+ non-biopsy group. [Results] Twenty-six patients were extracted. Among them, 10 patients (38%) were ML group, 11 patients (42%) were BL group and 5 patients (20%) were non-biopsy group. Their clinical features (ML/BL/non-biopsy group) were male; 36.8/42.1/21.1%, mean age; 64.6/56.7/63.3 years old, mean disease duration; 13.6 /11.6/11.8 years, concomitant mean MTX dose; 9.7/8.1/7.2 mg/week. Seven patients were treated with chemotherapy, whereas 2 patients improved after discontinuation of MTX. [Conclusion] Histological investigation is highly recommended for lymphadenopathy persisting after discontinuation of MTX.

P2-007

Treatmet option and risk factor for MTX associated Lymphoproliferative disorders

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Conflict of interest: None

Background. Lymphoproliferative disorders (LPD) occasionally develop in patients treated with MTX, and are known as MTX-associated LPD (MTX-LPD). We don't have criteria for MTX-LPD treatment. **Objective.** We investigate the clinical characteristics and risk factor of MTX-LPD case that was discontinued MTX in RA patients. **Methods.** We selected the patients who developed LPD during MTX treatment. Additionally, the selected MTX-LPD patients were divided into patients who were followed-up after the MTX withdrawal alone (MTX withdrawal group) and patients who were administered chemotherapy (chemotherapy group), and we weighed these two group. We selected patients who did not develop LPD under MTX treatment (MTX non-LPD group). **Results.** There were 33 patients in the MTX-LPD group. The MTX withdrawal group consisted of 12 patients and the chemotherapy group had 21 patients. Many cases in MTX withdrawal group had a single extranodal lesion and a "good risk" and over status according to the R-IPI classification. Additionally, The mean MTX dose was a risk factor for MTX-LPD. **Conclusions.** We suggest that the number of lesion and R-IPI classification would be supported the decision of MTX-LPD treatment. Additionally, MTX is a risk factor for LPD onset in RA patients.

P2-008

The prevalence of pulmonary artery hypertension in the outpatients with rheumatic diseases

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Conflict of interest: None

[Objectives] There have been few studies that have evaluated the prevalence of pulmonary artery hypertension (PAH) in the outpatients with connective tissue diseases (CTD). We performed screening of PAH using transthoracic echocardiography to characterize the CTD-PAH. **[Methods]** A total of 78 outpatients with CTD being followed up at our hospital were recruited consecutively. The study patients consisted of systemic lupus erythematosus (SLE, n=27), rheumatoid arthritis (RA, n=12), systemic sclerosis (SSc, n=15), mixed connective tissue disease (MCTD, n=10), polymyalgia rheumatica (PMR, n=6) and others (n=8). PAH was defined as an estimated systolic pulmonary arterial pressure (esPAP) >30 mmHg by doppler echocardiography. We also tested BNP titers, electrocardiogram and chest roentgenogram and classified WHO functional class. **[Results]** Sixteen out of 78 patients were diagnosed as having PAH by echocardiography. The prevalence of PAH in each CTD were as follows; 26.7% in SSc, 25.9% in SLE, 25.0% in RA, 16.7% in PMR and 10.0% in MCTD. Only 6 patients had esPAP>35mmHg and 3 patients (36mmHg, 35mmHg, 35mmHg) underwent right heart catheterization (RHC). No one had mean PA pressure>25mmHg measured by RHC. **[Conclusion]** Echocardiography may overestimate the degree of PAH compared with RHC.

P2-009

Development of a culture method for synovial explant of rheumatoid arthritis

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Conflict of interest: None

[Objective] The etiology of the chronic synovitis in rheumatoid arthritis (RA) is unclear. Studying animal models of RA or synovial cells from RA patients may not precisely reflect the pathology of RA synovitis. Synovial explant in Scid mice (SCID-HuRAg) is an alternative but is not convenient. Therefore, development of an experimental system recapitulating the synovial pathology is need. [Methods] An air-liquid interface (ALI) culture method was employed for culturing symovial explants. Submerged explant culture, single cell suspension culture of synovial cells, and the SCID-HuRAg system were used as the controls. Histological examination, flow cytometric analysis, and cytokine measurement were performed. [Results] The histological feature of RA synovitis was well maintained in the explants cultured by the ALI method, next to those of SCID-HuRAg. Loss of inflammatory cells was evident in the explants of the submerged culture. Flow cytometer analysis confirmed the survival of lymphocytes and macrophages in the ALI culture. IL-6 production was sustained in the ALI culture, which was decreased by an addition of anti-TNF-a antibody. [Conclusion] ALI culture of RA synovial explant might be useful for analyzing the pathogenesis of RA and for screening anti-rheumatic drugs.

P2-010

Analysis of the factors contributing to hyperplasia of intimal lining layer in three-dimensional organ culture of synovial fibroblasts

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Conflict of interest: None

【Objective】To examine the mechanism of hypertrophic intimal lining layer (ILL) of RA synovium.【Methods】We made three-dimensional micromass organ culture (3-D culture) under the stimulation with TNFα, PDGF, and/or TGFβ. Micromasses were stained with hematoxylin and eosin to assess the hyperplasia, and the expression of PI3K isoforms and activation of PI3K-Akt pathway were studied by RT-PCR, Western blot and ELISA. FLS transfected with siRNA were conducted with 3-D culture.【Results】Of the 3-D culture with the combination of TNFα, PDGF and TGFβ (TPT condition), the hyperplasia of ILL occurred distinctively and PI3KΔ mRNA was expressed higher than the others. In monolayer FLS, TPT condition similarly enhanced the expression of PI3KΔ, and persistent activation of PI3K-Akt pathway was detected. Knockdown of PI3KΔ significantly diminished ILL hypertrophy of FLS micromass in TPT condition.【Conclusion】These results suggest that inducible PI3KΔ regulate the formation of hypertrophic synovial lining via activation of Akt, and inhibition of PI3KΔ might be an alternative therapeutic approach to control proliferative synovium.

P2-011

Functional CDK6 expression controlled by SPACIA1 in RA synoviocyte proliferation

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Conflict of interest: None

[Objectives] SPACIA1 is a novel gene associated with abnormal synovial proliferation. We previously reported that *SPACIA1* siRNA inhibited the proliferation of RA synovial fibroblasts (RASFs) and delayed the cell cycle at G1 phase. We identified *CDK6*, one of cell cycle regulator genes at G1 phase, which is reduced by half with *SPACIA1* siRNA in RASFs. However, the mechanisms behind this process are still unclear. [Methods] To confirm whether CDK6 is functional in proliferation of RASFs, we examined the effect of *CDK6* siRNA on the proliferation induced by serum or TNF-α. RASFs were transfected with *CDK6* siRNA. The culture medium was changed to DMEM supplemented with 1% FBS, 10% FBS and/or 10 ng/ml TNF-α. Finally, 72 hours after transfection, we determined the relative values of viable RASFs, using the Cell Counting Kit-8. [Results] *CDK6* siRNA suppressed the proliferation of RASFs that were stimulated with 10% FBS. This effect was stronger than that of the control siRNA. Furthermore, the inhibitory effect of *CDK6* siRNA on the proliferation of RASFs were enhanced by TNF-α. [Conclusion] *CDK6* knockdown inhibited the proliferation of RASFs. CDK6 is functionally involved in proliferation of cultured RASFs, at least. We are planning to detect the CDK6 expression in normal and RA synovial tissue.

P2-012

The role of Synoviolin in weight control

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Conflict of interest: Yes

[Objectives] Obesity is associated with an increased risk of developing rheumatoid arthritis and is a risk factor for medical treatment resistance by anti-TNF alpha drugs. However, the mechanism is not understood. Synoviolin was identified from cDNA of rheumatoid synovial cells. We demonstrated that overexpression of Synoviolin in transgenic mice leads to advanced arthropathy and that heterozygous knockout mice were resistance to arthritis and fibrosis. In addition to quality control of ER proteins, Synoviolin entraps and degrades tumor suppressor p53 in the cytoplasm, thereby negatively regulates p53-dependent transcription, cell cycle arrest, and apoptosis. For further understanding of Synoviolin function *in vivo*, we used the strategy of gene disruption, and found that homozygous Synoviolin knockout mice died *in utero* around E13.5. However, the role of Synoviolin in adult mice is still unknown. [Methods] We generated conditional knockout mice of *Synoviolin* [Results] We discovered a novel role for Synoviolin in weight control system. [Conclusion] Our data suggested that Synoviolin may be a key factor which connects obesity and rheumatoid arthritis.

P2-013

The effect of an affibody on productions of inflammatory mediators

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Conflict of interest: None

[Objectives] An affibody is derived from one of domain of cell wall protein, Protein A of *Staphylococcus aureus* and it has molecular weight as 6 kDa. We developed affibody molecules with the ability to selectively bind to Ras, from a combinatorial library displayed on bacteriophage. The present study we investigated the effects of affibody molecules on synovial cell functions using human synovial fibroblast cell line. [Methods] Using phage display library, an affibody clone which can bind to Ras protein was screened from combinatorial library. Several clones were examined for inhibitory effect on production of inflammatory mediators and proliferation of a synovial cell. [Results] We have shown the inhibitory effect of affibody for proliferation and inflammatory mediator production such as IL-6 and PGE2 by synovial cells. In this presentation, we will discuss about the possibilities of affibody to regulate signal transduction for proliferation and inflammatory mediator production by synovial cells in rheumatoid arthritis. [Conclusion] An inhibitory effect of an affibody to a signal transduction cascade was suggested by results of above experiments on inflammatory mediator production and cell proliferation.

P2-014

Roles of Helios in cytokine production in human CD4$^+$ T cells

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Conflict of interest: None

[Objectives] It has recently been reported that the alteration of the frequency of Helios$^+$ cells in Tregs is associated with various human diseases. The aim of this study is to elucidate the regulation of Helios expression in CD4$^+$ T cells and its roles in CD4$^+$ T cell function. [Methods] We examined the effect of IL-6 and/or TGF-β on Helios expression and cytokine production of CD4$^+$ T cells from healthy donors by intracellular staining. We also examined Helios gene expression in CD4$^+$ T cells before and after Tocilizumab (TCZ) therapy by DNA microarray in RA patients who showed good clinical responses to Tocilizumab (TCZ). [Results] IL-6 inhibited the development of not only Helios$^+$ Foxp3$^+$ CD4$^+$ Tregs but also Helios$^+$ Foxp3$^-$ CD4$^+$ T cells. The production of IL-17A and IL-4 but not of IL-10 was significantly reduced in Helios$^+$ CD4$^+$ T cells as compared with that in Helios$^-$ CD4$^+$ T cells in the presence of TGF-β. TCZ therapy increased Helios gene signals in CD4$^+$ T cells in RA

patients who showed good clinical responses to the therapy. [Conclusion] Helios induced by TGF-β plays an important role in the down-regulation of cytokine production in $CD4^+$ T cells and may be involved in the pathogenesis of RA.

P2-015

Attenuation of murine autoimmune arthritis by treatment with mTOR inhibitor and IL-2 cytokine

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Conflict of interest: None

[Objectives] IL-2 cytokine/mIL-2 antibody (JES6-1) complexes (IL-2CAc) stimulate CD25 (IL-2 receptor α) on T cells and proliferate regulatory T cells (Treg) in mice. Everolimus (Eve. mTOR inhibitor) suppress mTOR complex1 and enhance Foxp3 expression in naïve T cells. There are no detailed analysis on the effect of Eve+IL2CA combination therapy on autoimmune arthritis. [Methods] We have examined the effect of Eve+IL2CAc combination therapy on murine autoimmune arthritis model, Collagen antibody induced arthritis model (CAIA, BALB/c), and SKG mice. [Results] The ratio of regulatory T cells (Treg) in CD4+ Tcells are markedly increased by Eve+IL2CAc combination therapy in both model mice. Furthermore, maximum arthritis severity are significantly suppressed by these treatment. [Conclusion] Combination of IL2 cytokine and mTOR inhibitors may become the effective therapy for human rheumatoid arthritis.

P2-016

Voltage-dependent anion channels (VDACs, porin) expressed in the plasma membrane regulate the differentiation and function of human osteoclasts The 2nd report: an analysis of time laplse

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Conflict of interest: Yes

[Objectives] We have recently demonstrated that voltage-dependent anion channels (VDACs, porin) are expressed in the plasma membrane of human osteoclasts. In the current study, we analyzed the effect of anti-VDAC antibodies on the differentiation and resorption activity of human osteoclasts. [Methods] Human osteoclasts were differentiated on standard plastic plates or plates with a thin layer of adherent human bone particles. The cultures were performed with anti-VDAC antibodies or control antibodies. At the end of the culture, the cells cultured on the standard plates were immunohistologically stained by anti-vitronectin receptor antibodies. The cells cultured on the plates with bone particles were removed, then the areas of the resorption pits were measured. [Results] Anti-VDAC antibodies inhibited both differentiation and bone resorption of human osteoclasts compared with control antibodies. [Conclusion] We demonstrated the inhibitory effect of anti-VDAC antibodies on differentiation and bone resorption of human osteoclasts using a time lapse method

P2-017

Efficacy of Protein kinase C-induced tolerogenic dendritic cells in vivo and comparison among various tolerogenic dendritic cells

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Conflict of interest: None

[Objectives] Tolerogenic dendritic cells (tDCs) are considered as a useful method to the therapy for autoimmune diseases. The following properties are necessary for clinical grade tDCs; 1) CCR7 expression; 2) stability under inflammatory condition; and 3) induction of Tregs. Previously, we presented characterization of protein kinase C inhibitor (PKCI)-induced tDCs. In this study, we show efficacy of PKCI-tDCs in vivo and comparison among various tDCs. [Methods] Mouse PKCI-tDCs were generated from mouse bone marrow cells using bisindolylmaleimide I (PKCI) and transferred into GVHD model mice. We compared migratory capacity, stability, and functional properties among human tDCs generated with IL-10, TGF-beta, Vit D3, Dexa, or Rapa. [Results] Mouse PKCI-tDCs had similar phenotypes and properties to human PKCI-tDCs. The administration of PKCI-tDCs protected the mice from lethal GVHD, and 80% of them survived for 50 days. In contrast, all iDCs-, and mDCs-treated mice died within 30 days. Furthermore, of the above human tDCs, PKCI-tDCs had most suitable clinical grade. [Conclusion] PKCI-tDCs are expected as a clinical grade tDCs.

P2-018

JAK inhibitor tofacitinib can suppress the disease activity of SLE via regulating IFN and CD28 signaling pathway in CD4+ T cells

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Conflict of interest: None

[Objectives] We reported that JAK/STAT pathway-mediated regulation of INF-related genes may have an important role in the disease activity of SLE through analyzing peripheral blood CD3+ T cells obtained from SLE patients. Therefore, the application possibility of JAK inhibitor tofacitinib (TOFA) was investigated for the new SLE therapy. [Methods] Monotherapy with low and high dose TOFA or dual therapy with TOFA and dexamethasone (DEXA) had been administered to MRL/lpr for ten weeks and BWF1 for seven weeks and we evaluated the disease condition. [Results] Anti-DNA antibody titers were decreased in TOFA administered groups. Both glomerular and interstitial nephritis were also ameliorated. Deposition of immunoglobulin and complements were diminished. Dual therapy with DEXA indicated stronger inhibitory effect comparing with monotherapy. Additionally, the expression of IFN and CD28 signaling pathway related genes were suppressed in CD4+ T cells. [Conclusion] We confirmed that both TOFA monotherapy and dual therapy with DEXA could suppress the disease activity of both SLE mouse with different genetic background. The functional mechanism was supposed that TOFA regulated IFN and CD28 signaling pathway in CD4+ T cells. TOFA showed the possibility to be applied for new SLE treatment.

P2-019

Pathological significance of Osteoclast differentiation in TIARP-deficient mice

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Conflict of interest: None

[Objectives] TIARP is a six-transmembrane protein induced by TNF-α and IL-6, and its deficient mice develop spontaneous arthritis. Previous studies suggested that TIARP was dominantly expressed on CD11b+ cells, and functions as a negative regulator in inflammation via suppressing STAT3 and NFκB activation. However, nothing is known about the role of TIARP in inflammatory bone erosion and osteoclast differentiation. **[Objective]** To elucidate the role of TIARP in osteoclast differentiation. **[Methods]** 1) mRNA was isolated from joints of TIARP deficient mice (TIARP-/-) and wild type mice (WT). NFATc1 and CTSK gene expression were assessed by realtime-PCR. Fixed paw joints were stained by toluidine blue and TRAP staining. 2) Bone marrow cells from TIARP-/- and WT mice were cultured with M-CSF and RANKL for 7 days, and osteoclasts were assessed by TRAP staining. **[Results]** 1) TIARP -/- showed higher NFATc1 and CTSK expression in joints than WT. Osteoclasts were increased and bone erosion was more severe in

TIARP-/- than WT. 2) The numbers of multi-nucleated TRAP-positive cells were higher from TIARP-/- bone marrow cells than from WT. **[Conclusion]** These findings suggest that TIARP suppress inflammatory bone erosion through the inhibiting osteoclast differentiation.

P2-020

The role of E3 ubiquitin ligase Synoviolin in bone destruction of rheumatoid arthritis

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Conflict of interest: None

[Objectives] The symptoms of rheumatoid arthritis (RA) are based on the many processes; chronic inflammation, outgrowth of synovial cells, bone destruction and fibrosis. We carried out immunoscreening using anti-rheumatoid synovial cell antibody, and cloned 'Synoviolin'. Synoviolin is endoplasmic reticulum (ER)-resident E3 ubiquitin ligases, and is involved in ER-associated degradation (ERAD). Synoviolin is highly expressed in synoviocytes of patients with RA. We postulate that the hyperactivation of the ERAD by synoviolin results in prevention of ER-stress-induced apoptosis leading to synovial hyperplasia. Furthermore, it was showed that Synoviolin is also involved in fibrosis. In this study, we investigated the role of synoviolin in bone and cartilage using Synoviolin conditional knockout (cKO) mice. [Methods] To understand the role of Synoviolin in bone destruction of RA, we generated tamoxifen -inducible cKO mice that carry homozygous floxed-*Synoviolin* alleles and CAG-CreER^{TM} transgene because of embryonic lethality of synoviolin knockout mice. [Results] Synoviolin cKO mice were completely died within 21 days after tamoxifen administration. Tamoxifen injected cKO mice showed a sever weight loss, although there was no difference in food intake between cKO mice and control mice.

P2-021

Deficiency of leptin signaling ameliorates SLE lesions in MRL/Mp-lpr mice

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Conflict of interest: None

[Objectives] Leptin is a 16kDa peptide hormone that is secreted mainly by adipocytes. Leptin decreases food intake, increases energy expenditure, and reduces body weight via leptin receptors within the ventromedial hypothalamus. Recent studies reveal that leptin may play a role in the regulation of the immune systems. To explore the role of leptin in the development of murine lupus, leptin deficient mice (C57BL/6J-ob/ob), were backcrossed onto the MRL/Mp-lpr mice. [Methods] Leptin deficient mice (C57BL/6J-ob/ob) were backcrossed onto the MRL/Mp-lpr mice and we produced MRL/Mp-lpr-ob/ob mice. The numbers of splenocytes were calculated and analyzed by flow cytometry. Anti-double stranded DNA antibody was analyzed by ELISA. [Results] Splenocytes were reduced in MRL/Mp-lpr-ob/ob mice. Anti-double stranded DNA antibody was suppressed in MRL/Mp-lpr-ob/ob mice. [Conclusion] Abnormality of MRL/Mp-lpr mice was suppressed by introducing leptin deficiency. The present results suggest that blockade of leptin signaling might be of therapeutic benefit in patients with SLE and other autoimmune disease.

P2-022

Endogenous Tim-1 promotes severe systemic autoimmunity and renal disease MRL-Fas^{lpr} mice

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Conflict of interest: None

[Objectives] The T-cell immunoglobulin mucin-1 (Tim-1), also known as kidney injury molecule-1 (kim-1) modulates CD4+ T-cell responses and is also expressed by damaged proximal tubules within the kidney. This study investigated the effects of an inhibitory anti-Tim-1 antibody (RMT1-10) in lupus-prone MRL-*Fas^{lpr}* mice. [Methods] MRL-*Fas^{lpr}* mice were treated with RMT1-10 or a control antibody intraperitoneally twice weekly from three mo of age for sixteen wks. [Results] RMT1-10 treatment significantly improved survival, limited the development of lymphadenopathy and skin lesions, preserved renal function and decreased proteinuria, reduced serum anti-DNA antibody levels and attenuated renal leukocyte accumulation. Th1 and Th17 cellular responses systemically and intrarenally were reduced, but regulatory T and B cells were increased. RMT1-10 treatment also reduced glomerular immunoglobulin and C3 deposition, suppressed cellular proliferation and apoptosis. Urinary excretion and renal expression of kim-1 was reduced, reflecting diminished interstitial injury. [Conclusion] As RMT1-10 attenuated established lupus nephritis, manipulating immune system T-cell immunoglobulin mucin 1 may represent a therapeutic strategy in autoimmune diseases affecting the kidney.

P2-023

IL-6 signal blockade ameliorates spontaneously occurring rheumatoid arthritis in an FcgRIIB-deficient mouse model through loss of the receptor activator of NF-kB ligand/osteoprotegerin balance

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Conflict of interest: None

[Objectives] To clarify the role of IL-6 in the pathogenesis of RA observed in our newly established RA-prone FcgRIIB-deficient B6 mice, designated KO1. [Methods] Forty-five of 4-month-old KO1 mice were divided into three groups. First group was none-treated, second was treated with control rat IgG and third was with anti-mIL-6R (MR16.1) during 6 months. The incidence and severity of RA and transcription levels of inflammatory cytokines/chemokines and RANKL/ OPG in ankle joints were compared among three groups of KO1 mice. [Results] Compared with two control groups, the development of RA was markedly suppressed in MR16.1-treated group associated with the lower serum anti-CCP antibody levels. In ankle joints, mRNA expression levels of MCP-1 and TNFa were significantly suppressed and RANKL/OPG ratio was markedly reduced in MR16.1-treated group. [Conclusion] IL-6 may contribute RA in KO1 mice through up-regulated production of anti-CCP antibodies, augmented inflammatory responses and the increased in RANKL/OPG ratio.

P2-024

Anti-IL-6 Receptor Antibody Normalizes Production of Wnt Inhibitors in a Mouse Model of Collagen-Induced Arthritis

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Conflict of interest: None

[Objectives] The Wnt pathway plays an important role in bone formation and regeneration. This pathway is regulated by several inhibitors such as DKK-1 and sclerostin. We examined how Wnt inhibitors were affected by blockade of IL-6 in CIA mice. [Methods] CIA mice were injected with either anti-mouse IL-6 receptor antibody (MR16-1) on Days 0 and 21 or TNFR-Fc 3 times per week from Day 0. Serum Wnt inhibitors (DKK-1 and sclerostin) on Day 35 (peak of swelling) were measured by ELISA. Bone volume (BV/TV) of hind limbs and lumbar spines on Day 56 was analysed by μCT. [Results] BV/TV of hind limbs and lumbar spines in CIA mice was decreased. MR16-1 and TNFR-Fc each sup-

pressed bone loss in hind limbs compared with untreated CIA mice. On the other hand, bone loss in lumbar spines was suppressed by only MR16-1. In CIA mice, DKK-1 was higher and sclerostin was lower than non-immunized mice. MR16-1 and TNFR-Fc each suppressed DKK-1 compared with untreated CIA mice. However sclerostin was increased by only MR16-1. [Conclusion] Although it is necessary to examine the function of DKK-1 and sclerostin in CIA, our findings suggested that anti-IL-6 receptor antibody would have a beneficial effect on both periarticular and systemic bone loss by normalizing the Wnt pathway in inflammatory arthritis.

P2-025

The behaviors of SOCS-1 and -3 in arthritis mice treated with anti-IL-6 receptor antibody

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Conflict of interest: None

[Objectives] It was reported that levels of suppressor of cytokine signaling (SOCS)-1 and -3, well-known feedback factors of inflammation, are high in RA. However, the effects of RA drug, anti-IL-6 receptor antibody (anti-IL-6R), on SOCS-1 and -3 is still unclear. We investigated the efficacy of anti-IL-6R on SOCS-1 and -3 levels, using a mouse model of arthritis. **[Methods]** Glucose-6-phosphate isomerase (GPI)-induced arthritis was triggered in mice by intradermal injection of recombinant GPI. Anti-mouse IL-6R (MR16-1) was intraperitoneally administered at a dose of 4 mg 5 days after immunization (Day 5). Arthritis scores were evaluated by observation. Expression levels of SOCS-1 and -3 in the hind limbs and blood on Days 14 were measured by real-time PCR and ELISA. **[Results]** The arthritis score reached peak swelling on Day 14 in arthritis mice. SOCS-1 and -3 levels in hind limbs and blood of arthritis mice were significantly higher than those of non-immunized mice. MR16-1 significantly suppressed the arthritis score and SOCS-3 levels in blood and hind limbs on Day 14. On the other hand, MR16-1 didn't suppress SOCS-1 in blood and hind limbs on Day 14. **[Conclusion]** We demonstrated that the anti-arthritic effect of MR16-1 was prominently involved in the behaviors of SOCS-1 and -3.

P2-026

B cell specific deficiency of FcγRIIB is required for autoantibody production, but not enough for early onset lupus nephritis in B6.*Yaa* mice

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Conflict of interest: None

[Objectives] B6 mice with *Yaa* mutation did not develop lupus nephritis; however, B6.*Yaa* mice defective in the inhibitory FcγRIIB (FcγRIIB$^{-/-}$.*Yaa*) do develop severe lupus. To unravel the underlying disease mechanisms, we aim to analyse the cell type specific contribution of FcγRIIB deficiency. [Methods] We generated B6.*Yaa* mice with either B cell or DC specific FcγRIIB deficiency by crossing B6.*Yaa* mice with CD19Cre or CD11cCre transgenic mice respectively and mice with floxed *Fcgγ2b* alleles (FcγRIIB$^{fl/fl}$) (collaborated with Dr. J.S.Verbeek; Leiden University). We compared the development of lupus between these mice and FcγRIIB$^{-/-}$.*Yaa* mice. [Results] CD11cCre. FcγRIIB$^{fl/fl}$.*Yaa* mice showed no evidence of lupus nephritis. Compared to FcγRIIB$^{-/-}$.*Yaa* mice, CD19Cre. FcγRIIB$^{fl/fl}$.*Yaa* mice showed the delayed onset and less severe lupus, irrespective of the comparable high serum autoantibody levels. Disease severity was associated with the increase in frequency of peripheral CD11b^{+}Gr^{-}CCR2^{-}monocytes. [Conclusion] In B6.*Yaa* mice, FcγRIIB-deficiency on B cells is sufficient for the production of high levels of autoantibodies but is not enough for early development of lupus nephritis. Severe lupus observed in FcγRIIB$^{-/-}$.*Yaa* mice requires FcγRIIB-deficiency on other cell types.

P2-027

Targeting therapy of citrullinated antigen-specific B cells attenuates collagen-induced arthritis

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Conflict of interest: None

[Objectives] B-cell depletion therapy in RA has problems such as relapse of tuberculosis and reactivation of hepatitis B. These problems were supposed to be resolved by focusing on depletion of pathogenic antigen-specific B cells using epitope tetramer conjugated with immunotoxin. [Methods] Arthritis was induced by immunizing DBA/1J with Bovine Type II collagen (CII). Toxin-conjugated peptide tetramers, which have the ability to deplete antigen-specific B cells, were intravenously administrated. Non-cytotoxic tetramer, anti-CD20 antibody, anti-CD79β antibody and PBS were also administrated for comparison. The incidence, arthritis score and titers of antibodies to peptides were evaluated. [Results] In mice administered citrullinated C1 epitope of CII (CIA1) tetramer, anti-CIA1 antibody completely disappeared as compared with PBS group and the onset of arthritis was delayed. Because the titers of antibodies to U1 epitope of CII were not significantly different from CIA1 and PBS group, it was shown that depleted B cells were antigen-specific. [Conclusion] The tetramer of the citrullinated peptide with cytotoxicity was effective to improve arthritis. Targeting of citrullinated antigen-specific B cells might be a new strategy of RA treatment.

P2-028

The significance of anti DNA antibody on rheumatoid arthritis with treatment of biologics

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Conflict of interest: None

[Objectives] Anti DNA antibody is sometimes detected from rheumatoid arthritis (RA) patients during anti-TNFα therapy and its positive case can lead to drug-induced lupus (DIL). We analyzed the association between clinical factors and the induction of anti DNA antibody. [Methods] 92 patients were collected in Sapporo medical university. Any biologic was started as an initial treatment and sustained at least for 12 months. Anti DNA antibodies were measured by RIA method during biologic therapy and the positive rates were analyzed in terms of biologics, sex, duration of therapy, methotrexate use, glucocorticoid use and with Sjögren's syndrome (SS) or not. [Results] 24% of patients were positive for anti DNA antibody. The positive rate showed 32% for IFX, 24% for ETN, 10% for ADA and 11% for TCZ. The rate was not significantly different between anti-TNFα treated patients and IL-6 inhibitor treated ones. But the rate tended to be less on ADA and TCZ. Anti DNA antibody was more detectable on females and SS associated patients. [Conclusion] Although the occurrence of DIL is rare, anti DNA antibody is positive for 25% of RA patients. The positivity of anti DNA antibody was suggested to be important to select the appropriate biologic.

P2-029

Measurement of CD64 on neutrophils in patients with systemic vasculitis

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Conflict of interest: None

[Objectives] To examine the relationship of disease activity and expression level of CD64 on neutrophils in patients with systemic vasculitis. [Methods] We measured neutrophil CD64 expression in patients with systemic vasculitis in the active and inactive phase of vasculitis disease quantitatively by flow cytometry. Cut-off point for CD64 positivity was 2000 molecules/cell as defined in our previous study. [Results] We compared neutrophil CD64 expression in 4 large vessel vasuculitis (Takayasu arteritis; 2, Giant cell arteritis; 2), 3 medium vessel vasculitis (Polyarteritis nodosa; 3), and 14 small vessel vasculitis (Malignant rheumatoid arthritis; 6, Cryoglobulinemic vasculitis; 1, Microscopic polyarteritis; 4, Wegener's Granulomatosis; 3). The statistical examination was difficult in large and medium vessel vasculitis because of small numbers of samples in this study. The expression level of neutrophils CD64 from patients with small vessel vasculitis in active phase was 3573±687 molecules/cell (mean ± SEM), which was significantly higher than the expression level in inactive phase of disease (1281±198 molecules/cell). [Conclusion] The expression of CD64 on neutrophils tended to reflect disease activity in patients with small vessel systemic vasculitis. Further studies are needed.

P2-030

Factors that influence the serum MMP-3 concentrations (Multivariate analysis of 527 rheumatoid arthritis patients) - Prednisolone 5mg doubles MMP-3

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Conflict of interest: None

[Objectives] Serum MMP-3 concentration is very useful tool in the diagnosis and the evaluations of treatments and prognosis of rheumatoid arthritis patients. However, its evaluation is difficult because it is influenced by renal function, dose of corticosteroids and etc. Therefor we tried to reveal the extent of the influence of those factors on it. [Method] Data of 527 RA patients were gathered in two medical centers. The data included serum MMP-3 concentration, sex, age, disease duration, eGFR (calculated by serum Cr), CRP, and dose of prednisolone (PSL). The data were analyzed by using multivariate analysis. [Results] The rate of female was 77.1%. The averages were age-62.1 years (SD 13.2), disease duration-9.75 years (median 7), eGFR-62.1 ml/min./1.73m^2 (SD 13.2), CRP-0.73mg/dl, and the dose of PSL -2.11mg/day. We determined the multiple regression formula with serum MMP-3 as a response variable, and those factors as explanatory variables. The formula was log (MMP-3)=-0.191*[female]+0.00928*[age] +0.143*[log (CRP)] +0.146*[dose of PSL]+0.0026*[A center]. (R^2=0.460, any regression coefficients were significantly not zero. [Conclusion] Serum MMP-3 concentration is influenced by sex, age (eGFR), CRP, and dose of PSL. The increase of PSL by 5mg increases it to about double.

P2-031

Comparison of QFT-3G and T-SPOT.TB for the screening of latent tuberculosis infection in Japanese rheumatoid arthritis patients

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Conflict of interest: None

To evaluate the clinical utility of QFT-3G test and T-SPOT.TB for the screening of the risk of latent tuberculosis (TB) infection in Japanese rheumatoid arthritis patients, we compared between the TB past infection group (n=32) and non-TB infection group (n=33) according from chest CT findings or previous history with stimultaneous measuring of these IGRAs tests and peripheral blood CD4 positive cell count. The positive QFT at cut off 0.35 and 0.1 IU/ml (intermediate range) of the past TB infection group was 22% and 9%, respectively. The sensitivity and specificity of QFT-3G was 31.3% and 93.9%, respectively. The positive T-SPOT. TB of the past TB infection group was 15.6% (SFC≧8), 6.3% (SFC 6,7) and 3.1% (SFC 5). The sensitivity and specificity of T-SPOT.TB at the cut off range more than 6 SFC was 21.9% and 100%, respectively. Of 65 RA patients, the decreased CD4 positive cells (<500/μl) was seen in 34 (52%), however the PHA mitogen response of either QFT-3G or T-SPOT. TB was not decreased. Only 1 patient of QFT-3G result was determined an indeterminate result. The agreement of these tests was high incidence, but we considered the negative results could not be ruled out the negative past infection of TB due to the low positive rate of the QFT-3G and T-SPOT.TB test.

P2-032

Specific Biomarkers in the Synovial Fluid May Help to Diagnose as Rheumatoid Arthritis

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Conflict of interest: None

[Objectives] The biomarker for the diagnosis of rheumatoid arthritis is well-known from the serum. However, there is a little evidence from the sample of synovial fluid in the diagnosis of rheumatoid arthritis. The purpose of this study is to investigate the efficacy of synovial fluid to diagnose the rheumatoid arthritis. [Methods] One hundred and ninety five patients were examined their synovial fluid from the inflamed knee. There were 46 rheumatoid arthritis patients (Ave. age was 64.3, radiological classification was stage I: 16, stage II: 22, stage III: 6, and stage IV: 2) and 149 osteoarthris of the knee (Ave. age was 66.7, radiological classification was grade II: 86, grade III: 55, and grade IV: 8) patients. The aspirates was immediately frozen under -20 C and examined for the several biomarkers (IL-1α, IL-β, IL-RA, IL-6, MMP-3, TNF-α, and hyaluronic acid). [Results] We developed the IL index which means the value that multiply the number of IL-6 and TNF-α. In the number of IL index, there were 4 out of 149 which more than 8000 in the osteoarthritis knee, on the other hand, there were 45 out of 46 which more than 8000 in the rheumatoid knee. [Conclusion] The IL-index possibly be a diagnostic tool for the rheumatoid arthritis.

P2-033

Clinical Investigation of Autonomic Nervous System Dysfunction in Systemic Sclerosis

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Conflict of interest: None

[Objectives] In systemic sclerosis (SSc) patients, autonomic nervous system dysfunction is a very important pathology of developing multiple organ failure such as cardiovascular events and gastrointestinal dysmotilities. We investigated autonomic nervous system dysfunction (ANSD) in patients with SSc [Methods] Twenty SSc patients (two males, eighteen females, aged 58.7±14.5 years old) were enrolled in this study. Their mean disease duration is 7.25±5.54 years old. Patients classified into diffuse type and limited type, 14 patients and 6 patients respectively. We analyzed the autonomic nerve system by coefficient of variation of RR interval (CVR-R), deep breathing test (DBT) and standing 30:15 ratio (RR30/RR15) using 12 lead electrocardiographic examination, and evaluate these with clinical features and serological parameters [Results] Five patients (25%) of 20 patients presented with decreased all parameter of ANSD. The ANSD group had higher the RA-RV pressure gradient using

ultracardiography. diffuse type patients SSc associated with ILD revealed low RR30/RR15. These were no significant differences in both specific autoantibodies and modified rodnan total skin score. [Conclusion] Our data indicated diffuse type SSc patients associated with ILD or PAH should be investigated ANSD.

P2-034

Investigation of the association between physical and ultrasound (US) examination in rheumatoid arthritis (RA)

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Conflict of interest: None

[Objectives] To investigate the association the US asessment in the wrist and finger joint of the RA with each tender joint and swollen joint presence. [Methods] A total of 70 RA patients (15 men, woman 55, average age 67 years old) who examined by US in October, 2011 for six months. Arthritis in US was classified by PD grade1 more or GS grade2 or more, and classified into 4 groups; observed both tender and swollen (TS), tender/no swollen (T), no tender/swollen (S), no tender/no swollen (N) by physical examination, and analyzed association with US each. [Results] Arthritis observed by US in TS 81% (18/57), T 36% (18/50), S 71% (58/82), N 7% (97/1350), was associated with swollen than tender ($p = 0.0001$). In TS group, US finding was observed in 95% (21/22) in the wrist, 84% (16/19) in the MCP, 59% (7/17) in the IP / PIP, and was less in the IP / PIP many wrists in ($p<0.05$, $p<0.01$). In N group, US finding was observed 28% (23/81) in the wrist, 9% (56/624) in the MCP, 3% (18/645) in IP / PIP, significant in the wrist ($p<0.01$). [Conclusion] Based on the ultrasound findings, physical examination of IP / PIP joint tends to be false positives of arthritis, and wrist tends to be false-negative. US-related findings and examination findings vary depending on joint site.

P2-035

Effect of aging in blood serum test for rheumatoid arthritis patients

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Conflict of interest: None

[Objectives] Aging of rheumatoid arthritis (RA) patient becomes major problem in society with aging. RA has been recognized as middle age disease, however, aged patients increases in decades. This affects large influence on RA treatment strategy. We have investigated the influence of aging in blood tests in order to understand aging in RA patient. [Methods] We have measured serum hemoglobin, leukocyte, neutrophil, lymphocyte, AST, ALT, ALP, LDH, BUN, Uric acid, creatinine, LDL and HDL cholesterol, triglyceride, sodium (Na), chlorine (Cl), potassium (K), calcium (Ca), rheumatoid factor, anti-CCP antibody (ACPA), anti-nucleic antibody (ANA), P1NP, TRACP-5b, KL-6, and CRP from 6824 specimens of 413 RA patients. Correlation with aging is analyzed with linear regression analysis for each. [Results] Item that demonstrated no correlation with aging was AST, ACPA, P1NP, and KL-6. The other have demonstrated significant linear regression with aging ($p<0.01$). [Conclusion] RA patient reduces blood cell counts, Na, Cl, Ca, lipid concentration, ANA, and renal function, while increases K and bone resorption with aging. These phenomena make increase of sensitivity for drug, and suggested necessity of drug intervention for osteoporosis. We need concise control on RA treatment for aged patients.

P2-036

Examination of Talbot-lau X-ray system used early rheumatoid arthritis

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Conflict of interest: None

[Objectives] Biologics is change rheumatoid arthritis treatment. Especially structural joint damage of rheumatoid arthritis patient made disability. Nearly early rheumatoid arthritis a diagnosis and effective treatment can protect joint damage. It possible Talbot-Lau X-ray system find early rheumatoid arthritis. [Methods] Talbot-Lau X-ray system used hand X-ray. Steinbrocker stage 1 or2 patient 21 cases (Female 15, male 6) analyze. [Results] Rheumatoid arthritis stage 1 case thickness of cartilage is 704μm. Normal case is 786μm. Some of case cartilage line irregular may aggressive joint damage. [Conclusion] So far Tarbot-Lau X-ray system unknown a diagnosis but early rheumatoid arthritis is possible effective X-ray finding.

P2-037

Don't rely on CRP too much. The fact that patient in BOOLEAN remission progressed bone erosion taught us

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Conflict of interest: None

[Objectives] Diagnosis of very early RA (VERA) is difficult when CRP is negative, especially when the patient is also seronegative. This report investigate CRP in first visit RA patients who have not treated yet. Also present a BOOLEAN remission case who have progressive bone erosion. [Methods] 146 RA patients who have visited my Clinic Since May 2011 to May 2013. 24 who have not treated ever before are investigated. [Results] 17/24 (70.9%) are CRP positive. 7/24 (29.1%) are CRP negative. ESR, MMP-3 are CRPpositive group 16-139 (average 65.9), 28.2-3142 (ave. 40.2.2), CRP negative group 3-28 (ave. 17.4), 26.5-73.8 (ave. 52.6) respectively. Although, RF positive rate, ACPA positive rate are CRP positive group 70.6%, 76.4%, CRPnegative group 71.4%, 85.7%respectively. A case of BOOLEAN remission who had progressive bone erosion is CRP negative, only Left 3MTP had tenderness. But Ultrasound (US) revealed active sinovitis. [Conclusion] in VERA and Near Remission, If US remission is not achieved, there is a possibility that Joint damage progress even when CRP is negative. US is necessary in diagnosis of VERA and true remission.

P2-038

Quantitative measurement of the synovial vascularity by indocyanine green- fluorescent video vasculography in rheumatoid arthritis

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Conflict of interest: None

[Objective] Strong relation exists between abnormal synovial vascularity (SV) and joint inflammation in rheumatoid arthritis (RA). Power Doppler sonography (PDS) is useful modality to detect and assess SV, however it requires complicated scanning technique that affects output. Indocyanine green (ICG) is fluorescent agent which is commonly used in ocular fundus examination. Simple video camera system can visualize fluorescent image of microscopic vascular flow. We studied quantitative measurement of abnormal SV by using the ICG-fluorescent video vasculography. [Methods] Finger joints of patients with RA were assessed by both ICG-fluorescent video vasculography and PDS. Quantitative SV and maximum value of fluorescent intensity (FI-max) were obtained. [Results] FI-max of joints with positive SV were significantly higher than those of joints with negative SV. There was relation between quantitative SV and FI-max. [Conclusions] ICG-fluorescent video vasculography could assess abnormal SV and joint inflammation in RA.

P2-039

Relation between synovial vascularity and joint destruction in patients with rheumatoid arthritis in long-term clinical low disease activity

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Conflict of interest: None

[Objective] To study change in synovial vascularity and joint destruction in rheumatoid arthritis (RA) with long-term clinical low disease activity. [Methods] Fifteen patients with RA were analyzed (DAS28-ESR<3.2 for 2 years). Synovial vascularity (SV) of finger joints (MCP and PIP) was assessed by power Doppler sonography at baseline, 8th, 20th and 52nd weeks. Joint destruction was assessed according to Genant-modified Sharp score at baseline and 52nd weeks. [Results] Structural alteration of joints with positive SV significantly increased than joints with negative SV in the observational period. Joint space narrowing (JSN) showed relation with this structural alteration. [Discussion] In RA patients with long-term clinical low disease activity, joints with positive SV may have risk of joint destruction, especially risk of JSN, resulting adverse affect on joint function.

P2-040

The utility of assessment by ultrasound in rheumatoid arthritis patients treated with biologic DMARDs

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Conflict of interest: None

[Objectives] We evaluated utility of assessment by ultrasound (US) in rheumatoid arthritis (RA) patients treated with biologic DMARDs. [Methods] Twenty-nine patients (mean of age: 58 years-old, that of disease durations: 58 months, that of DAS28: 5.34) were included. We evaluated the associations between US findings and clinical course during 6 months. The twenty-two joints (bilateral MCP, PIP joints, wrist) were assessed by US at baseline and 3 months. Each joint was scored for gray scale and power doppler on scale from 0 to 3. Therapeutic responsiveness was evaluated by SRM (standardized response mean). [Results] US synovitis scores (SRM -0.68--0.71) were less responsive than clinical composite measure (SRM -1.1--1.3). US synovitis scores were more responsive in early patients (SRM-1.1) than long-standing patients (SRM -0.64), and in order of MCP, PIP and wrist in the individual joint level. Improvement of US synovitis scores during 3 months was associated with therapeutic responsiveness by EULAR response criteria. [Conclusion] The responsiveness of US synovitis scores were dependent on disease durations or difference of joint sites. Although early improvement of clinical disease activity was achieved by biologic DMARDs, it may take time to improve actual synovitis activity.

P2-041

The usefulness of the database for ultrasonography in rheumatoid arthritis

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Conflict of interest: None

[Objectives] To evaluate the usefulness of Filemaker database (FMDB) for ultrasonography (US) in rheumatoid arthritis. [Methods] We share preexisting medical system as a data source with FMDB using the patient identification (ID) as a relation key in our hospital. Input method and output format reflect the opinion of medical doctors and co-medical staffs, and we have minimized the necessary keyboard operation. We compared the time required to make reports before and after the introduction of FMDB, and summarized the opinions of operators. [Results] We have about 1,600 cases per year of fingers and hands US, and old reports were handwritten paper reports. Ultrasonography operators had to find case history from a mass of data, and calculate the quantitative and the semi-quantitative data by themselves. The complicated preparation had took an average of 87 seconds, but after the introduction of FMDB, they only need to input the patient ID in a few seconds, and all calculation was automated. [Conclusion] The advantage of user-made FMDB is that we could make flexible DB reflect the opinion of medical doctors and co-medical staffs who are familiar with the actual medical situation, and FMDB could reduce our burden. The meaningful introduction of FMDB simplified the statistical reuse.

P2-042

Diagnostic role of joint, enthesis ultrasound in the diagnosis of early arthritis with negative serology (RF, ACPA)

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Conflict of interest: None

[Objectives] Patients of early arthritis with negative serology (RF, ACPA) often do not meet ACR/EULAR2010 criteria for rheumatoid arthritis (RA), and remain undiagnosed. For these cases, spondyloarthropathy (SpA), which is underrecognized in Japan, should be suspected. SpA International Society recently proposed a criteria (ASAS2011) to capture broader patients of only peripheral manifestation. This study is to assess both clinical course of these cases, and validity of ultrasonography (US) for diagnosis. [Methods] 10 patients of undifferentiated early arthritis were followed up prospectively (mean 2 years). [Results] 2patients had bilateral knee arthrits initially. One of them has developed polyarthitis including finger joints 1 year later, and been diagnosed as RA. The other remained undiagnosed. 6 patients, whose arthritis were not persistent, had past or present enthesitis. US examination provided 1) confirmation of inflammation at symptomatic enthesis; 2) detection of inflammation at asymptomatic joint, enthesis; 3) recognition of dactylitis, which was overlooked by clinical examination. They were classified as peripheral SpA by pivotal information from US. [Conclusion] Clinical follow-up with US examination may provide detection of early SpA, as well as early diagnosis for RA.

P2-043

Ultrasonographic assessment is associated with disease activity in patients rheumatoid arthritis

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Conflict of interest: None

Objective To examine associations between ultrasonography (US) assessments of a large number of joints or separated joint and traditional clinical and laboratory assessments of disease activity in patients with rheumatoid arthritis (RA). **Methoids** Thirty-two RA patients who participated in KABUKI study were examined by US (Gray scale (GS) and power Doppler (PD)) with use of a semi-quantitative (0 to 3) score of 28 joints, 46 points at baseline and 0, 12, 24 and 48 weeks after initiating treatment with adalimumab. GS and PD scores for the different joint combinations or separations were generated. **RESULTS:** Large joints US assessment such as knee and elbow highly correlated with laboratory variables (CRP and MMP-3) (MMP-3; Knee GS: r=0.530, PD: r=0.361, p<0.001, elbow GS: r=0.416, PD: r=0.422, p<0.001). The MP and PIP joints US scores were highly associated with clinical assessments (DAS28 GS: r=0.341, PD: r=0.311, p<0.01). The US score of both a

large number of joints and separated joint were highly correlated with Doctor`s VAS. Both GS and PD had similar magnitude to composite indexes. **CONCLUSION:** Large joints GS score correlate well with the inflammation marker, and small joints GS score is associated with disease activity score.

P2-044

The evaluation methods of the disease activity of rheumatoid arthritis by ultrasound examination

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Conflict of interest: None

[Objective] To analyze the evaluation methods of the disease activity (DA) of the patients with RA using US examination. [Methods] We analyzed retrospectively 18 patients with RA who had received US before the administration of biologics (BIO) and 6 months after that. Twenty-two joints including bilateral 1-5 PIP joints, 1-5 MP joints and wrists were examined by US. DA was measured by DAS28-CRP, the total GS score (the total GS), the total GS of the GS positive joints detected by the first US (the LMT total GS), the total PD score (the total PD), the total PD of the PD positive joints by the first US (the LMT total PD) and the mean of the PD score of the PD positive joints by the first US (the LMT mean PD). The values before and after BIO were compared by the paired t-test. [Results] DAS28-CRP decreased after BIO significantly (4.0 ± 1.0, 2.7 ± 0.8) ($p < 0.01$). The total GS, the LMT total GS and the total PD decreased; however, not significantly (24.5 ± 15.5, 24.4 ± 16.6; 24.5 ± 15.5, 18.2 ± 12.8; 11.2 ± 9.2, 7.2 ± 5.4; respectively). The LMT total PD and the LMT mean PD decreased significantly (11.2 ± 9.2, 4.8 ± 4.7; 1.83 ± 0.41, 0.95 ± 0.68; respectively) ($p < 0.01$). [Conclusion] The LMT total PD and the LMT mean PD were useful for the assessment of the DA of RA.

P2-045

Musculoskeletal ultrasonography is useful in the differential diagnosis of rheumatic disease

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Conflict of interest: None

[Objectives] We investigated whether musculoskeletal ultrasonography (MSKUS) is useful in the differential diagnosis of rheumatic disease. [Methods] 193 early arthritis patients were enrolled. We evaluated synovitis and tenosynovitis of bilateral wrist and finger joints from 22 sites and another affected joints in MSKUS. [Results] The final diagnoses of the patients were RA (n=90), UA (n=25), fibromyalgia (n=11), PMR (n=8), cristal induced arthritis (n=6), OA (n=6), palindromic rheumatism (n=5), Sjogren syndrome (n=4), vasculitis syndrome (n=3), SLE (n=3), SSc (n=3), IBD related arthritis (n=2), and reactive arthritis (n=2). The number of the patients with synovitis or tenosynovitis at any joint in MSKUS (PD positive) were 115, and all patients with RA had PD signal. In the PD positive patients, total GS/PD scores, max GS/PD scores and affected tenosynovitis rate were significantly higher in RA (n=90) than in non-RA (n=60). The frequency of the patients with PD grade≧2 was prominent in RA (79%) than in non-RA (30%). [Conclusion] MSKUS, especially with the findings of synovial proliferation and strong signal (PD grade≧2) is useful in the diagnosis of RA. Clinical diagnosis by exclusion as well as the findings of MSKUS is important to the correct diagnosis of rheumatic disease.

P2-046

Significance of viral DNA and *HLA-DRB1* polymorphisms in rheumatoid synovial tissues

Ryo Takamatsu[1,2], Tomoko Hasunuma[2], Natsuko Kusunoki[2], Kotaro Shikano[2], Ayako Kubota[1], Yoshiyasu Miyazaki[1], Takashi Nakamura[1], Hiroshi Takahashi[1], Shinichi Kawai[2]
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Conflict of interest: None

[Objectives] Microorganisms have been reported as candidates in pathogenesis of rheumatoid arthritis (RA), however, most of studies were conducted by serum analysis. We tried to detect viral DNA in synovial tissue from patients with RA and osteoarthritis (OA) as controls. *Epstein-Barr nuclear antigen 1* (*EBNA-1*) of Epstein-Barr virus (EBV) gene and the structural protein gene *VP1* of human parvovirus B19 (B19) gene were investigated. We also determined the allele of disease susceptibility gene, *HLA-DRB1* in RA patients. [Methods] Synovial tissues (RA 155 cases, OA 157 cases) that were collected at total knee replacement surgery. Genome DNA was extracted from synovial tissue. Target genes were amplified by nested polymerase chain reaction, then the extracted PCR products in the target bands were analyzed by a direct sequencing method. [Results] The incidences of *EBNA-1* and *VP1* (77% and 100%, respectively) in RA synovial tissue were almost the same as those (71% and 100%, respectively) in OA synovial tissue. Gene sequence analysis revealed that there is no difference in mutation patterns of these viral DNA, and also *HLA-DRB1* polymorphisms between RA and OA synovial tissues. [Conclusion] EBV and/or B19 infection themselves might not play a pathogenic role in Japanese RA patients.

P2-047

Algorithms Using Genome-Wide SNP Analysis for Prediction of Progression of Joint Space Narrowing (JSN) or Erosion (E) in Rheumatoid Arthritis Patients Using Data from Multiple Medical Cohorts

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Conflict of interest: None

[Objectives] We developed SNP algorithms with an aim of enabling prediction of progression of JSN/E by means of genome-wide SNP analysis using multiple medical cohorts. **[Methods]** 124 RA patients whose disease duration was within 5 years were enrolled. Twenty-five patients had JSN/E score of ≧ 5 (rapid progression of JSN (RJ)), 99 had JSN/E score of < 5 (slow progression of JSN (SJ)), 21 had an E/JSN score of ≧ 1 (rapid progression of E (RE)), and 103 had E/JSN score of < 1 (slow progression of E (SE)). We scored a relationship between each SNP and progression of JSN/E, the estimated total score of the 10 SNPs (estimated scoring in each SNP was as follows: homo allele in the majority in RJ (RE) group: +1 point, hetero allele: 0 point, and homo allele in the majority of SJ (SE) group: -1 point), and examined relationships between the rapid and slow group, and the total score. **[Results]** Accuracy of the algorithm for distinguishing the RJ group from the SJ group was 86.3%. Accuracy of the algorithm for distinguishing the RE group from the SE group was 93.6%. **[Conclusion]** This SNP algorithm may be useful in initially distinguishing rapid progression of joint space narrowing or erosion.

P2-048

Preliminary search for RA-responsible genes using SNP differences between RA child (C) genome and non-RA parent (P) genome

Satoru Koyano[1], Keiko Funahashi[1], Takeshi Nakamura[2], Takako Miura[2], Kosuke Okuda[2], Tsukasa Matsubara[2]
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Conflict of interest: None

[Objectives] We preliminarily searched RA-responsible genes using SNP differences between RA child genome and non-RA parent genome. **[Methods]** Nine RA children and each 9 non-RA parents were enrolled in this study. 176,140 SNPs which are common between HumanHap 300K chip and HumanOmni 2.5M chip were analyzed. Association analyses between 176,140 SNPs of C and those of P were examined by Fisher's exact test ($p < 0.05$). We extracted SNP sites under the following categories: allele frequencies in P were ~0.5 and allele frequencies in C were ~0, P ~0 and C ~0.5, P ~1 and C ~0, P ~0 and C ~1. **[Results]** Forty-seven SNP sites whose allele frequencies in P were 0.4-0.6 and those in C were $\leqq 0.1$ were found. Furthermore, 7 SNP ($P \leqq 0.1$ and C 0.4-0.6), 13 SNP ($P \geqq 0.8$ and $C \leqq 0.3$) and 0 SNP sites ($C \geqq 0.8$) were found. Part of these SNP sites lied on the ADAM metalloprotease family genes. **[Conclusion]** Based on these preliminary data, we will search for RA-responsible genes by increasing sample sizes.

P2-049

Clinical significance of the anti cyclic citrullinated peptide (CCP) antibody and rheumatoid factor of a patient with rheumatoid arthritis

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Conflict of interest: None

[Objectives] To evaluate the association between anti CCP antibody and rheumatoid factor (RAPA) and some inflammatory markers. [Methods] The retrospective study of 202 patients with rheumatoid arthritis to meet the ACR classification criteria in 1987. We divided those into 4 groups; is anti CCP antibody and RAPA double-positive, either positive, each negative and evaluated CRP, MMP-3, Granulocyte and r-globulin, respectively in 4 groups and divided those into a negative group, low level group and the high level group by an anti-CCP antibody level and examined 4 inflammatory markers, respectively; and as for RAPA similarly. [Results] Anti CCP antibody and RAPA with CRP, MMP-3 and Granulocyte was unrelated, respectively but was related to the r-globulin synergistically. (U-test $P < 0.05$) Also, the r-globulin had a correlation with CRP and MMP-3. ($\rho = 0.393$, 0.333, respectively, $P < 0.001$) [Conclusion] The anti CCP antibody and rheumatoid factor are associated with r-globulin synergistically and enhance an immune phenomenon and chronic inflammation. Also, r-globulin is associated with acute inflammation such as CRP, MMP-3. We guess the presence of anti CCP antibody and rheumatoid factor cause acute inflammation through an immune phenomenon and chronic inflammation in rheumatoid arthritis.

P2-050

Estimation of the clinical characteristic of rheumatoid factor and anti-CCP antibody (ACPA) positive and negative rheumatoid arthritis patients by NinJa2012 data base in Japan

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Conflict of interest: None

[Objectives] To estimate the clinical characteristics of rheumatoid factor (RF) and anti-CCP antibody (ACPA) in the rheumatoid arthritis patients of NinJa 2012 registry in Japan. [Methods] Of 11940 patients registered in NinJa 2012, 3972 patients were categorized to four groups, Group A: RF+/ACPA+, Group B: RF+/ ACPA-, Group C: RF-/ACPA+, and Group D: RF-/ACPA-. [Results] The average of the age of onset and the disease duration were 51.3 years old (yo) and 10.7 years (y) in Group A, 52.0 yo and 9.9 y in Group B, 51.1 yo and 9.7 y in Group C, and 57.0 yo and 6.6 y in Group D, respectively. The percentage of Steinbrocker stage classification of group I or II was 59.0% in Group A, 72.5% in Group B, 57.7% in Group C, and 80.3% in Group D. Glucocorticoid was given to 42.4% of patients in Group A, 31.7% in Group B, 39.0% in Group C, and 35.1% in Group D. MTX was given to 66.1% of patients, 52.8%, 69.1%, and 57.1%, and Biologics was 26.2%, 14.2%, 29.7%, and 15.9%, respectively. The rate of achievement of DAS28 remission or low disease activity was 53.2% in Group A, 63.5% in Group B, 58.8% in Group C, and 73.0% in Group D. [Conclusion] ACPA may be more influenced to disease activity of rheumatoid arthritis than RF in the patients of NinJa 2012 registry.

P2-051

Using the National Database of Rheumatic Diseases by iR-net in Japan (NinJa) to investigate the effects of joint disease on modified Health Assessment Questionnaire (mHAQ) scores in rheumatoid arthritis (RA) patients

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Conflict of interest: None

[Objectives] Using NinJa, the present study investigated the effect of unilateral and bilateral disease in the shoulder, elbow, wrist, hip, knee, ankle, finger, and toe joints on mHAQ scores. [Methods] The subjects were the 9,212 patients (1,766 men, 7,466 women) registered in NinJa in FY 2011. The presence or absence of disease in each joint (swelling and pain were considered as disease) and whether the disease was unilateral or bilateral were investigated. The correlations between disease of each joint and mHAQ scores were investigated using logistic regression analysis. [Results] Significant correlations were observed between the mHAQ score and unilateral and bilateral disease of all joints apart from bilateral disease of the hip and unilateral and bilateral disease of the toes. The odds ratio for each joint unilaterally and bilaterally, respectively, were as follows: shoulder, 1.8 and 4.0; elbow, 1.8 and 2.6; wrist, 1.5 and 1.9; hip, 3.0 and 1.7; knee, 1.9 and 2.6; ankle, 2.0 and 2.3; finger, 1.2 and 1.4; and toe, 1.1 and 1.0. [Conclusion] While mHAQ scores were significantly affected by disease in almost all joints, a greater effect was increasing order of ankle, knee, elbow and shoulder. Bilateral disease tended to have a greater effect in these major joints and the wrist.

P2-052

The establishment of GP88 (progranulin) measurement method and its dynamics; a new biomarker of rheumatoid arthritis

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Conflict of interest: None

[Objectives] It is a glycoprotein of about 88,000 molecular weight to cell membrane structure, GP88 has been reported for homology with Progranulin. We have now examined for the purpose of establishing measurement methods of GP88 (ELISA), it was observed trends in rheumatoid arthritis patient serum. [Methods] We have investigated 65 cases of rheumatoid arthritis (RA) patients, 5 Infliximab-treated patients, and 24 osteoarthritis (OA) patients. In addition, there were 149 healthy volunteers provided by Health Science Resource Center from (RECHS) (male 78, female 71). [Results] The measured width was varied greatly from the lowest value 20.0 ng/ml to the highest value 50.0 ng/ml, and an average value was 40.1 ng/ml. Divided into separate men and women, in men aged 25 to 68 years (mean 54.2 years) GP88 was 40.5 ± 14.3 ng/ml, in women aged 28 to 69 yaers (mean 51.0 years) GP88 was 41.0 ± 10.9ng/

ml. GP88 in RA patients was significantly higher than that of OA patients, RA; 51.2 ± 12.5ng/ml and OA; 43.9 ± 5.8ng/ml, ($p < 0.01$). [Conclusion] GP88-ELISA assay system, the newly produced, is can be used as a system for measuring in daily use without any problems in reproducibility. GP88 might become one of the useful biomarkers in diagnosis and predict of effectiveness of RA patients.

P2-053

Amino acid and periodontal profiles in rheumatoid arthritis patients with anti-TNF therapy

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Conflict of interest: None

[Objectives] Tumor necrosis factor-alpha (TNF-α) and amino acids have been suggested to be associated with rheumatoid arthritis (RA) and periodontitis. This study was undertaken to compare the amino acid and periodontal profiles between RA patients with and without anti-TNF therapy. [Methods] The study participants consisted of 52 RA patients with and without anti-TNF therapy (n = 26 for RA-TNF group, and n = 26 for RA-C group) and 29 healthy controls. Clinical periodontal and rheumatologic parameters and plasma levels of cytokines, inflammatory markers and amino acids were evaluated. [Results] The RA-TNF group showed a significantly lower bleeding on probing score and a significantly higher TNF-α level than the RA-C group. Six amino acids (glycine, glutamine, glutamic acid, histidine, tryptophan, and ornithine) were significantly different in the concentrations among the three groups. Of these, a significantly negative correlation was found between glycine and histidine levels and periodontal destruction levels in the RA-control subgroup. No associations were obtained between amino acid and periodontal profiles in the RA-anti-TNF group. [Conclusion] These results suggest a difference in the amino acid and periodontal profiles between RA patients with and without anti-TNF therapy.

P2-054

A multicenter evaluation of related factors of probable RA and undifferentiated arthritis (Pure study)

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[1]Sagawa Akira Rheumatology Clinic, [2]Hosui Sogo Medical Clinic, [3]Ohnishi Internal Medicine and Rheumatology Clinic, [4]Sapporo City General Hospital, [5]Yamanotedoriyagi Hospital, [6]Hokkaido Medical Center for Rheumatic Diseases, [7]KKR Sapporo Medical Center Tonan Hospital, [8]Ohsaki Clinic

Conflict of interest: None

[Objectives] To observe the clinical courses of anti-CCP antibody and RF negative patients with inflammatory arthritis suggestive of RA and assess the diagnosis of RA. [Methods] The subjects were anti-CCP antibody and RF negative cases of suspected RA who visited facilities after JAN-2008. Their total scores according to the ACR/EULAR classification criteria for RA were recorded with the bases for the diagnosis of RA by attending physicians for assessment. [Results] The subjects were 44 patients (39 females) aged 21-82 (59.7 ± 13.1). The values of anti-CCP antibody and RF were 0.6-2.9 (0.78 ± 0.49) and 0-9 (2.11 ± 2.17), respectively. The bases for the diagnosis of RA were X-ray in 4 cases, ultrasound in no case, MRI in 2 cases, joint findings in 25 cases, and several test results in other cases. The recorded total scores according to the ACR/EULAR classification criteria for RA ranged from 1 to 7 (4.3 ± 1.3). [Conclusion] The diagnosis of anti-CCP antibody and RF negative RA, which definitely exists, is difficult and tends to be delayed due to its low score according to the classification criteria. It is considered that joint findings are most useful for the early diagnosis of RA and that imaging diagnosis such as joint ultrasound and MRI should also be introduced actively.

P2-055

The association with the disease activity of rheumatoid arthritis, the titer of rheumatoid factor, and serum immunoglobulin level

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Conflict of interest: None

[Objectives] We retrospectively analyze the titer of rheumatoid factor (RF) and serum immunoglobulin level in decreasing the activity of rheumatoid arthritis (RA). [Methods] 89 cases of 74 patients are included. They are satisfied with DAS28-ESR EULAR response (>1.2 DAS28-ESR deterioration) in six month and the measurement of serum RF, IgG, IgA and IgM level. We separate them into RF negative, RF augmentation and RF deterioration group. The serum IgG, IgA and IgM level were compared before and after treatment. [Results] 32 cases are RF negative, 12 RF augmentation and 45 RF deterioration. The IgG titer of RF deterioration group is only statistically depressed before and after treatment. Moreover, the number of cases in which serum immunoglobulin level increase and decrease associated with the RF titer is statistically larger about IgG than about IgA and IgM. [Conclusion] The RF measured by latex agglutination is generally IgM type, but IgG and IgA type can be detected. We observe statistically that the serum IgG titer, not but IgA and IgM, increase and decrease associated with the RF titer. It is probable that IgG type serum RF level, not but IgM type, is mainly depressed when RF positive RA patient is treated.

P2-056

What factors influence HAQ-DI in patients with rheumatoid arthritis?

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Conflict of interest: None

[Objectives] To analyze correlations of the Stanford Health Assessment Questionnaire disability index (HAQ-DI) with other measures of clinical status in patients with RA. [Methods] The function capacity of 119 patients with women RA who were from 40 years to 69 years was assessed according to HAQ-DI. Other variables studied included Larsen scores for radiographic damage of shoulders, elbows, wrists, fingers, hips, knees, ankles, and feet, DAS28CRP, drug therapy. An erosion joints count (EJC) was defined as the number of joints >= 2 by Larsen scores. Multiple linear regression was used to identify factors affecting HAQ-DI. [Results] The mean HAQ-DI was 0.45, the mean ETC 8.6, and mean DAS28CRP 2.49. Fifty-one patients (43%) received biologics, 79 patients (66%) methotrexate, and 20 patients (17%) prednisolone. Seventy-eight (66%) patients were in HAQ-DI remission (<0.5), 74 (62%) in DAS28CRP remission (<2.60). Twenty-eight percents of variance in HAQ-DI score could be explained; the most significant explanatory variables were the DAS28CRP, EJC, and prednisolone. [Conclusion] HAQ-DI was influenced by disease activity, joints damage, and prednisolone. To keep functional capacity in RA patients, we should lower arthritis activity and prevent joints damage.

P2-057

The association between rheumatoid factor and cardiovascular disease risk factors: an analysis of 39,966 apparently healthy participants

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Conflict of interest: None

[Objectives] This study examines whether RF is independently associated with the various risk factors established for CVD in apparently healthy individuals. [Methods] From April 2012 to March 2013, all participants attending the Center for Preventive Medicine at St. Luke's Inter-

national Hospital for the annual health checkup were included in this study. RF is included in routine measurements. Participants with previously diagnosed RA were excluded. Remaining non-RA participants were divided into two groups by RF sero-positivity (>15 IU/ml). Using this as the primary outcome, we compared several parameters including several well-known cardiovascular risk factors between two groups. [Results] Of 42,303 individuals presenting for health checkup, 39,966 met inclusion criteria (mean age 52.1±12.3, %women 52.3%). Of these, 4,496 (11.2%) were seropositive for RF. On univariate analysis, RF (+) individuals were more likely to be higher value in %women, mean age, BMI, waist circumference, SBP, CHO, LDL, TG, HbA1c, FBG and %smoking history. Multivariate analysis revealed that mean age, %women, waist circumference, SBP, HbA1c and FBG. [Conclusion] This cross-sectional study showed that RF in non-RA patient is correlated with several well-known CVD risk factors.

P2-058

Assessment of salt intake in rheumatoid arthritis (RA) patients

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Conflict of interest: None

[Objectives] It was reported that increased salt concentrations in vivo markedly boost the induction of murine TH17 cells autoimmune diseases. We assessed the association between salt intake and disease activity in RA patients. [Methods] The study group consisted of 192 RA patients. We calculated salt intake by equations from guidelines of the Japanese Society of Hypertension. We assessed the association with RA disease activity. [Results] The average salt intake in RA patients was 8.36±2.87 g/day. Salt intake in RA patients had no correlation with RA disease activity, but was correlated with low density lipoprotein cholesterol (LDL-Cho) calculated by the Friedelwald formula, albumin, and GNRI. When we compared characteristics among patients achieving the desired values of salt intake according to the Japanese Ministry of Health, Labour and Welfare (≧9g, male, ≧7.5g, female), and those not achieving them, the former were significantly heavier, had significantly higher BMI, higher LDL-Cho, higher albumin, and higher GNRI, but did not show any significant difference in RA disease activity. [Conclusion] No correlation was noted between salt intake and RA disease activity, whereas salt intake and nutrition status were correlated in RA patients.

P2-059

Serum Interleukin 6 Before and After Therapy with Tocilizumab Is a Principal Biomarker in Patients with Rheumatoid Arthritis

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Conflict of interest: None

[Objectives] Biologic treatments including the humanized anti-interleukin 6 (anti-IL-6) receptor antibody tocilizumab (TCZ) provide therapeutic options for patients with rheumatoid arthritis (RA). We investigated useful biomarkers to predict the responsiveness to TCZ by measurement of serum proinflammatory cytokine concentrations. [Methods] Serum samples were collected from 61 patients with RA before biologic treatment and at 4 weeks after initial administration of either TCZ (n = 32) or infliximab (IFX; n = 29) Disease Activity Score of 28 joints (DAS28) was determined at baseline and after treatment. [Results] Only the IL-6 level was significantly correlated with DAS28 before treatment. The IL-6 level before treatment was positively correlated with DAS 28 after TCZ treatment, and was significantly lower in TCZ-responsive patients than in TCZ-resistant patients. DAS28 after TCZ was significantly lower than after administration of IFX in patients with low pretreatment IL-6. These results indicate that low serum IL-6 is associated with a favorable response to TCZ. [Conclusion] Measurement of serum IL-6 in RA before treatment may be useful to estimate residual disease activity after TCZ treatment and to predict responsiveness to TCZ treatment.

P2-060

Can we predict a serum MMP-3 level of patients with female rheumatoid arthritis started biological agents newly from disease activity

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Conflict of interest: None

[Objectives] We consider that the serum MMP-3 level is useful for medication in patients with rheumatoid arthritis. However, there are few studies that examined relations with the disease activity. Therefore we examined the relations of disease activity and serum MMP-3 level using the data of the RA patients who started biological agents newly. [Methods] Patients with female RA started biological agents newly were examined the relations of disease activity and the serum MMP-3 level, start of therapy 14 weeks and 30 weeks, in a period from 2008 through 2013. In addition, we excluded which used corticosteroid. The method of analysis used a Spearman Rank-Order Correlation Coefficient and simple linear regression analysis. [Results] 52 people are included (IFN22, ETN4, TCZ11, ADA9, ABT6), the median age were 59.5 years old. The MMP-3 level significantly correlated with all disease activity score ($p<0.05$). It was the results, DAS28 ($p<0.05$), SDAI ($p<0.05$) and CDAI ($p<0.05$) as a result of simple linear regression analysis. As for the predicted value of the MMP-3 level from remission criteria are DAS28 92.4ng/ml (14weeks) 94.8ng/ml (30weeks), SDAI (66.8ng/ml, 66.0ng/ml), CDAI (63.2ng/ml, 68.0ng/ml). [Conclusion] We can infer a serum MMP-3 level from disease activity score of RA in the female RA patients.

P2-061

Plasma short-talin is a new rheumatoid arthritis monitoring biomarker

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Conflict of interest: Yes

[Objectives] We have already reported that short-talin, which was specifically expressed in RA patient plasma, was a diagnostic biomarker with higher sensitivity and specificity than ACPA. In this paper, we investigated whether the plasma short-talin can be an RA biomarker. [Methods] RA was diagnosed as the 2010 Rheumatoid Arthritis Classification Criteria. Plasma and sera were obtained simultaneously from 54 RA patients (Age, 59.8±14.2 y/o; DAS28, 4.55 ± 1.08). Eighteen (33.3 %) of these 54 patients were untreated, and 20 patients (37.0%) were treated with biologics DMARD at the time of collecting blood samples. Plasma short-talin was quantified using a sandwich ELISA with anti-short talin capture and detecting antibodies. Serum ACPA was measured using a commercial ELISA kit. RA activity at the time of collecting blood samples was estimated using DAS28, SDAI, and CDAI. [Results] The expression of the plasma short-talin was significantly correlated with DAS28 ($r=0.39$, $p=0.0068$), SDAI ($r=0.38$, $p=0.010$), CDAI ($r=0.33$, $p=0.028$), and ACPA ($r=0.65$, $p=0.0008$). However, plasma short-talin level was not correlated with ESR, CRP, and MMP-3. [Conclusion] Plasma short-talin could be an RA monitoring biomarker independent of the inflammatory markers like ESR and CRP.

P2-062

MMP3 as a predictor identifying a subgroup of rheumatoid arthritis patients with structural remission receiving methotrexate (MTX) monotherapy

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Conflict of interest: None

[Objectives] To evaluate efficacy of MTX monotherapy and discover the predictor identifying a subgroup of rheumatoid patients with structural remission. [Methods] [Results] The 161 patients were with increased activity (mean: DAS28-4ESR 5.5, CRP 2.6mg/dL) and radiographic progression (mean: ΔTSS 7.9) on initiation of MTX. Disease activity was improved yearly from baseline to 3yrs: DAS28-ESR (4) from 5.5±1.2 to 3.7±1.4, %DAS28 remission from 2% to 22%, mHAQ from 0.54±0.47 to 0.16±0.31, and %mHAQ remission from 16% to 62%. Structural remission was increased from 62/161 (21.7%) to 69/137 (50.4%), whereas CRRP changed from 55/161 (34.2%) to 28/137 (20.4%) and RRP from 35/ 161 (21.7%) to 15/137 (10.9%). ROC analyses showed that MMP3 level of less than 103.7 ng/ml at baseline was significantly associated with structural remission, with negative prediction value (NPV) 55/62 (88.7%) and 60/62 (96.8%) for CRRP and RRP, respectively. [Conclusion] A substantial proportion of rheumatoid patients can be treated to become structural remission with MTX monotherapy, where we identified basal MMP3 level below 103.7 mg/ml as a predictor identifying a subgroup with structural remission.

P2-063

In vitro cytokine production in proliferating CD4+ T cells and the effect of anti-TNF-alpha agents in patients with rheumatoid arthritis

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Conflict of interest: None

[Objectives] In patients with RA, we analyze in vitro cytokine production in proliferating CD4+ T cells and the effect of anti-TNF-alpha (tumor necrosis factor-alpha) agents (TNF-alpha blockers). [Methods] Peripheral blood mononuclear cells (PBMCs) from 19 patients with RA were labeled with CFSE [5 (and 6) carboxyfluorescein diacetate, succinimidyl ester] and cultured with ConA for 3 days. CD4+ T cells were assessed for cytokine production, IFN-gamma, IL-4 and TNF-alpha in proliferation by flow cytometry. We examined association of these parameters with clinical response of TNF-alpha blockers in short (2W), medium (24W) and long (3Y) term studies. [Results] Good responders of TNF-alpha blockers was associated with lower TNF-alpha production in proliferating CD4+ T cells in short term ($p<0.05$). Increased production of IFN-gamma ($p<0.05$) in proliferating CD4+ T cells was associated with good responders in long term. [Conclusion] In vitro analysis of cytokine production in proliferating CD4+ T cells, prior to treatment of TNF-alpha blockers, may work as possible markers of efficacy of TNF-alpha blockers in RA patients.

P2-064

Relationship between the multi-biomarker disease activity (MBDA) score and structural outcome in patients with RA treated with TNF inhibitors

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Conflict of interest: None

[Objectives] To assess relationship between the MBDA score and ΔmTSS in RA patients treated with TNF inhibitors (TNFi). [Methods] 141 patients treated with TNFi for 1 year with clinical and radiographic data and serum samples from 0 and 52 weeks were evaluated; 83 patients also had serum and clinical data at 24 weeks. Serum concentrations of 12 biomarkers were measured to generate the MBDA score using the Vectra® DA algorithm (1-100). X-rays were scored by two readers for ΔmTSS (0-52weeks). [Results] Baseline characteristics were (mean): age 58 years, duration 103 months, MTX 86%, DAS28-ESR 5.7, MBDA score 61, mTSS 68. Baseline MBDA score tended to be greater in patients with higher ΔmTSS. At 24 weeks, 88% of patients with DAS28-ESR>3.2 and low MBDA score (≦29) had ΔmTSS≦0.5, vs. 68% with DAS28-ESR≦3.2 and MBDA score>29. If patients with 3 visits (baseline, week 24, and week 52) had low MBDA scores at 2 or 3 visits, they were more likely to have ΔmTSS≦0.5 (OR=14.3, p=0.002). Similarly if they had high MBDA scores (>44) at 2 or 3 visits they were more likely to have ΔmTSS>3 (OR=15.3, p=0.002). [Conclusion] MBDA score provided added value to DAS28-ESR at 24 weeks for predicting ΔmTSS≦0.5 in RA patients treated with TNFi. Multiple high or low MBDA scores were associated with ΔmTSS.

P2-065

Plasma pentraxin 3 concentration is associated with progression of radiographic joint damage in females with rheumatoid arthritis

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Conflict of interest: None

[Objectives] Pentraxin 3 (PTX3) is produced by macrophages, vascular endothelial cells, synoviocytes and chondrocytes in response to the inflammatory stimuli such as IL-1β and TNF-α. PTX3 is regarded as a sensitive biomarker responding to local inflammation. PTX3 is also strongly expressed in human atherosclerotic plaque. Plasma PTX3 increases in patients with myocardial infarction. Patients with RA have chronic inflammation and increased atherosclerosis. We investigated the association between plasma PTX3 levels and progression of joint destruction or atherosclerosis. [Methods] We measured plasma PTX3 levels in 72 female patients with RA (58±12 years) and 80 healthy ones (71±6 years). Modified Sharp score and plaque score were evaluated in RA females. [Results] PTX3 levels were significantly higher in RA females (4.05±2.91 ng/mL) than healthy ones (1.61±1.05 ng/mL, $P<0.001$). In RA females, PTX3 levels were correlated with serum CRP ($P=0.02$), MMP-3 ($P=0.005$) or albumin ($P<0.001$) but not related to age. Plasma PTX3 levels were associated with 3 years Δtotal Sharp score, Δerosion score and ΔJSN score but not with Δplaque score evaluated by carotid ultrasonography in RA females. [Conclusion] Elevated plasma PTX3 may be useful to predict progression of joint damage in patients with RA.

P2-066

Characterization of the multi-biomarker disease activity (MBDA) score patients with rheumatoid arthritis (RA) treated with Tocilizumab (TCZ)

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Conflict of interest: None

[Objectives] To validate the multi-biomarker disease activity (MBDA) score in patients with rheumatoid arthritis (RA) treated with Tocilizumab (TCZ). [Metods] The analysis was conducted on 52 RA patients treated with TCZ for at least 1 year. Serum concentrations of 12 biomarkers were measured at 0, 24 and 52 weeks, and combined using the Vectra® DA algorithm to obtain MBDA score (1-100). Association of MBDA score with disease activity (DAS28-ESR), joint damage (mTSS) and disability (HAQ) were assessed. [Results] Median baseline characteristics were: age 56.6, duration 12.4 years, DAS28-ESR 5.6, MBDA score 57.5. MBDA score correlated with DAS28-ESR at baseline ($r=0.54$, $p<0.001$) and week 52 ($r=0.46$, $p<0.001$). Over 1 year, median MBDA score decreased by 25% vs. 58% for DAS28-ESR; ΔMBDA correlated with ΔDAS28-ESR ($r=0.47$, $p<0.001$). All subjects with low MBDA scores (≦29) at week 24 achieved both ΔmTSS≦0.5 and ΔHAQ≦0.5 at week 52 (n=5). Over 1 year, all biomarkers decreased (median change: -99% for CRP and -97% for SAA) except for IL-6 which increased

(+24%). [Conclusion] MBDA score reflected disease activity and decreased in patients with RA treated with TCZ. More data are needed in TCZ treated patients to assess whether MBDA score is a predictor of radiographic and functional outcomes.

P2-067

Investigation of the causes of death in patients using biological agents

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Conflict of interest: None

[Objectives] To investigate the causes of death in patients with rheumatoid arthritis (RA who were using biological agents. [Methods] We investigated the causes of death in 405 RA patients who used biological agents before April 30, 2013. [Results] Subjects included 85 men and 320 women who were aged 22–83 years (mean age, 58.9 years) at the time of first use of biological agents. They had a 1–50-year history (mean, 9.3 years) of RA. Currently, 348 patients are alive (85.9%), 30 patients (7.4%) have been transferred to another hospital (7.4%), and 27 (6.7%) have died. The deaths occurred in 9 men and 18 women aged 34–82 years (mean, 68 years), with a disease duration of 1–40 years (mean, 12.7 years). The cause of death was malignant tumor (lymphoma, colorectal cancer, lung cancer, renal cancer, pancreatic cancer, and chondrosarcoma) in 11 cases, pneumonia in 6, cerebrovascular disturbance in 3, heart failure in 2, and gastrointestinal hemorrhage, diverticulitis, peritonitis, bone marrow suppression, and traffic accident in 1 case each. [Conclusion] Our analysis of the causes of death in patients with RA using biological agents showed that more patients tended to be older with a longer disease duration. Malignant tumor was the most common cause of death, followed by pneumonia.

P2-068

Investigation of factors influencing physical function mid-term status after total knee replacement and total hip replacement using the NinJa database

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Conflict of interest: None

[Objectives] NinJa was used to investigate factors which influence physical function after TKA and THA. [Methods] We identified 122 patients (13 men, 109 women) for TKA and 59 patients (6 men, 53 women) registered with NinJa who underwent TKA from 2004 to 2008, and who had a 5-year follow-up without any other surgical procedures. The numbers and values of candidate factors were compared between the cases with better mHAQ scores (group B) and the cases with worse mHAQ scores (group W) at the five year follow-up relative to the baseline score. Examined factors included age, disease duration, stage, class, mHAQ, CRP, ESR, PtPainVAS, PtGVAS, DrVAS, DAS28, CDAI, and SDAI. [Results] In group B of TKA, age was younger and mHAQ, PtPainVAS, PtGVAS, DrVAS, DAS28, DAS28CRP, CDAI and SDAI were higher than those in group W whereas in THA, PtPainVAS, PtGVAS and DrVAS were higher preoperatively. Both in TKA and in THA, the improvement rates of DAS28, DAS28CRP, CDA, and SDAI in group B were higher than those in group W postoperatively. [Conclusion] Our results suggest that the effect of TKA and THA on physical function improvement continues for a mid-term duration even among RA patients with relatively high physical dysfunction when the disease activity is controlled.

P2-069

Rheumatoid factor is crucial for the treatment of elderly-onset rheumatoid arthritis

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Conflict of interest: None

[Objectives] We evaluated the outcome of the treatment for elderly-onset rheumatoid arthritis (EORA) to reveal the special feature. [Methods] Fifty outpatients (17 men and 33 women) with EORA who were treated in our department were investigated with the clinical records. The average age of RA onset was 66.9 years (61-82) and the average of the disease duration was 7.4 years (1-24). 39 patients have positive rheumatoid factor (RF). DAS28ESR was calculated in each patient, and compared among the separate group of (a) positive RF treated with Methotrexate or biologics, (b) positive RF with treated with others, (c) negative RF treated with Methotrexate or biologics, (b) negative RF with treated with others. [Results] DAS28ESR was the following, (a) 2.95±1.02, (b) 3.23±0.82, (c) 2.24±0.48, (d) 2.32±0.66. And the percentage of patients with remission was (a) 44%, (b) 17%, (c) 86%, (d) 75%, respectively. [Conclusion] The EORA patients with negative RF have better response for the treatment compared with those with positive RF. In negative RF EORA group, Methotrexate should be used as the first line drug, and biologics should be considered to use in case of uncontrolled disease activity.

P2-070

Inhibition of radiographic joint damage progression in patients with rheumatoid arthritis preserving RAPID3 remission during 1 year

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Conflict of interest: None

[Objectives] To investigate radiographic joint damages (RJD) in patients with rheumatoid arthritis (RA) preserving RAPID3 remission during 1 year. [Methods] RJD were analyzed by using modified total sharp scoring method (mTSS) in hands and feet X-ray films of RA patients with RAPID3 remission at baseline and 1 year later. [Results] RAPID3 remissions were observed in 285 patients out of 1262 RA patients (22.6%) at cross-sectional study from last year. 77 patients (63.6%) preserved RAPID3 remission during 1 year from 121 patients available for the medical examination 1 year after the first RAPID3 remission. Mean baseline clinical data of patients preserving RAPID3 remission were as follows: age; 60.7 years, duration of RA; 63.4 months, DAS28-ESR; 2.21 (remission rates 74%), CDAI; 3.8 (remission rates 42%), anti-CCP; 137 U/ml (62.3% positive), RF; 47.1 IU/ml (53.2% positive). Mean radiographic data indicated as follows: baseline mTSS; 16.4, baseline mTSS/year; 6.43 and △mTSS/y; 0.09. Structural remissions were observed in 66 patients out of 77 (85.7%). [Conclusion] RAPID3 includes the three patients-reported outcome measures: pain, global estimate for RA, and physical function. Our data showed preservation of patients' based remission during 1 year inhibited progression of RJD.

P2-071

Plasama exchange as a second line treatment for the patients with malignant rheumatoid arthritis

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Conflict of interest: None

[Background] Malignant rheumatoid arthritis (MRA) was designated as rheumatoid arthritis (RA) with extra-articular manifestation, such as vasculitis and interstitial pneumonitis, which could cause fatal outcome.

MRA is usually treated with corticosteroid, and methylprednisolone pulse therapy and immunosuppressants are highly useful for severe MRA. [Purpose] We conducted this study to evaluate the clinical feature and treatment of MRA. [Patients and Method] Four patients with MRA were enrolled. We examined the clinical feature and outcome of these patients. [Result] Two patients were MRA with cutaneous ulcer, and 2 of them were accompanied by interstitial pneumonitis. All MRA patients were given methyprednisolone pulse therapy and high dose prednisolone. Three patients were treated with plasma exchange and no patients were treated with cyclophophamide. All 4 patients entertained clinical patients and discharged. [Conclusion] Plasma exchange should be considered as second line therapy for the patients with MRA who were refractory to conventional steroid treatment.

P2-072

A case of bronchiolitis obliterans organizing pneumonia (BOOP) with rheumatoid arthritis in the course of the therapy with anti-TNF biologics

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Conflict of interest: None

A 45 years–old female was admitted to our hospital because of high fever and severe cough. She was diagnosed as RA at the age of 19 and treated with several kinds of conventional synthetic DMARDs (csDMARDs). But her disease activity was not controlled well, then biological DMARD (bDMARD) was started in combination with csDMARDs. First bDMARD was Infliximab but stopped because of the shock at the time of injection. Next, Etanercept was started and continued for three years with low disease activity. Depite this treatment, her bone destruction progressed and she had to undergo four artificial joint replacements. After that several bDMARD was tried with a view to prevent the bone destruction but the treatment was resistant. Finally Etanercept was selected again. After three months, a lung involvement was detected by chest CT. Her blood test showed white blood count 11700/mm^3 and CRP level was 13.5mg/dl. Serum KL-6 and SP-D was normal. She was treated several antibiotics but her condition didn't change at all. Finally she underwent the bronchoscopic examination and diagnosed as BOOP with the good response of PSL treatment. This is an unique case of BOOP with RA occuring in the treatment with bDMARD of TNF inhibitor.

P2-073

Clinical improvement with a treatment of tacrolimus in a case of rheumatoid arthritis complicated with respiratory disorder

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Conflict of interest: None

A 68 year-old man was referred to our hospital because of dyspnea on effort. He was diagnosed as seropositive rheumatoid arthritis (RA) with chronic bronchitis about ten years ago. At first he was treated with MTX and bucillamine but his arthralgia was gradually getting worse. Then he was considered to use biological DMARD. His chest CT scan image showed chronic broncitis and widely scattered pleuritis, then he had taken tuberculosis drugs for 6 months. Because the treatment with Infliximab and MTX was not so effective, we stopped the MTX treatment changed to the treatment with low dose of tacrolimus. Until now, his RA activity was under control without worsening the respiratory involvement. Tacrolimus might be a hopeful drug in RA patients with respiratory disorder.

P2-074

A case report of elderly-onset rheumatoid arthritis accompanying constrictive pericarditis, pleuritis and organizing pneumonia

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Conflict of interest: None

An 81-year-old male with rheumatoid arthritis had been treated with salazosulfapyridine, celecoxib and prednisolone since 2012. He had been aware of dyspnea on exertion and chest pain exacerbating at inspiration since May 2013. Chest X-ray and echocardiogram showed cardiomegaly and pericardial effusion, and he was referred to our hospital. CAT scan showed pericardial effusion and pleural effusion dominantly on the left side. Ibuprofen was started, ruling out infection, malignancy and Dressler syndrome. Nine days after admission, he developed organizing pneumonia, and 60 mg/day of prednisolone was started. Pericardial effusion, pleural effusion and organizing pneumonia were ameliorated immediately. Invasive hemodynamic evaluation showed characteristic W-type and dip-and-plateau pattern waveform in the right atrium and the right ventricle, respectively. Therefore he was diagnosed as having constrictive pericarditis. [Clinical significance] A rare case of elderly-onset rheumatoid arthritis accompanied by constrictive pericarditis, pleuritis and organizing pneumonia shortly after the development of arthritis is reported.

P2-075

Pericardial effusion on Etanercept therapy for rheumatoid arthritis

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Conflict of interest: None

The patient was a 53 year-old woman, who had rheumatoid arthritis (RA) that had developed in 2000. She was treated only with 25mg/week of Etanercept (ETN), and methotrexate had not been administered for chronic kidney disease. Arthralgia had worsened from the beginning of 2013, then she had suffered from fever and dry cough since June 2013. Because of these symptoms and bilateral pedal edema from July, 2013, she was admitted to our hospital. ETN was stopped because of the possibility of infection, and diuretic was given for congestion. The pericardial fluid gradually decreased and sampling was impossible by the pericardiocentesis. A pericardial biopsy under the local anesthesia was also impossible due to pain. In FDG-PET/CT, abnormal accumulation except diffuse accumulation to epicardium was not observed. No findings to suggest an infection, a malignant causes or other conective tissue disease was observed in systemic search, so pericarditis with RA or ETN-induced pericarditis were suspected. Ten mg/day of PSL was started for arthralgia, then pericardial effusion disappeared. This case suggests that we must need to be vigilant for extra-articular manifestations in patients with rheumatoid arthritis treated with TNF-inhibitors.

P2-076

Immunodeficiency-associated lymphoproliferative disorders in two patients with rheumatoid arthritis

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Conflict of interest: None

[Objectives] Methotrexate (MTX) and biologics have been widely used to treat in patients with rheumatoid arthritis (RA). Immunodeficiency-associated lymphoproliferative disorders (IA-LPD) refers to lymphoid proliferation or lymphoma developing in a patient received immunosuppressive drugs. We report two cases of IA-LPD with RA. [Case1] A 62-year-old woman with RA (stage III, class 1) for 5 years had been treated with MTX or biologics. She developed soft tumor in her groin. She was diagnosed IA-LPD at internal medicine. Spontaneous remission of LPD was obtained after cessation of MTX therapy. [Case2] A 62-year-old woman with RA (stage IV, class 2) for 12 years had been treated with

MTX, biologics, or bucillamine and salazosulfapyridine. She developed soft tumor in her axilla. She was diagnosed IA-LPD at internal medicine. Spontaneous remission of LPD was obtained after cessation of DMARDS therapy. [Conclusion] RA itself and drugs for RA are considered to be risk factors for development of IA-LPD. The two cases obtained spontaneous remission of LPD after cessation of MTX or DMARDS, and achieved low disease activity for RA after tocilizumab therapy.

P2-077

RA activity was decreased after thymectomy for lymphofollicular thymic hyperplasia: a case report

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Conflict of interest: None

A 58-year-old woman had been treated RA and Sjögren's syndrome of for 11 years. She had been treated with methotrexate (6 mg/w), but polyarthritis was deteriorated two years before. Thorax computerized tomography for the purpose of screening of beginning biologics showed a mass at anterior mediastinum (4.3 x 1.8 mm). Follow-up had done with thoracic surgeon concurrently, etanercept (ETN) (25 mg/w) was started, but polyarthritis was continued. After 14 months, Thorax computerized tomography showed the mass growing up (4.4 x 2.0 cm). Pathologic finding of the tissue from thoracoscopic thymectomy was lymphofollicular thymic hyperplasia (LTH). Arthritic symptom improved soon after surgery keeping negative state of inflammation. Accordingly, methotrexate (MTX) was reduced to 4mg/w after 6 months, ETN was reduced to 25 mg/10d after 9 months, 25 mg/2w after 16 months. Evaluated histologic feature of LTH with RA showed large lymph follicles, including a number of follicular helper T (Tfh) memory B cells, which significantly increased compared with myasthenia gravis. Tfh cell seemed to regulate development of memory B and plasma cells. Reduction of MTX achieved with surgical intervention. Contribution of f LTH in RA was highly suspected in the disease activity of RA activity.

P2-078

Methtrexate-associated lymphoproliferative disorders which caused bilateral hydronephrosis in a patient with rheumatoid arthritis treated with tocilizumab and methotrexate

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Conflict of interest: None

Methotrexate (MTX) is one of the common cause of iatrogenic-associated lymphoproliferative disorder (LPD), and approximately 40-50% of MTX-related LPD cases occur in extranodal sites. We reported a case of rheumatoid arthritis (RA) undergoing MTX therapy who developed MTX-LPD. A 70-year-old man with rheumatoid arthritis had been treated with weekly low-dose MTX and tocilizumab for 5 years. He was pointed out bilateral hydronephrosis by medical examinations. CT examination revealed that the cause of bilateral hydronephrosis were bilateral retroperitoneal tumors. Biopsy specimens showed atypical lymphoid cell infiltration. Clonally rearranged immunoglobulin heavy chain JH gene was not detected by Southern blot analysis. He was diagnosed with lymphoplasmacytic proliferative lesion due to immunodeficiency caused by MTX administration. He was interrupted MTX therapy and had recieved a careful monitoring of tumor size in CT examination. Increased awareness is needed on the possible occurrence of LPD spontaneous remission following immunosuppressant discontinuation, after that it is therefore advisable to have a careful monitoring of the patient for some weeks, before starting cytotoxic therapy.

P2-079

Methotrexate-associated lymphoproliferative disorder (MTX-LPD) occurring in the testis of a patient with rheumatoid arthritis (RA)

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Conflict of interest: None

A 61-year-old man treated with MTX 8mg/week for RA since February 2007 was started on Infliximab (IFX) in June 2007, inducing remission. IFX was stopped in May 2008. In February 2011 RA was exacerbated and MTX was increased to 10mg/week with initiation of Abatacept from May 2011, leading to remission again. In December 2012, he was presented to the urology department complaining of left scrotal swelling. Left high ligation of testis was performed. Pathological examination revealed a diffuse large B-cell lymphoma (DLBCL) originating from the left testis. EBVDNA was negative. CS I A. From February MTX and ABT was stopped, and he underwent adjuvant chemotherapy consisting of R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristin, prednisone) with intrathecal chemotherapy for central nervous system prophylaxis and prophylactic radiotherapy to the contralateral testis. He had no evidence of recurrence. It is well recognized that patients of RA with MTX develop MTX-LPD, which cases often occur in extranodal sites like skin and gastrointestinal tract. However, the occurrence of MTX-LPD in the testis is extremely rare and we report this case with literal consideration.

P2-080

Predictive Factors of Beneficial Response of Iguratimod in patients with rheumatoid arthritis: A single center experience

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Conflict of interest: None

PURPOSE: To evaluate the efficacy of Iguratimod (IGU) and the factors predicting the response to IGU in patients with rheumatoid arthritis retrospectively. METHODS: Twenty three patients administrated IGU from November 2012 to October 2013 in our hospital were enrolled. DAS28-ESR, DAS28-CRP, SDAI, CDAI, mHAQ, EULAR response criteria were evaluated in fifteen patients available to observe for 12 week or more. RESULTS: The average age and duration of disease were 71.6 years old and 12.7 years, respectively. Seven patients had renal disorder and eight patients were associated with interstitial lung disease. In 12 weeks, DAS28-ESR and DAS28-CRP improved significantly from 5.06±0.91 to 3.62±0.93 ($p<0.01$) and 4.66±0.77 3.25±0.81 ($p<0.01$), respectively. Seven patients achieved low disease activity or less. Six patients were considered as moderate response (MR), whereas nine as no response (NR). No statistical significance was observed between two groups in age, duration of disease, disease activity at baseline, and rate of MTX medication. Serum IgG and CRP level at baseline was significantly higher in MR group. CONCLUSIONS: We observed effectiveness of IGU in clinical practice. It was suggested that serum IgG and CRP level at baseline may predict the response to IGU.

P2-081

Efficacy of increasing dose of methotrexate for elderly rheumatoid arthritis patients

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Conflict of interest: None

[Objectives] We investigated the efficacy of increasing dose of MTX for elderly rheumatoid arthritis (RA) patients. [Methods] We examined

36 cases of elderly RA patients (mean 71.5±4.5 years) whose MTX dose was increased to 10mg/w or more after 65 years old. [Results] Mean DAS28-CRP (4) was improved from 3.37±1.08 to 2.75±1.08 after 6 months (MTX dose was increased from 7.8±0.6 to 11.0±1.4mg/w). DAS28-CRP (4) was 2.71±10.6 after 12 months (n=26). DAS28-ESR (4) was improved from 4.14±1.09 to 3.41±1.13 after 6 months (n=34, p<0.01), it remained 3.36±1.10 after 12 months (n=26). Mean SDAI was improved from 14.12±8.25 to 10.16±7.31 (n=29, p<0.01). 33 cases used folic acid. One case reduced to 8mg/w again within 6 months due to insufficient effect. Within 6 months after dosing up of MTX, two cases started biologics, six cases started other DMARDs. 21 cases had used PSL when dosing up MTX, 24 cases used PSL 6 months later. In 15 cases who started MTX within 6 months before dosing up, mean DAS28-CRP (4) was improved from 3.25±0.91 to 2.47±0.99, but it was only improved from 3.46±1.21 to 2.97±1.12 in 20 cases who had taken MTX more than 6 months before dosing up. [Conclusion] Our data suggested the efficacy of increasing dose of MTX for elderly RA patients and early dosing up may be more effective.

P2-082

Clinical efficacy of the synthetic anti-rheumatic drug, iguratimod, for patients with rheumatoid arthritis

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Conflict of interest: None

[Objectives] Iguratimod (IGU) is newly synthetic DMARDs and under clinical use to the rheumatoid arthritis (RA) patients from 2012 in Japan. We examined the clinical effects of the IGU therapies for RA patients in our department. [Methods] Forty one (15 men, 26 women) patients to whom IGU were administerd, from September, 2012 to April, 2013 in our department, were included in this study. The clinical therapeutic process by 24 weeks after the initiation of IGU were analyzed (LOCF). The age of this cohort was 68.9±10.9 years old, and the disease duration 14.7 ±12.7 years. [Results] Before IGU treatment; CRP 1.4±1.7 mg/dl, ESR 51.2±27.9 mm/h, MMP-3 223.5±183.3 ng/ml, DAS28-ESR (4) 5.0±1.7, DAS28-CRP (4) 4.1±1.7, SDAI 25.8±19.7 and CDAI 24.4±19.1. MTX combination rate; 59.2%, the mean dose of MTX; 9.0±3.1mg/week, PSL combination rate; 52.4% and the amount of PSL; 4.9±2.6 mg/day. Twenty six cases continued the IGU therapies during 24 weeks; CRP 1.1±1.9 mg/dl, ESR 44.3±28.0 mm/h, MMP-3 208.1±255.2 ng/ml, DAS28-ESR (4) 3.9±1.4, DAS28-CRP (4) 3.0±1.3, SDAI 13.0±12.7 and CDAI 11.9±2.0. All parameters except for MMP-3 were significantly reduced at week 24 of the IGU therapy. [Conclusion] The IGU might clinically be one of the useful synthetic DMARDs to RA patient.

P2-083

Efficacy of Iguratimod in patients with rheumatoid arthritis treated without methotrexate

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Conflict of interest: None

[Objectives] Iguratimod (IGU) is a novel disease-modifying anti-rheumatic drug (DMARD) that has been shown to have an anti-inflammatory effect and inhibition of immunoglobulin production. In a clinical trial, IGU was not inferior to that of salazosulfapyridine (SASP) in patients with rheumatoid arthritis (RA) and efficacy in patients with RA treated with methotrexate (MTX). However, few studies have examined the efficacy of IGU in patients with RA treated without MTX in a routine care. In this study, we investigated the efficacy of IGU in patients with RA treated without MTX. [Methods] Patients treated without MTX and taking IGU for longer than 12 weeks were included, from the Nagoya university-affiliated hospital. We retrospectively reviewed the clinical data. [Results] Numbers of patients were twenty-four. Mean age was 69.9 years old and mean disease duration was thirty years. The reasons for inability to use MTX were adverse events of MTX and lung problem. Mean DAS28-ESR was 5.03 at baseline, and 4.32 at 12 weeks (p=0.053). EULAR good responses were 17%, and 33% had moderate responses. Drug retention rate were 87.5% at 12 weeks. [Conclusion] These data provide support for the possible use of IGU in patients with RA unusable of MTX.

P2-084

Education for patients who receive the full dose MTX treatment in the clinic

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Conflict of interest: None

[Objectives] We studied, from the viewpoint of nursing in the clinic, the risks and benefits of the full dose MTX treatment for the patients who inadequately responded to the conventional dose of MTX. [Methods] We examined 48 patients (6 males and 42 females) who received full dose MTX treatment about 1) DAS28 2) CRP 3) HAQ-DI 4) mTSS 5) the side effects. The average patient age was 51.3 years old (26-68), the average disease duration was 9.6 years (3-25). The patients were treated between May 2011 and Nov 2013 (3-30 months). We distributed booklets which described the emergency guidance and contact information to the patients. [Results] All the parameters (1-3) were improved by increasing the MTX dose. The progress in mTSS was not seen in 23 patients (47.9%). We found adverse effects occurred in 33.3% patients: severe 2 cases. [Conclusion] The symptoms improved capacity dependent manner by MTX Full dose administration. Side effects with caution because of side effects increase is expected over time in the future. I felt the need to reduce time lag of up to medical consultation from side effects generated to the prevention of further aggravation.

P2-085

***HLA-DRB1*08:02* is associated with bucillamine-induced proteinuria in Japanese rheumatoid arthritis patients: a case-control study**

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Conflict of interest: Yes

[Objectives] Bucillamine (Buc) is one of the commonly used disease-modifying anti-rheumatic drugs (DMARDs) in Japan. Drug-induced proteinuria can occur in rheumatoid arthritis (RA) patients treated with Buc, and represents a drug hypersensitivity reaction. Striking associations of human leukocyte antigen (HLA) alleles with adverse reactions have recently been reported for many drugs. [Methods] We investigated the association of HLA class II with Buc-induced proteinuria (BI-Pro) in 485 Japanese RA patients treated with Buc, of which 25 had developed BI-Pro. [Results] This study showed a highly significant association of *DRB1*08:02* with BI-Pro (P=1.09X10^{-6}, corrected P [Pc]=1.96X10^{-5}, odds ratio [OR] 25.17, 95% confidence interval [CI] 7.98-79.38). *DQB1*04:02* was also significantly associated with increased risk of BI-Pro (P=2.44X10^{-5}, Pc=2.69X10^{-4}, OR 10.35, 95%CI 3.99-26.83). [Conclusion] We detected striking HLA class II associations with proteinuria induced by Buc in Japanese RA patients. This association merits confirmation in future large-scale studies for its potential clinical usefulness as a biomarker to prevent adverse reactions.

P2-086

Efficacy and safety of Infliximab; dose escalation and shortening of interval in biologic-naïve rheumatoid arthritis patients with high disease activity

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Conflict of interest: None

Objectives: Infliximab (IFX) is used for treatment of rheumatoid arthritis (RA) patients with higher disease activity, adopting a strategy of dose escalation with shortening of the interval. We investigated the efficacy and safety of this strategy. *Methods:* Biologic-naïve RA patients who had been treated with methotrexate (MTX), and prescribed IFX or other TNF inhibitors at Niigata Rheumatic Center between July 2011 and July 2013 were enrolled. The patients' data were obtained retrospectively from their medical records. *Results:* Twenty-four patients who received IFX, and 74 patients who received other TNF inhibitors (adalimumab 32, etanercept 27, golimumab 13, and certolizumab pegol 2) were included in this study. There were no significant inter-group differences in patient background factors or dose of MTX and prednisolone. The IFX group had greater DAS28 (4) ESR (5.23 ± 0.98 vs. 4.48 ± 1.20; P=0.006). The follow-up period was 256 ± 214 days and the 8-week dose equivalent of IFX was 9.5 ± 4.0 mg/kg/8wk at the last visit. DAS28 (4) ESR improved from 5.23 ± 0.98 to 3.40 ±1.4 ($p<0.001$). *Conclusion:* IFX administered to RA patients with high disease activity and had a favorable clinical effect. IFX dose intensification and dose interval reduction were highly effective for them.

P2-087

Total joint arthroplasty due to the complicationrepetitive of on and off intra-articular bleeding associated with Iguratimod

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Conflict of interest: None

[Background] A new DMARD; Iguratimod (IGU) was released in 2012 and several reports showed good efficacy. However unexpected bleeding in combination with warfarin (WF) was reported, then combination use with WF is basically prohibited. We have experienced the recurrent intra-articular bleeding despite no use of WF after we started to use IGU. [Case report] A 69 year-old female who is affected rheumatoid arthritis for 10 years, achieved clinical remission with adalimumab. In 2012, colon cancer was detected from colon polyp, and then we had to give up adalimumab. We tried some other DMARDs but could not maintain remission. We started to use IGU from March in 2013. She recognized the knee joint swelling after walking in April and was diagnosed as intra-articular bleeding. Bleeding continued on and off even after we gave up using IGU. We found the synovium proliferation in MRI and tried the synovectomy, however bleeding continued. Moreover, an angiography did not show any vascular lesion. Finally, we performed the total knee arthroplasty. [Discussion] Ten cases were reported with unexpected bleeding associate with IGU by August in 2013, bleeding severely continued even IGU was stopped in some cases. We considered we should take care for the bleeding even if we use IGU without WF.

P2-088

Efficacy and safety of a novel disease-modifying antirheumatic drug, iguratimod, as an add-on therapy for patients with rheumatoid arthritis

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Conflict of interest: None

Objectives: We examined the efficacy and safety of iguratimod (IGU). *Methods:* RA patients who had been prescribed IGU as add-on therapy between September 2012 and April 2013 were enrolled. The patients' data were obtained retrospectively from their medical records. Patients involving discontinuation of IGU or treatment intensification were excluded from subsequent data collection, and missing data were imput by the Last-Observation-Carried-Forward method. The efficacy of IGU was evaluated at week 24. *Results:* Twenty-eight patients received IGU as add-on therpay. Five patients who discontinued taking IGU within one week were excluded and the other 23 were enrolled. These patients had a mean age of 65.6 ±12.4 years and a mean disease duration of 7.5±8.3 years. During the follow-up period, 4 patients required further treatment intensification, and 2 discontinued IGU because of pulmonary hemorrhage in 1 and malignant lymphoma in 1. DAS28 (4)ESR improved from 4.3±1.15 to 3.57±1.19 ($p<0.001$). Although IGU had limited effectiveness in patients with high disease activity in DAS28 (4)ESR, 6 patients achieved low disease activity and 4 achieved remission among 16 patients with moderate disease activity. *Conclusion:* IGU is effective for RA patients with moderate disease activity.

P2-089

RA threpy with 2 conventional DMARDs with or without Biological agents: the clinical feature of the Bio and non-Bio group

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Conflict of interest: None

[Objectives] The therapy guideline for rheumatoid arthritis (RA) showed that the high disease activity patients with poor prognosis need 2 DMARDs or biological agents (Bio). [Methods] We tryed to treat RA patiens within 2DMARDs firstly, then if we did not achieve the goal for RA therapy (achieved remission or low disease activity), treated with additonal Bio. We divided RA patients to 2 groups, to achieve goal for RA therapy with Bio as the Bio group, without Bio as the non-Bio group. [Results] During the patients achieved the goal for therapy, we finded 76 cases of the Bio group, 173 cases of the non-Bio group. We evaluated clinical features at the first visit in the both group. The age of onset was significantly lower in the Bio group (52.1±13.5 vs 60.3±15.4), DAS28 (4ESR) was significantly higher in the Bio group (5.06±0.88 vs 4.66±1.17). There was no significant difference for disease duration, RF, and CCP titer in both groups. In the patients with high disease activity 38.1% needed Bio. [Conclusion] Our data suggests that at the time of first visit, it is difficult to judge the need for Bio. It is recommended that RA patients are firstly treated within 2 DMARDs, then tryed with additional Bio.

P2-090

Transition of disease activity and persistency in infliximab (IFX) therapy

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Conflict of interest: None

[Objectives] To describe early and long term efficacy of IFX for RA patients in daily clinical practice. [Methods] 50 RA patients treated by IFX were examined. Changes of DAS28 (ESR) were evaluated by LOCF method. Drug survival rate was calculated by Kaplan-Meier estimates. [Results] DAS28 (ESR) were 6.04 at baseline. After 1, 2, 4, 8, 12, 24, 30, 36, 42, 48, 54, 60 months, DAS28 (ESR) were 4.16, 4.04, 3.91, 3.73, 3.83, 3.85, 3.97, 3.89, 3.78, 3.67, 3.74, 3.73, 3.72, 3.68, good/moderate response rate were 22/82%, 26/80%, 32/84%, 42/80%, 32/78%, 36/80%, 36/76%, 32/78%, 42/78%, 44/78%, 38/78%, 42/78%, 44/78%, 44/78%, DAS28 (ESR) remission/LDA achievement rate were 12/26%, 20/28%,

20/34%, 22/46%, 22/38%, 20/40%, 30/38%, 28/36%, 28/44%, 34/46%, 28/42%, 30/44%, 32/46%, 32/46%, cumulative persistency rate were 90%, 88%, 78%, 74%, 72%, 70%, 56%, 52%, 50%, 48%, 43%, 33%, 30%, 26% respectively. Good response rate and remission/LDA achievement rate continued increasing until 6 months, went up and down 6 to 24 months, and were maintained afterwards. Most of discontinuation occurred within 24 months. [Conclusion] In IFX therapy, adequate clinical effect was shown within 8 months, effect attenuation was seen after that. Remission was maintained for a long term in the ongoing cases.

P2-091

Comparison on good control group and poor control group in treatment of RA with infliximab

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Suita Municipal Hospital

Conflict of interest: None

[Objectives] This good group and bad group by examining the background, To consider relevant factors. [Methods] From Feburary 2006 To July 2013 A 22 Example. Men 5, Women 17. IFX age averaged 59.8 years old (19-82). when the final examination DAS28CRP As 2.7 Less than the good control group, 2.7 Over the poor controls and. IFX of anti CCP antibody, IFX RF, MMP-3, CRP, MTX at the introduction and final examination for amount of, PSL amount, DAS28CRP about examined. [Results] The good control 8 group 8, The poor 14group. When the age of each averaged 60.3 Years old, 58.9 Years old. IFX of anti CCP antibody positive rate was 85.7% (83.6 ~ 721), 83.3% (38.1~300<), RF positive rate of 85.7% (17-81), 83.3% (36 ~ 232), MMP-3 average 157.8, 257.2, CRP0.56, 2.53, MTX7.4 mg, 5.7 mg, PSL 2.2 mg, 4.5 mg, DAS28CRP3.64, 3.95, final examination when RF positivity 57.1 % (17 ~ 40), 77 % (48-139), MMP-3 Average 121.4, 247.5, CRP, 0.13, 2.88, MTX 6.6 6.4, PSL0.71, 3.46, DAS28CRP2.05, 3.79. [Conclusion] I Is a bad example when you deploy MMP-3 High, CRP Is high, Anti CCP Antibodies, RF That there was no difference in prevalence RF The number was higher in. Anti CCPantibody 721 is good control group. Final MMP-3, CRP, RFcould be indicators of therapeutic effects.

P2-092

The examination of S-DAI remission and adherence rate in the Rheumatoid arthritis treatment with biological agents

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Conflict of interest: Yes

[Objectives] To examine the efficacy and safety with 6 kinds of biological agents (Bio) in Rheumatoid arthritis (RA) patients. [Methods] We examined the outpatient number of RA, Bio users, clinical remission (S-DAI), and Biotherapy adherence by overveiwing of clinical record respectively since April 2012 to October 2013. According to these data, we analyzed efficacy and safety with 6 kinds of Bio. [Results] The number of RA was 233 (47 males and 187 females) and Bio user was 61, so that rate of Bio user was 26.0%. Each Bio user was 14 Eternercept (ETN), 15 Tocilizumab (TCZ), 15 Abatacept (ABT), 3 Infliximab (IFX), 9 Golimumab (GRI), and 1 Adalimumab (ADA). The remission and adherence rate was ETN 50/78%, TCZ 44/80%, ABT 35/82%, IFX 14/43%, GRI 57/100% and ADA 0/0%, respectively. The discontinuation by serious adverb events occurred 3 cases, including 1 virus eruption (IFX), 1 leg ulcer with infection (IFX), 1 interstitial pneumonia (ABT), [Conclusion] The therapy of GRI, ENT, ACT was good enough both remission and adherence rate. ETN therapy was the cheapest because weekly half dose of ETN was enough to maintain remission status with Japanese RA patients.

P2-093

Comparison examination between the patient satisfaction and disease activity after changing from the syringe type to the pen type of etanercept

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Conflict of interest: None

[Objectives] The pen type (PEN type) of etanercept (ETN) raised the convenience of the rheumatoid arthritis patient (RA) with impaired hands rather than the syringe type (SC type). We considered change of patient satisfaction and disease activity with change of a medication method. [Methods] In ten RA changed from SC type to the PEN type at our clinic in the period from July to November, 2013, we investigated 27 items on patient satisfaction by the questionnaire. We also considered a change of disease activity. [Results] PEN type is dominant over SC type in terms of easy nature, convenience, reliability, and safety. And PEN type was excellent in feeling nature, device property, painlessness, and a use intention. After changing to PEN type, the disease activity of RA improved. [Conclusion] A change from SC type to PEN type was made satisfactorily. PEN types dominate patient satisfaction and a disease activity of ETN injection. Since PEN type is used without being seen a needle, it led to mitigation of the mental burden by the fear of a needle. Meanwhile, since the pincushion prevention function is attached to the PEN type, mitigation of risks, such as infection is expected. PEN type usefulness was shown as a medication method of biologics.

P2-094

Efficacy of enhanced infliximab therapy vs switch to other boDMARD in incomplete response against infliximab among rheumatoid arthritis patients

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Conflict of interest: None

[Objectives] To examine the efficacy of enhanced infliximab (IFX) therapy and switch to other boDMARD, in incomplete responders with rheumatoid arthritis (RA). [Methods] We enrolled and classified all cases that received at least either one of treatments such as ≧1mg/kg dose escalation of IFX or shortening of interval infusion by ≧1 week (group I), switch to other boDMARD (group II), within 104 weeks after starting IFX. Efficay in each group was evaluated by ΔDAS28ESR after 8 weeks of intensive therapy. [Results] 20 patients (16 females, mean age 53 yo, 33 cases) were included. In group I (N=23), mean dose escalation of 15 cases was 2.0mg/kg, mean period shortening of infusion interval of 8 cases was 1.9 weeks. In all cases of group II (N=10), switch to other TNF blockers was performed. Each average of ΔDAS28ESR was -0.2 in group I, -1.6 in group II (vs group I, p <0.0001), respectively. There was no difference of corticosteroid and methotrexate dose before strengthening therapy in two groups. Mean DAS28ESR at start of intensive treatment was no significant difference in each group, but seemed to be higher in group II (5.1 in group I, 5.7 in group II). [Conclusion] Switch to other TNF blockers was more effective than enhanced IFX therapy.

P2-095

Evaluation of Extended-Interval Adalimumab Dosing

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Conflict of interest: Yes

[Objectives and Methods] Extended-interval adalimumab (ADA) dosing is difficult due to anti-drug antibody production. Before this phenomenon received particular attention, extended-interval ADA dosing was performed at our hospital depending on patients' wishes or their clinical characteristics. We included 50 rheumatoid arthritis (RA) patients treated with ADA at our hospital, and reviewed their characteristics, treatment efficacy, persistence rate, and drugs used concomitantly; we also assessed the potential for extended-interval ADA dosing in RA. [Results] The patients were divided into 2 groups: 40 mg ADA every other week and ADA not greater than 40 mg every 4 weeks. The corresponding

mean ages were 54 and 68 years; rates of concomitant methotrexate use were 84% and 63%; persistence rates after 1 year were 64.5% and 68.4%; and changes in Disease Activity Score 28 based on C-reactive protein were 4.47→2.97 and 4.29→2.58. Extended-interval dosing in older patients did not reduce treatment efficacy, and maintenance therapy was successful in 3 patients whose dosing intervals extended beyond 4 weeks from the middle of the treatment period. [Conclusion] Our results suggest the potential for extended-interval ADA dosing in older RA patients and for post-remission therapy.

P2-096

Transition of disease activity and persistency in etanercept (ETN) therapy

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Conflict of interest: None

[Objectives] To describe early and long term efficacy of ETN in daily clinical practice. [Methods] 39 RA patients treated by ETN were examined. Changes of DAS28 (ESR) were evaluated by LOCF method. Drug survival rate was calculated by Kaplan-Meier estimates. [Results] DAS28 (ESR) were 6.04 at baseline. After 1, 2, 4, 8, 12, 24, 30, 36, 42, 48, 54, 60 months, DAS28 (ESR) were 4.16, 4.04, 3.91, 3.73, 3.83, 3.85, 3.97, 3.89, 3.78, 3.67, 3.74, 3.73, 3.72, 3.68, good/moderate response rate were 22/82%, 26/80%, 32/84%, 42/80%, 32/78%, 36/80%, 36/76%, 32/78%, 42/78%, 44/78%, 38/78%, 42/78%, 44/78%, 44/78%, DAS28 (ESR) remission/LDA achievement rate were 12/26%, 20/28%, 20/34%, 22/46%, 22/38%, 20/40%, 30/38%, 28/36%, 28/44%, 34/46%, 28/42%, 30/44%, 32/46%, 32/46%, cumulative persistency rate were 90%, 88%, 78%, 74%, 72%, 70%, 56%, 52%, 50%, 48%, 43%, 33%, 30%, 26% respectively. Good response rate continued going up to 30 months, and were maintained afterwards. Remission/LDA achievement rate continued increasing until 36 months, slightly lowered after that. [Conclusion] In ETN therapy, minor/major clinical effect was shown within 1/30 months. Remission rate went on rising for a long term. Effect attenuation occurred gradually after 10 months.

P2-097

Cooperation of the hospital and polyclinic for rheumatoid arthritis treatment in Yamagata area (YARANNA network)

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Conflict of interest: None

[Objectives] Many rheumatoid arthritis (RA) patients have to continue the treatment because most of them are not reached total and drug-free remission yet, even using biologics. They gathered for the new treatment in the central hospital in their local area because of potent of free access to any medical facilities in Japan. [Methods] We organized the hospital and polyclinic cooperation (referral system) in Yamagata area (Yamagata Area Rheumatoid Arthritis Neo Noticeable Associated Network; YARANNA network) and questionnaire survey. [Results] We received forty-one replies (89%) for our questionnaire. All facilities agreed the importance of foundation of the hospital and polyclinic cooperation. Fourteen facilities have the subcutaneous biologic agents and two have the intravenous agents. [Conclusion] It is important that rheumatoid patients have their own family doctor and expert doctor in their areas for their long therapy.

P2-098

Usage experience of Golimumab 100mg without MTX towards elderly RA patients

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Conflict of interest: None

[Objectives] We examined the effectiveness and the safety of Golimumab 100mg towards six elderly RA patients who cannot use MTX at our hospital. [Methods] The subjects are six RA patients who have been introduced to Golimumab (GOL) during the period of March 2012 and October 2013. The patients'background is as follows; they are all female with an average age of 74.0 and an average disease duration of 17.5 years, and are all unable to use MTX. Three patients used PSL (average dose: 2.0mg/day). All subjects were naive to biological treatment. We examined disease activeness using SDAI at 12w and 24w after introduction. [Results] At 24w, all six patients continued GOL, thus the continuity rate was 100%. We did not find any side effects related to kidney function disorder or respiratory diseases which were the reasons of not being able to use MTX. Average SDAI was 26.5 before tretment and significant improved to 9.59 at 12w (P=0.0076) and to 6.85 at 24w (P=0.0015). Average patient VAS was 7.08 before treatment and significant improved to 3.17cm at 12w and to 2.67cm at 24w, and significant improvement was observed (P=0.00019). [Conclusion] Although continual observation is necessary, safety and effectiveness can be expected with GOL 100mg monotherapy towards elderly RA patients.

P2-099

Narratives of the patients with rheumatoid arthritis who receive etanercept in different delivery systems - reportage from Hokkaido

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Conflict of interest: None

[Objectives] Rheumatoid arthritis (RA) patients who are treated with etanercept in Hokkaido. [Methods] We apply four different etanercept delivery systems: 25 mg vial, 25 mg pre-filled syringe, 50 mg pre-filled syringe and 50 mg pre-filled pen. Narratives of the patients with RA who receive etanercept in these four systems are reported and discussed here. [Results] High patient satisfaction was achieved in each of four systems. These systems were seldom confused, because we distinctly recignised that there were four different delivery systems. No patient reported serious adverse events. [Conclusion] Narratives of the patients have been rarely reported. These narratives here reveal that the patients with RA wish the various administration of etanercept, including self-administration or intra-articular administration.

P2-100

Narratives of the patients with rheumatoid arthritis who receive etanercept in different delivery systems - reportage from Ehime

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Department of Orthopaedic Surgery, Juzen General Hospital, Ehime, Japan

Conflict of interest: None

[Objectives] Rheumatoid arthritis (RA) patients who are treated with etanercept in Ehime. [Methods] We apply four different etanercept delivery systems: 25 mg vial, 25 mg pre-filled syringe, 50 mg pre-filled syringe and 50 mg pre-filled pen. Narratives of the patients with RA who receive etanercept in these four systems are reported and discussed here. [Results] High patient satisfaction was achieved in each of four systems. These systems were seldom confused, because we distinctly recignised that there were four different delivery systems. No patient reported serious adverse events. [Conclusion] Narratives of the patients have been rarely reported. These narratives here reveal that the patients with RA wish the various administration of etanercept, including self-administration or intra-articular administration.

P2-101

Golimumab–Analysis of 48 cases in this hospital–

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Conflict of interest: None

[Purpose] We reported in the last JCR meeting on an intractable and multi-drug resistant RA patient who markedly responded to golimumab (GLM) at 100 mg. We further analyzed the efficacy and safety of GLM in this hospital. [Result] We treated 48 patients between the launch of GLM and the end of Oct. 2013 (10 males, 38 females; Age 30–49 years, 27%; 50–69 years, 58%; 60–69 years, 27%; 70–79 years, 13%; and 80–89 years, 2%). Medication with biologics was absent in 45% and present in 55% before GLM. MTX was concomitantly used in 37 cases (73%), and the dose was 10–16 mg/W in 25%. Prednisolone was given at ≥5 mg/day in 43%, a higher rate than the standard level in this hospital. The GLM-treatment was discontinued in 11 cases (23%) because of ineffectiveness in 5, phlegmon in 1, malaise in 1, interstitial pneumonia in 1, and hospital transfer or financial reasons in 3 cases. The mean DAS-ESR scores were 3.88 and 4.68 before treatment and 2.48 and 2.82 after 52 weeks in the 50-mg and 100-mg GLM groups, respectively. [Conclusion] GLM was frequently administered to intractable and treatment-resistant RA patients in this hospital. The outcome was favorable and the continuation rate was high. Subcutaneous GLM once in 4 weeks seems to be a favorable treatment even in intractable patients.

P2-102

Long-term follow up of infliximab in RA

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Conflict of interest: None

[Purpose] To elucidate the clinical effects and survival rates of infliximab (IFX) on 160 cases with RA. [Method] Twenty male and 140 female RA patients were treated with IFX between 2004 and 2013. The mean age was 59.7 years old, the mean duration of disease was 15.8 years. The mean serum level of CRP was 2.76 mg/dl, ESR was 49.0 mm/h, and DAS28-ESR 5.4 at the time of initiation. The mean dosage of prednisolone was 4.82 mg/day. All patients were naïve to biologics. [Result] Among 160 patients, 50 escaped from our follow-up because of transfer or death. Seventy patients (44%) discontinued IFX, because of primary or secondary failure in 39 (24%), adverse effects in 18 (11%) and onset of other disease in 7 (4%). Forty patients (25.0%) continued IFX. At the final observation, the mean DAS28-ESR was 2.93. Twenty three patients achieved remission or low disease activity and 9 patients were free of IFX after remission. Ten patients could continue IFX by dose escalation or shorting of dosing interval. Five-year survival rate rose from 45% to 70 % after 2009 when dose escalation was approved. [Conclusion] Whereas some patients showed inadequate response to IFX, the survival rate improved after dose-escalation was approved. Nine patients achieved IFX-free.

P2-103

Experience in the use of infliximab (IFX) in our clinic

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Conflict of interest: None

[Purpose] To investigate the continued IFX therapy of RA [Method] We investigated 40 cases (8 M, 32 F) treated with IFX after 2003 in our clinic. The Steinbrocker stage I, II, III and IV were 1, 9, 19 and 11 cases, respectively. [Result] Of 40 cases, 19 continued therapy of IFX, 7 had bio-free status and 14 were withdrawn. Of the continued therapy cases, 10, 7 and 2 required usual dose (3 mg/kg), 4-6 week reduction of dosing period and dose increase (6 mg/kg), respectively; and, 11 had inflammation signal by joint echography and required the injection of triamcinolone acetonide (TA) 40 mg into the painful joints. Of the 11 cases, 6 were the usual dose (3 each of the stages III and IV) and 5 were the reduced-period/ increased-dose (4: stage III, 1: stage IV). The IFX effect persisted after injection into the painful joints and by the reduced- period (2 of 3 in the stage II cases). Of 14 withdrawal cases, 9 had attenuation of effect despite increased dose and reduced-period, 2 and 3 were due to allergy and malignant tumors, respectively. [Conclusion] The disease activity could be controlled by reduced- period/increased dose of IFX for moderately active cases, and by addition of TA injection into the painful wrist, knee, shoulder, elbow and foot joints for severe progressive cases.

P2-104

Efficacy of golimumab after infliximab failure in patients with active rheumatoid arthritis

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Conflict of interest: None

[Objectives] To evaluate efficacy of golimumab (GLM) after infliximab (IFX) failure in patients with active rheumatoid arthritis. [Methods] A man and eight women were included in this study. The mean age was 56.3 years old at switching to GLM. Efficacy of GLM was evaluated using DAS28-ESR and DAS28-CRP at initiation of GLM, after 4week and 12week. The reason of switching from IFX to GLM was also investigated. [Results] The mean DAS28-ESR at 0w, 4w and 12w was 3.74, 3.01 and 2.65 and that of DAS28-CRP was 3.08, 2.31, 2.06, respectively. Significant decrease in DAS28-ESR and DAS28-CRP was seen at week 4 and week 12 compared with baseline value. While GLM was ineffective in one case, another one experienced side effects after switching to GLM. The reasons of switching from IFX to GLM was ineffectiveness (n=6), side effects (n=2) and other (n=1). Even after infusion reaction of IFX, GLM was well-tolerated. Although GLM was discontinued in 2 patients, DAS28 was significantly decreased in other patients. [Conclusion] It was suggested that GLM was one of the good option in RA patients of IFX failure.

P2-105

Case report: biological treatment in early rheumatoid arthritis

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Medical Corporation Matsui Orthopedic Clinic

Conflict of interest: None

[Objectives] To examine the efficacy and safety of biologics with rheumatoid arthritis (RA) patient within 6 months after the onset in our hospital. [Methods] 14 cases of RA patients started biological treatment within 6 months after the onset and the treatment with biologics for more than six months (IFX 9 cases, ADA 3 cases, GOL 1 case, TCZ 1 case). Mean age was 51 years old, Stage & Class was 1 in all cases and the mean MTX dose was 6.7mg / w. [Results] With the exception of 1 case of discontinuation due to adverse events, 13 cases are treated continuously. Average DAS28 (CRP) decreased after administration to 1.37 from the administration before 3.89, and 12 cases (92.3%) achieved clinical remission. In addition, 4 cases achieved bio-free remission, and among these patients, 1 case could stop all drug treatment as drug-free remission. The other 8 patients on the treatment with biologics reached to the deep remission as below 1.9 in DAS28 and bio-free is expected. [Conclusion] Introducing biologics at an early stage of six months disease duration, it was possible to obtain a high response rate in remission and achieve not only bio-free remission but also drug-free.

P2-106

The treatment after remission inducing by Biologics in rheumatoid arthritis

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Conflict of interest: None

[Objectives] To evaluate treatment after biologics withdrawal of patients with rheumatoid arthritis in clinical remission [Methods] Eleven of 30 cases in remission defined as ACR/EULAR, led to discontinue treatment with biologics, were analyzed about DAS28 (3)CRP, RF, MMP-3 at time of induction of biologics and time of withdrawal, clinical course after discontinue of biologics, treatment if relapsed and others. [Results] Biologics discontinued were 6 infliximab 5 etanercept. At the time of induction of biologics, DAS28 (3)CRP, RF (*IUmL*), MMP-3 (*ng/mL*) were by each 3.20~5.04 (avg.4.00), 9.5~538 (avg.113), 60.5~654 (avg.288), at the time of withdrawal were 1.22~1.93 (avg.1.50), 9.8~387 (avg.59.4), 10.0~54.2 (avg.37.1). 6 cases were maintained remission but 5 cases were relapsed after stopping usage of biologics. The duration from withdrawal to relapse were one month to 24 months (avg.7.3). All of 6 cases were treated by the same biologics. 5 cases were in clinical remission again but one needed other biologics. [Conclusion] Relapse rate of withdrawal in clinical remission were almost same as another study. It was possible to discontinue etanercept tend to relapse. From a point of view of side effect from long-term administration, it might be meaningful to reduce usage of biologics.

P2-107

Clinical evaluation in RA patients treated with etanercept (ETN) in orthopedic clinic

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Conflict of interest: None

The patients with ETN therapy for more than 1 year in clinic were examined. They were 6 men and 38 women with average age 58.6 years and average mean disease duration was 13.5years. 32cases were treated with ETN combined with MTX. 39 patients are Naïve cases, 5patients are switch cases. 33 sugical treatments (synovectomy, hand and foot reconstruction) in 16 cases with ETN therapy were performed. The mean DAS28-CRP score changed from 5.99 at baseline to 2.66 at 24 weeks. Disease activity evaluated by DAS28-CRP was moderate 4, low 5, remission 16 at evaluated endpoint. The retention rate was 81.7% at 3years, 74.6% at 5years. Synovectomy for painful joint could to improve the retention rate of ETN therapy. ETN therapy to RA patients seems to effective and safe in orthopedic clinic.

P2-108

Effectiveness of switching Biologics in patients with Rheumatoid arthritis

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Conflict of interest: None

【background】many RA patients improved with 7 types of Biologics nowadays, but some patients has little effect Remission in an early stage prevents joint destruction, so we should focus on switching to other Biologics.【Objectives】RA patient at our hospital. we assessed effectiveness of switching biologics activities of diseases before and after switching and reasons for switching【Methods】we assessed patients with RA at our hospital using Biologics. We retrospectively evaluated patients who could be observerd for more 3 month. We assessed the selective bias of switching in 24 Patients with RA (47Switching).【result】Average age was 67yo, disease duration 8.3y, CDAI score 19, DAS28 (ESR) 4.3, and DAS28 (CRP) 3.3 at the start point. Bioloigics included anti- TNFalpha at 81% before swithcing. Biologics after swithing included a-TNFalpha at 57%. The choice of Biologics was not associated with the above backgrounds, but non-TNFalpha occupied 75% after switching. Almost all patients were improved after 6months. We selected Biologics not by patients age, disease duration, activity and sex.

P2-109

RA therapeutic effect of early intervention with adalimumab (ADA) in low-dose MTX combination

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Conflict of interest: None

[Objectives] In analyzing the clinical effect of low dose MTX combination with Adalimumab (ADA), we report early treatment with ADA plus low-dose MTX and achievement of clinical remission in biologics naïve patient. [Methods] Criteria on a 24-week disease duration and ADA administration (40mg every other week) in combination with low-dose MTX (4mg ~ 6mg). Disease activity was analyzed with CRP, ESR, MMP-3, VAS, and DAS28. [Results] In total 64 patients, 41 cases were included in the continuation. 4 cases were matched with the criteria and reached to the clinical remission in ADA therapy with low-dose MTX. Patient background was biological naïve, disease duration 6 month, MTX dose 4 ~ 6mg, Stage I ~ III, Class I ~ II, average 70 years old. DAS28 in RA patients baseline was 6.80 to 4.59, and ADA treatment with the low-dose MTX achieved remission after four weeks. Other biological naïve RA patients with DAS28 (6.45 to 6.80) achieved a remission within three to six months. Low-value of CRP, ESR, VAS, and MMP-3 was associated with the achievement of clinical remission in over time-course. [Conclusion] In RA patients with high disease activity, if biological naïve patient is applied by the early treatment with ADA, the rapid clinical remission can be achieved in combination with low-dose MTX.

P2-110

Efficacy study of adalimumab in RA patients

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Conflict of interest: None

[Objectives] Adalimumab (ADA), among other biological agents, is available in a self-injectable form requiring low dosing frequency, hence having the advantage of adjustable visit intervals. We examined clinical responses to ADA therapy. [Subjects and Methods] Fifteen patients treated with ADA since November 2008 at our department were studied. Mean age was 53 years and mean illness duration was 12 years. Assessment parameters were clinical and physical-functional evaluations. In 6 patients receiving ADA for at least 3 years, in particular, mTSS and joint ultrasonographic findings were also appraised by imaging evaluation. [Results] The DAS28-CRP score showed low disease activity in 70% of the patients studied. The percentage showing structural remission (mTSS <0.5/year) was 67%, 83%, and 100% at 1, 2, and 3 years of ADA treatment, respectively. The PD score on joint ultrasonography was grade 0, 1, 2, and 3 in 4, 1, 1, and 0 patients, respectively, at 3 years of ADA therapy. [Conclusion] ADA treatment improved clinical and physical-functional assessments and, particularly in patients treated for 3 years or longer, suppressed structural deterioration with joint ultrasonographic evidence of reduced disease activity.

P2-111

Efficacy of Golimumab in patients with rheumatoid arthritis. -Analying QOL obtained by SF-36v2-

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Conflict of interest: None

[Purpose]: Effect of Golimumab (GLM) on rheumatoid arthritis (RA) was evaluated. **[Methods]:** Naïve was defined as RA patients receiving GLM as first biologics (bio). Switch was composed of RA patients given GLM because of invalid to other bio. Efficacy of GLM received during 15 months (mo) was assessed by indicators of disease activities. Quality of daily live (QOL) was measured by SF-36v2. **[Results]:** Subcutaneous infection occurred in 2 patients of switch and other 2 patients became ineffective for GLM after 4mo administration. In these RA patients GLM was discontinued. In 6 naïve patients treated with GLM, DAS28-CRP was 3.6 at baseline and was decreased to 2.1 at 15 mo. Value of SDAI was 26.5 at baseline and reduced to 6.9 at 15mo. Disease activity was not improved in switch. After 15 mo medication of GLM, three component summary scores (3 CSS) of SF-36v2 showed values of 22.1 in PCS, 46.8 in MCS and 41.5 in RCS, those were closer to Japanese standard values as compared to levels of 22.1 in PCS, 46.8 in MCS, 41.5 in RCS of RA patients not receiving bio. **[Conclusion]:** Usefulness of GLM was found in naïve receiving for 15 mo but was not recognized in switch It was suggested that therapy with GLM could improve QOL, especially 3CSS of RA patients to Jananese standard values in SF-36v2.

P2-112

The investigation of patients treated with Etanercept (ETN) in Akita Cohort in 2013

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Conflict of interest: None

[Objectives] To investigate the patients treated with etanercept (ETN) who registered with the Akita Orthopedic group on Rheumatoid Arthritis (AORA). [Material and Methods] 242 patients were treated with ETN who registered with AORA in 2013. Of these, 208 patients were comprised the subjects of the present study. [Results] The patient characteristics were as follows: there were 37 males and 171 females, the mean age was 62 years and the mean disease duration was 180 months. ETN had been administrated with a mean duration of 33 months. One hundred and fifty-one patients had been prescribed methotrexate (MTX) with a mean dose of 7.0 mg, and 101 patients had been prescribed a steroid (PSL) with a mean dose of 3.8 mg. The DAS28ESR (4) could be calculated in 179 patents, and the mean was 3.14. One hundred and fifty patients could continue ETN treatment during the investigation with a mean duration of 38 months. The mean DAS28ESR (4) was 3.05 as calculated in 128 patients. Fifty-eight patients could not continue ETN treatment during the investigation with a mean duration of 20 months. They were unable to continue ETN treatment, because of a decreasing effect, financial reasons and so on.

P2-113

Trends among patients using infliximab (IFX) from data registered in the Akita Orthopedic Group on Rheumatoid Arthritis (AORA) database

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Conflict of interest: None

[Objectives] To investigate trends among patients using IFX from data registered in the AORA database. [Methods] Background at the initiation of treatment, treatment continuation rate, and treatment effects were investigated for a total of 132 patients (females, 77.3%; mean age at initiation of treatment, 58 years; mean duration of illness, 10.3 years; mean PSL dose, 4.2 mg; mean CRP level, 2.46 mg/dl; mean MMP-3 level, 260.3 ng/ml) given IFX who were registered in the AORA database before the end of July 2013. [Results] DAS28-CRP was able to be assessed at the initiation of treatment for 86 patients (mean score, 4.52). The cumulative IFX continuation rate was 81.5% and 48% after one and three years, respectively. IFX was discontinued in 82 of 132 patients; the main reasons included insufficient response (n=28), adverse events (n=27), and remission (n=4). IFX was continued in 47 of 132 patients (mean continuation period, 3.7 years). Among patients continuing IFX, the mean PSL dose had been reduced to 1.7 mg at the time of the final survey, with reductions in CRP and MMP-3 to a mean of 0.56 mg/dl and 71.8 ng/ml, respectively. DAS28-CRP decreased to a mean of 2.38, and was <2.3 in 52.3% of patients. [Conclusion] We reported trends among patients using IFX from the AORA database.

P2-114

Clinical efficacy and safety in patients with rheumatoid arthritis in our hospital after Japanese clinical trials of Certolizumab Pegol

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Conflict of interest: None

[Objective] To evaluate efficacy and safety of certolizumab pegol (CZP) with rheumatoid arthritis (RA) patients in our hospital after Japanese clinical trials. **[Methods]** Two clinical trials, the J-RAPID study (concomitant MTX) and the HIKARI study were conducted until March this year in Japan, subsequently we evaluated its efficacy and safety. **[Results]** Ten patients (3 males, 7 females) in our hospital, 6 patients of J-RAPID study and 4 patients of HIKARI study (without MTX) were entered, average age at entry was 50.2 years old, duration of RA was 5.6 years, 4 patients were administered prednisolone, 4 patients DMARDs (other than MTX) during the clinical trials (142-184 weeks). At the end of the clinical studys, 9 of 10 patients were maintained clinical remission. By 13-30 weeks after clinical trials, 7 patients of remission were CZP-free, 2 patients were continued to administration of CZP and one was registered to other clinical study due to worsening of RA. Purulent lesion of toenails, headache and nausea, pharyngitis and mild pneumonia occurred one by one each. **[Conclusion]** Seven of 10 patients maintained CZP-free (3 patients of MTX were dose-escalated, one was added tacrolimus), 2 patients of continuation of CZP also maintained remission without change of DMARDs in our hospital.

P2-115

Efficacy and safety of adalimumab + MTX in RA patients who had not previously received MTX

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Conflict of interest: None

[Background] The recent approval enabled ADA to be used to patients with rapid progression of structural damage, even if they had not had previous treatment. [Objectives] To investigate efficacy and safety of ADA + MTX in patients who had not previously received MTX or biologics. [Methods] 3 patients with RA were reviewd retrospectively. [Case1] A 33-year-old-female, disease duration 11 months, Stage II, DAS28-ESR 4.53, SDAI 13.9, ACPA positive, RF positive, MTX8mg/w. ADA was discontinued at week 7 due to the lack of efficacy. [Case2] A 80-year-old-female, disease duration 9 months, Stage II, DAS28-ESR 4.96, SDAI 19.4 at baseline, ACPA positive, RF positive, MTX6mg/w. At week 4 DAS28-ESR 2.36, SDAI 4.17, at week 12 DAS28-ESR 2.14, SDAI 0.95. The clinical remission had been maintained for 2 years. [Case3] A 38-year-male, disease duration 4 months, Stage II, DAS28-

ESR 5.85, SDAI 28.36 at baseline, ACPA negative, RF negative, MTX-8mg/w. He achieved clinical remission at week 8, DAS28-ESR 1.17, SDAI 1.42, and the clinical remission had been maintained for 1 year and 6 months. Adverse events were not observed in these 3 cases. [Conclusion] ADA in combination with MTX was tolerated and efficacious in RA patients who had not previously received MTX or biologics.

P2-116

Survey of the Status of Use of Biological Preparations to Treat Rheumatoid Arthritis Patients in our Institution (forth report)

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Conflict of interest: None

[Objectives] We conducted a survey on the status of use of six biological preparations to treat rheumatoid arthritis in our institution. [Methods] Biological preparations were used to treat 140 cases, and consisted of Infliximab (INF) in 68, Etanercept (ETN) in 66, Tocilizumab (TCZ) in 45, Adalimumab (ADA) in 15, Abatacept (ABA) in 10, and Golimumab (GLM) in 19 cases. [Results] Treatment was discontinued in 9 INF cases, 19 ETN, 7 TCZ, 4 ADA, 3 ABA. Treatment was switched to another drug in 36 INF cases, 24 ETN, 9 TCZ, and 9 ADA, 4 ABA, and 2 GLM. Cases in which more than one drug was used because of attenuated or inadequate efficacy or adverse events consisted of one case in which 5 drugs were used, 5 cases in which 4 drugs were used, 13 cases in which 3 drugs were used, and 38 cases in which 2 drugs were used. The longest periods of use were: INF, 9 yr 5 mo; ETN, 8 yr 3 mo; TCZ, 6 yr 3 mo; ADA, 4 yr 11 mo; ABA, 1 yr 8 mo; GLM, 1 yr 9 mo. Administration was discontinued because of infection in 14 cases, one case was died. [Conclusion] Attenuation or inadequate efficacy and adverse events were observed with the biological preparations, and in the future it appears necessary to adjust the dose, dose interval, etc., of each of the drugs.

P2-117

Comparison of inhibitory effects to the damage progression of the joints among TNF inhibitors, etanercept, infliximab, and adalimumab

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Conflict of interest: None

[Objectives] This study was performed to examine the inhibitory effects to the damage progression of joints in the long-term affected patients with RA among infliximab (IFX), etanercept (ETN), and adalimumab (ADA). **[Methods]** ETN, IFX, and ADA were respectively administered to 61, 23, and 21 outpatients with RA who could be followed for more than 1 years by X-rays of the hands. The average ages at the start of treatment were 54.4 (ETN), 51.7 (IFX), and 56.7 years (ADA), and the periods from diagnosis to the start of treatment were 12.3 (ETN), 9.9 (IFX), and 10.6 years (ADA). We measured m-TSS of X-rays of the hands around the start of treatment and the latest X-rays during the follow-up period and compared the difference among TNF inhibitors. **[Results]** ⊿m-TSS of ETN, IFX, and ADA were +4.9, +1.0, and +8.6 points, respectively in the total score, and +3.6, +1.7, and +6.7 points, respectively in the joint space narrowing score, and +1.3, -0.7, and +1.9 points, respectively in the erosion score. **[Conclusions]** The damage progression of the hands in the long-term affected RA patient was not suppressed by TNF inhibitors. However IFX only shows the little damage progression to joint space narrowing and erosion of the hands compared with ETN and ADA.

P2-118

A case of rheumatoid arthritis complicated with organizing pneumonia during not only infliximab but also etanercept treatment

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Conflict of interest: None

A 57-year-old woman was diagnosed with rheumatoid arthritis in July 2006 on the basis of polyarthritis and presence of rheumatoid factor. She had persistent synovitis despite treatment with MTX, therefore infliximab was added in February 2009. She developed dry cough and right anterior chest pain a week before 3rd infusion of infliximab. Chest radiograph and chest computed tomography revealed multiple subpleural consolidation with air bronchogram. She was treated with antibiotics without any improvement of her conditions. The culture of bronchoalveolar (BAL) fluid was negative for any pathogens. The specimen of transbronchial lung biopsy (TBLB) revealed intraluminal polypoid fibrosis and lymphocytic alveolitis. So we diagnosed organizing pneumonia (OP). She was treated with PSL 30 mg/day, and then her symptom and chest radiography were improved. However, her arthritis was exacerbated with decreasing of PSL despite addition of MTX, therefore etanercept was added in January 2010. Her synovitis was improved. In August 2013, she suffered from general fatigue with active arthritis. Chest radiography revealed multiple infiltrates in the bilateral lung. We diagnosed OP on the basis of the results from BAL and TBLB. She was treated with PSL 30 mg/day, and then her condition was improved.

P2-119

The questionnaire for the patient who changed to the Penn type from syringe type of the etanercept

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Conflict of interest: None

[Objectives] The syringe type by myself-injection of etanercept was put on the market and played the important role in the medical treatment of Rheumatoid Arthritis (RA). The Penn type of automation was put on the market and medical treatment was using a syringe type or the Penn type as self-injection. For RA patient, it was unknown about whether there is any merit of switched pen type. We performed the questionnaire for the patient who changed to the Penn type from syringe type on the etanercept [Methods] The questionnaire was distributed and investigated from the syringe type patients who switched to the Penn type from syringe type. Consultation period was from September, 2013 to November, 2013. [Results] While 40% of patients answered that Penn type was easy, 30% of patients answered that syringe type was eas. Moreover, while 50% of patients answered that the Penn type was better about the infusion rate, 40% of patients answered that the syringe type was better. [Conclusion] Although convenience of change from the syringe type to the Penn type was improving by many patients, the opinion that the syringe type is better was also seen. Now, accumulation and factor analysis of the further data are conducted, and it unites and announces also about them.

P2-120

A case of rheumatoid arthritis complicated by dermatomyositis after administration of adalimumab

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Conflict of interest: None

<Introduction> The prognosis of rheumatoid arthritis has been remarkably improved by introduction of biologic agent. However, it is necessary to decide the indication by considering various adverse reactions. We report a case of rheumatoid arthritis that was complicated by dermatomyositis after administration of adalimumab (ADA). <Case> A 42 year-old woman. She was diagnosed as having rheumatoid arthritis in

April 2012 and was given methotrexate (6mg/week). Because her symptoms did not improved, despite increase of the dose (10mg/week), ADA started in April 2013. However, erythema on the face and Gottoron`s signs appeared 26 days after the start of ADA when she felt mild muscle weakness. Blood test showed elevation of the serum CPK (317IU/L) and aldolase (18.6U/L) and electromyography showed myogenic change. She was diagnosed as dermatomyositis. Given the possibility of the adverse reaction of ADA, it was discontinued and prednisolone (0.8mg/kg/day) started. Thereafter, fever, muscle weakness and rash gradually improved. <Discussion> Although rheumatoid arthritis might have been simply complicated by dermatomyositis, the latter could be an adverse reaction of ADA. Therefore it was thought necessary to pay attention to appearance of other autoimmune diseases during the Anti-TNF-α therapy

P2-121

Good disease control by bimonthly treatment with GLM and TCZ on 4 RA patients with insufficient efficacy despite TCZ

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Conflict of interest: None

[Objective] We investigated efficacy and safety of bimonthly treatment with Golimumab (GLM) and Tocilizumab (TCZ) on Rheumatoid Arthritis (RA) patients with insufficient efficacy despite TCZ. [Methods] We treated GLM and TCZ bimonthly for 4 RA patients (mean age: 50.4, mean duration: 8.9 years) with insufficient efficacy despite TCZ. in our clinic. [Results] Case 1 (female, age: 56, duration: 7 years, previous biologics: Etanercept): Bimonthly treatment was started at about 5 years after switching to TCZ. At 8 months after GLM treatment, CRP (0.02 to 0.02) and MMP-3 (10 to 27) were maintained low values. Case 2 (female, age: 72, duration: 11 years, previous biologics: Etanercept and Adalimumab): Bimonthly treatment was started at about 2 years after switching to TCZ. At 6 months after GLM treatment, RF (0.01 to 0.02) was decreased moderately. CRP (0.01 to 0.02) and MMP-3 (39 to 44) also were maintained a normal range. Now, these 2 patients have been controlled their disease activity without adverse events by bimonthly treatment. [Conclusion] We confirmed the efficacies and safety of bimonthly treatment with GLM and TCZ on RA patients despite TCZ, by suppressing a cytokine balance between TNF and IL-6. On annual meeting, we will show long term efficacies and safety of all 4 patients.

P2-122

Development of membranoproliferative glomerulonephritis (MPGN) during Etanercept (ETN) therapy for rheumatoid arthritis (RA)

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Conflict of interest: None

A 72-year-old man treated with MTX for RA and Sjogren' syndrome since July 2010 was started on ETN in September 2011, inducing remission. ETN was discontinued in September 2012. But in February 2013 ETN was restarted for the reason of his RA flare. In May, urinalysis revealed 1+ protein and 2+ heme. Serum creatinine was elevated to 1.1 mg/dl from 0.8 mg/dl and MTX was reduced to 6mg/week. In September, urinalysis revealed urinary protein excretion 2.6g/day and red blood cell casts. Serum albumin was 2.0 g/dl. Serologic tests revealed positive ANA (1:320, speckled and homogenous pattern), anti SS-A antibody. Both complement C3 and C4 were decreased. Tests for anti SS-A, ds-DNA, Sm, RNP, cardiolipin, GBM antibody and p-ANCA, c-ANCA, cryoglobulin were negative. Considering drug induced renal injury, ETN was stopped. Renal biopsy leaded to the diagnosis was MPGN. After stopping ETN, urinary protein excretion declined to 0.2g/day without treatment. This case is considered as ETN induced nephritis because it was developed after ETN therapy beginning and improved after ETN therapy withdrawal. The occurrence of nephritis induced by ETN without SLE and vasculitis is extremely rare and we report this case with literal consideration.

P2-123

A case of successful pregnancy and childbirth in a rheumatoid arthritis patient treated with etanercept

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Conflict of interest: None

[Introduction] We experienced a patient with rheumatoid arthritis (RA) who had a normal delivery under Etanercept (ETN) treatment. [Case reports] Without improvement with methotrexate (MTX) (10 mg/week, p.o.) and Predonine (5 mg/day, p.o.), a 24 year-old-woman started ETN 25mg subcutaneously twice weekly. She experienced complete remission of RA and her dose was decreased to MTX 4 mg/week and Etanercept 25mg/week and without predonine. We stopped MTX and added bucillamine (100mg/day, p.o.) with ETN 25mg/week because of her wish for pregnancy. After pregnancy, we changed RA therapy to ETN 25mg/twice week and bucillamine 100mg/every other day. RA had been successfully controled during pregnancy and she gave birth to a girl baby having no malformation at 40 weeks. [discussion] The RA patient needing some kind of treatment is reported with 40-50% during pregnancy. The biochemical changes such as elevation of estrogen and progesterone levels during pregnancy were related to the beneficial effect of pregnancy in RA and the shift in T cell function from Th1 phenotype to a Th2 may be impotant. [conclusion] This suggests that ETN may be selected to treat RA patients who desire pregnancy because ETN is high polymer glycoprotein and has little placenta transitivity.

P2-124

Variations in disease activity score-28 and simplified disease activity index after 3-month golimumab and infliximab therapy in rheumatoid arthritis patients

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Conflict of interest: None

[Objectives] We investigated the clinical efficacy of 3-month golimumab (GLM) and infliximab (IFX) therapy in rheumatoid arthritis (RA) patients. [Methods] Thirty-eight RA patients receiving GLM or IFX therapy (GLM, 8 patients; IFX, 30 patients) were included in the study, and the observation period was 3 months (GLM 12 weeks, IFX 14 weeks). The disease activity score (DAS-28) and simplified disease activity index (SDAI) were compared before and after 3 months of GLM and IFX administration. Student's t-test was used for statistical analysis. [Results] The mean age of patients in GLM and IFX group was 65.8 ± 12.9 and 59.3 ± 19.2 years, respectively. Before initiation of therapy, there was no significant difference in age, gender, disease duration, methotrexate dosage, DAS28, and SDAI between the two groups, except for prednisolone dosage ($p=0.014$). DAS28 and SDAI were significantly lower at the end of 3 months compared with those at baseline in both the groups (DAS28 $p=0.033$, $p<0.001$; SDAI $p=0.013$, $p<0.001$, respectively). There was no statistically significant difference in DAS28 and SDAI between both the groups ($p=0.676$ and $p=0.818$, respectively). [Conclusion] The findings suggested that early clinical efficacy can be expected after GLM as well as after IFX therapy.

P2-125

The efficacy of subcutaneous injection of Tocilizumab in patients with rheumatoid arthritis (RA)

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Conflict of interest: None

[Objectives] To assess the efficacy and availability of subcutaneous (SC) injection of Tocilizumab (TCZ). [Methods] In the TCZ treated patients of RA, we switched the infusion of TCZ to SC injection of TCZ-autoinjector. Then we compared the clinical course, medication, and background between such switched cases. [Results] The switching of 2 patients with monthly infusion of TCZ were successful to SC injection without problem. Another two switching cases experienced of RA disease flare including polyarthralgia, general fatigue and subfever, First female case had 66kg of body weight, 17 years of arthritis history, and almost remission after 26 times of monthly infusion of TCZ. She accepted five times SC injection but polyarthralgia, and CRP changing from 0.26 to 5.6mg/dl happened. In the second case, CRP level elevated to 4.5mg/dl from 0.04 after three times injection switched from 14 times of monthly administration. The dosage of methotrexate were same both at 6mg per week, and TCZ was first-applied biologics in these cases. [Conclusion] Switching of TCZ delivery route are not always successful in the patients who were kept in the good condition by TCZ monthly infusion. The difference of dose and frequency between each delivery reflect total efficacy of TCZ treatment.

P2-126

Efficacy of Tocilizumab in our Department study,

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Conflict of interest: None

[Methods] How to TCZ for assessed using the disease activity index (DAS28-ESR, CDAI). The number of cases in 25 cases, survey period was 102 per week. Divided into two groups of disease activity and age differences, compared the effectiveness of. (Retrospective study). Also group 2 of MTX, naive patients or switch cases even regarding differences in effectiveness compared and evaluated (retrospective study). [Results and conclusion: In TCZ assessment in DAS28-ESR, MTX treatment in MTX (+) improved tended. Naive switch, age, disease activity in a study also found no difference. Naïve and combination switch, age, disease activity and analysis also showed no difference. In evaluation in the CDAI in Naïve and switching analysis achieve remission in Naïve, differences were observed. Analyzed by age, disease activity, MTX presence in CDAI difference was observed. 102 Weeks in evaluation of DAS28-ESR when was in remission, but stayed in the evaluation of the CDAI in low disease activity. I thought in TCZ CDAI remission for the treatment goals in the future.

P2-127

The Efficacy of Tocilizumab in Changing from Intravenous to Subcutaneous

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Conflict of interest: None

[Objectives] Tocilizumab (TCZ) has been used by intravenous infusion. Recently subcutaneous injection has been able to be utilized. It is good for the shortening administration time and the unnecessary medicine preparation, while the drop of the efficacy is concerned because of the dose decrease or the dosage method change. We examined whether the efficacy would drop in changing from intravenous to subcutaneous. [Methods] RA patients who have been treated with intravenous TCZ for more than 4 months and wanted to change to subcutaneous TCZ voluntarily were included. We checked out the laboratory data, tender joint counts, swollen joint counts, VAS, global health assessments, DAS28, SDAI, CDAI and mHAQ before and after the change of TCZ administration route. [Results] Among 17 RA patients, 3 patients changed to subcutaneous TCZ injection. After the change to subcutaneous TCZ, two patients got worse. No items of the laboratory data were changed while patient VAS, DAS28, SDAI, CDAI and mHAQ became deteriorated. [Conclusion] In this study we demonstrated that some RA population would get worse in changing from intravenous TCZ infusion to subcutaneous TCZ injection. We must take care for patient VAS and status because the deterioration was not reflected to the laboratory data.

P2-128

The Efficacy and Susceptibility to Tocilizumab as Second Biologics in the Treatment of Rheumatoid Arthritis

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Conflict of interest: None

[Objectives] Tocilizumab (TCZ) has often been used as second biologics next to anti-TNF therapy. But nobody knows what kind of RA patients will be given a good effect by TCZ as second biologics. We examined what kind of RA patients would be given a better effect to TCZ. [Methods] We checked the background of RA patients; the sex and age, the laboratory data, the dosage of MTX and steroid, previous biologics, combined DMARDs, tender joint counts, swollen joint counts, VAS, global health assessments, DAS28, mHAQ before TCZ treatment. [Results] Among 16 RA patients, 12 patients were effective (Group E) and 4 patients were not effective (Group N). No significant difference was in the sex and age. No items except patient VAS and global health assessments had any significant difference. The mean patient VAS was 57.1 (E) vs. 93.7 (N) (P=0.008) and the mean patient global health assessments were 62.3 (E) vs. 94.0 (N) (P=0.02). [Conclusion] In this study we demonstrated that TCZ was also very effective as second biologics and its efficacy was recognized even in RA patients with high diseases activity. It was interesting that the susceptibility to TCZ did not depend on the laboratory data but patient VAS. As second biologics, TCZ should be used to RA patients of high disease activity but low VAS.

P2-129

Clinical evaluation of tocilizumab (TCZ) in patients with rheumatoid arthritis (RA)

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Conflict of interest: Yes

[Objectives] To analyze efficacy of TCZ on RA. Methods; Nineteen males and 52 females, with a mean age of 56.3±14.0 years, were studied. Mean disease duration; 12.1 ±8.6years. Steinbrockers stage; I 8, II: 9, III: 16, IV: 38. Mean ESR 53.5±39.1mm. Mean DAS28<ESR4>sc score; 5.2±1.6. The history of biological DMARDs use; 53. [Methods] The desease activity and efficacy of TCZ were evaluated by DAS28 <ESR4>score and EULAR response criteria. Adverse events and reasons of drop-out investigated. [Results] Mean DAS28<ESR4>s scores; 2.93 at 52 weeks, 3.02 at 104 weeks. Twenty eight patients were drop-out: ineffectiveness 6, remission 5, infections 4. Infections and insufficiency lead to treatment change at many subjects. [Conclusion] Efficacy of TCZ was seen in RA with, and short-disease duration, and young RA patients. The history of biological DMARDs aggravated efficacy of TCZ.

P2-130

Method development for rapid determination of tocilizumab in human plasma and preliminary trial in patients with rheumatoid arthritis

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Conflict of interest: Yes

[Objectives] The present study was aimed to develop a rapid deter-

mination of tocilizumab (TCZ) in human plasma using TCZ anti-idiotypic recombinant Fab (anti-Id rFab), and clarify the factors for inter-individual differences of efficacy of TCZ in patients with rheumatoid arthritis (RA). [Methods] Blood was taken from Japanese RA patients with initial administration of TCZ. TCZ, IL-6 and sIL-6 levels in plasma were monitored regularly. We used DAS28 as an index for disease activity. [Results] We developed a new ELISA that is most suitable for rapid determination of TCZ. We found a negative correlation between the variation of DAS28 from pre-treatment to 6 month after initial administration of TCZ (ΔDAS28 (0-6)) and TCZ levels at 6 month after initial administration. In addition, the variation of IL-6 levels from pre-treatment to 1 month after initial administration (ΔIL-6 (0-1)) have a negative correlation with ΔDAS28 (0-6). [Conclusion] We thought that the effect of TCZ was decreased, since a part of IL-6 receptor was not inhibited when TCZ level is low at 6 months after initial administration. Moreover, ΔIL-6 (0-1) may be a useful marker for prognostic prediction in RA patient treated with TCZ.

P2-131

An Examination at Week 104 of Tocilizumab (TCZ) Treatment in an Akita Cohort of Rheumatoid Arthritis (RA) Patients

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Conflict of interest: None

[Objective] The two-year continuation rate for TCZ administration was approximately 80% in an Akita cohort of RA patients. We investigated the efficacy of the treatment at week 104. **[Methods]** The subjects were RA patients registered in the database of Akita Orthopedic Group on Rheumatoid Arthritis (AORA). We examined the administration status of MTX and PSL, MMP-3 levels and disease activity. **[Results]** Of the 40 cases who stayed on TCZ for 104 weeks, 21 were treatment-naïve and 19 were being switched from another treatment at the start of administration. Mean age was 54 years and mean disease duration was 124 months; MTX was administered to 28 cases at 6.8 mg per week and PSL was to 20 cases at 5.5 mg per day; the CRP level was 2 mg/dL and the MMP-3 level was 254 ng/mL. At week 104, MTX was administered to 20 cases at 6.3 mg per week and PSL was to 12 cases at 2.8 mg per day; all but one case maintained negative CRP levels and the MMP-3 level was 60 ng/mL; the mHAQ was 0.36; the CDAI was 7.1, and 13 cases achieved remission, while 16 cases achieved low disease activity (LDA). **[Conclusions]** At week 104, the PSL dosage had been reduced and a half of all cases were not taking MTX. The levels of MMP-3 decreased. With regard to inducing remission and LDA, the outcomes were favorable.

P2-132

Clinical course of subcutaneous tocilizumab of rheumatoid arthritis–comparison with a clinical trial and observation of re-administration cases-

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Conflict of interest: None

[Objective] Subcutaneous tocilizumab (TCZ-SC) became available in Japan, however results in clinical practice are not shown. We assess clinical course in patients (pts) treated with TCZ-SC including re-administration cases. [Methods] Clinical courses in pts with rheumatoid arthritis (RA) treated with TCZ-SC after drug approval were assessed and compared with those in the clinical trial (MUSASHI study). Moreover, we assessed cases to whom TCZ-SC were re-administered after cessation of TCZ-SC in the clinical trial [Results] Eight pts were treated with TCZ-SC since May 2013. All were female, mean age was 60 yrs, 3 of them took MTX concomitantly and mean body weight was 47.5 (+-8.1) Kg. Compared to the clinical trial, pts were older and had lower body weight, and some of them took MTX. Four pts underwent assessment at 12 week. Mean DAS28 decreased from 4.3 to 2.7 and DAS remission was achieved in 3 pts, suggesting favorable effects. Two pts had relapse after cessation of TCZ-SC in the clinical trial, and re-administration of TCZ-SC ameliorated disease activity. [Conclusion] This case series suggests the efficacy of TCZ-SC in clinical practice as well as in clinical trials. Re-administration of TCZ-SC may be effective in pts who relapse after cessation of TCZ-SC.

P2-133

Induction of remission by short-term interval therapy of tocilizumab for the patient with highly active rheumatoid arthritis

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Conflict of interest: Yes

For the management of rheumatoid arthritis (RA), it is recommended to optimize therapy to ensure tight control. Tocilizumab (TCZ) is usually used at 8 mg/kg every two weeks for patients with Castleman's disease or juvenile idiopathic arthritis, whereas every four weeks for patients with RA. The disease condition of RA differs among patients, so interval and dosage of TCZ should be optimized according to each patient. We report a case with highly active RA who achieved remission by short-term interval therapy of TCZ. A 78 years old woman with RA was treated with 12 mg/day of methylprednisolone, 8 mg/week of MTX and infliximab in other hospital. She was introduced to our hospital because of high activity of RA with abnormal power doppler signals in many joints, CRP 14mg/dl, and DAS28-CRP 8.64. Biologics was changed from infliximab to TCZ. CRP decreased temporarily, but rose again, and severe arthralgia continued. The interval of TCZ therapy was shortened to three weeks, and finally CRP level decreased to normal and her symptom improved. The IL-6 level was so high 3440pg/ml before the therapy, and the short-term interval therapy resulted in the complete inhibition of IL-6. It is necessary to optimize interval of TCZ therapy depending on the levels of IL-6 and inflammation.

P2-134

Analysis of predictive factors for clinical remission in rheumatoid arthritis patients received Tocilizumab

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Conflict of interest: None

[Objectives] To examine the efficacy of tocilizumab (TCZ) in clinical practice, and to analyze predictive factors for clinical remission in RA patients. [Methods] Retrospective analysis of 69 patients at our hospital who could be observed for at least 24 weeks after introduction of TCZ was performed. Stratified analyses according to history of biological agent administration and disease duration were also conducted. Correlation between 24-weeks remission rate and the changes in WBC, neutrophil, platelet counts at 4 -week after treatment was examined. [Results] The 24-week DAS28-ESR remission rate was 61.8% and Boolean remission rate was 30.4%, both high rates. CDAI remission rate was also high at 30.4%. Long-term continuation rates were 75% after 2 years, which were better than other biological agents. DAS28-ESR remission rate at 24 weeks was significant high in patients showing negative CRP and 25% decrease in neutrophil counts at 4weeks after TCZ treatment. [Conclusion] The high efficacy of TCZ was confirmed by a variety of assessment methods, and negative CRP and 25% decrease in neutrophil counts at 4weeks after TCZ initiation might be predictive factors for clinical remission at 24 weeks.

P2-135

The questionnaire survey about switch from drop intravenous injection to subcutaneous injection of tocilizumab and its efficacy of therapy

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Conflict of interest: None

[Objectives] The subcutaneous injection of tocilizumab (TCZ-SC) was added to existing drop intravenous injection (IV). We now investigated the situation how patients really think about the switch of this medication through a questionnaire. [Methods] The 30 patients with TCZ-IV (26 females, 4 males) ware intended and investigated weather they want to switch the route or not and the reasons through a questionnaire. And we measured the outcome of 9 patients who switched the route to SC within three months before and after the switch with CDAI. [Results] Forty-three percent of patients (13/30) wanted to switch to SC because they can do it on an outpatient basis (50%). Thirty-nine percent wanted to continue TCZ-IV because of their habituation (39%), or availability of the 4 weeks interval administration (33%). Remission rate for CDAI with 9 patients who switched to SC was as follows; 3 months before, 1 month before, switched point, 1 month after, is 33.3, 33.3, 22.2, 11.1, 33.3%, respectively. [Conclusion] Beyond expectation, many patients wanted to continue TCZ-IV. That indicates us it is more difficult for patients especially coming a long distance to hospital every 2 weeks. The possibility of maintenance of its efficacy after switch IV to SC of TCZ was presented with this survey.

P2-136

Effect of tocilizumab as a first-line biologic agent in patients with rheumatoid arthritis

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Conflict of interest: None

[Objectives] We evaluated effect of tocilizumab as a first-line biologic agent in patients with rheumatoid arthritis. [Method] Twenty biologic-naive RA patients treated with tocilizumab (TCZ) or adalimumab (ADA) for more than 24 weeks were enrolled in this study. Ten patients with a mean age of 58 years were treated with TCZ and ten patients with a mean age of 63 years were treated with ADA. Disease Activity Score 28CRP (DAS28-CRP) and does of methotrexate were compared between two treatment groups. [Results] DAS28-CRP was significantly decreased from 4.31 to 2.22 ($P < 0.05$) in TCZ treated group and significantly decreased from 4.7 to 2.84 ($P < 0.05$) in ADA treated group. However, there was no significant difference in DAS28-CRP between two treatment groups. Dose of methotrexate was reduced from 8mg to 4mg ($P < 0.05$) in TCZ treated group whereas 5.3mg of methotrexate was not altered over a follow-up period in ADA treated group. [Conclusion] This study suggested that TCZ is as effective as TNF-alpha inhibitor in the first-line biologic agent for RA.

P2-137

Amelioration of cardiomyopathy with tocilizumab in a case of rheumatoid arthritis

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Conflict of interest: None

A 81-year-old woman with rheumatoid arthritis (RA) diagnosed in 1998. Cardiomyopathy was complicated, and medicated. Echocardiography confirmed that left ventricular wall motion was generally severe hypokinetic. Computed tomography confirmed no ischemic change of coronary artery. As disease activity was not controlled with 5mg of prednisolone, she was treated with Tocilizumab (TCZ) in September 2008. Subsequently, the disease activity of RA was decreased (DAS-28ESR 2.6) with withdrawal of prednisolone in February 2010. As described later, all of the cardiologic parameters were improved, ejection fraction (EF); 28% (before), 44% (2M after TCZ), 55% (42M after TCZ): cardiothoracic ratio (CTR); 68% (before), 62% (17M after TCZ), 61% (51M after TCZ): brain natriuretic peptide (BNP); 381pg/ml (before), 9.5pg/ml (30M after TCZ), 9.0pg/ml (54M after TCZ) TCZ improved the ventricular wall motion over 5 years without any additional treatment for heart failure, suggesting the involvement of IL-6 in the pathogenesis of cardiomyopathy.

P2-138

Olokizumab anti-interleukin 6 ligand antibody improves arterial stiffness with methotrexate-resistant active rheumatoid arthritis. A cohort programmded sub-study

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Conflict of interest: None

[Objectives] To examine the effect of olokizumab (OKZ) plus methotrexate (MTX) on arterial stiffness in MTX resistant RA patients in another cohort study programmed sub-analysis design. [Methods] 10 RA patients with moderate to severe active disease despite MTX treatment were received OKZ plus MTX. Arterial stiffness was assessed with cardio-ankle vascular index (CAVI) and augmentation index corrected for a heart rate of 75 beats per minute (AIx@75) at baseline and 24 weeks follow-up. Clinical data were collected at regular visits. CAVI is very similar to pulse wave velocity (PWV), and CAVI measures arterial wall stiffness independent of blood pressure and it is superior to brachial ankle PWV as an index of arterial stiffness. [Results] Treatment with OKZ (10.72 ± 1.72 and $9.51 \pm 1.42\%$; $p = 0.026$), attenuated the CAVI significantly from baseline to 24 weeks follow up. Treatment with OKZ (35.9 ± 8.6, 32.5 ± 3.6 %; $p = 0.018$) attenuated the Aix@75 significantly from baseline to 24 weeks follow up. On the other hand, fasting serum total cholesterol TC was significantly increased from baseline to follow-up at 24 weeks (211±21.2mg/dL, 232±24.2mg/dL, $p = 0.03$). [Conclusion] OKZ with MTX not only reduced RAdisease activity but also limited vascular damage in patients with MTX resistant active RA.

P2-139

Stopping Olokizumab in low disease activity or remission stables good control of disease activity but deteriorate arterial stiffness with methotrexate-resistant active rheumatoid arthritis

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Conflict of interest: None

[Background] Olokizumab (OKZ) anti-interleukin 6 ligand antibody are very efficacy with methotrexate-resistant active RA. However despite efficacy of OKZ, the clinical trials were abandoned. [Objectives] After stopping OKZ in low disease activity or remission, we switched Tocilizumab (TCZ) or, didn't use any biologics (patient decision). We studied disease activity and arterial stiffness after 12 weeks stopping OKZ. [Methods] 7 RA patients with low disease activity to remission were stopped OKZ. 4 RA patients were received TCZ, and 3 RA patients were received no biologic. Clinical data were collected at baseline and 12 weeks follow-up. Arterial stiffness was assessed with cardio-ankle vascular index (CAVI) and augmentation index (AIx@75) at baseline and 12 weeks follow-up. [Results] Disease activity of treatment with TCZ or no biogic remain stable disease actvity (delta 0.11, and 0.23) from baseline to 12 weeks follow up. Treatment with TCZ group remained good CAVI (delta 0.25) and Aix@75 (delta 2.11). On the other hand, Treatment with no biologic group worsened CAVI (delta 1.21) and Aix@75 (delta 4.3)

from baseline to 12 weeks follow up. [Conclusion] Blocking interleukin 6 improves arterial stiffness in rheumatoid arthritis irrespective of its disease activity control effects.

P2-140

Effect of abatacept on telomerase activity of lymphocytes in patient with rheumatoid arthritis

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Conflict of interest: Yes

[Objectives] Abatacept suppress the activation of T lymphocytes which are involved in pathogenesis of rheumatoid arthritis. And it was reported that telomerase activity of lymphocytes is upregulated when the lymphocytes are activated. Therefore we investigated effect of abatacept on telomerase activity of lymphocytes. [Methods] This study included 17 patients with rheumatoid arthritis starting treatment of abatacept from August 2012 to August 2013. We collected their peripheral blood samples before starting abatacept and from 4 weeks to16 weeks after the treatment. Then we measured telomerase activity of CD3 positive lymphocytes and CD19 positive lymphocytes by Telomeric Repeat Amplification Protocol (TRAP assay). [Results] Mean age of patients was 60.9. 4 men and 13 women were included. DAS28-ESR before treatment of abatacept was 4.03, and that after the treatment was2.72. Telomerase activity of CD3 positive lymphocytes decline from 0.3896 to 0.2310 ($p<0.05$), and that of CD19 positive lymphocytes also decline from 0.6811 to 0.3032 ($p<0.05$) [Conclusion] Treatment of rheumatoid arthritis including abatacept decrease telomerase activity of CD3 positive lymphocytes and CD19 positive lymphocytes

P2-141

A case in which abatacept was effective for autoimmune thrombocytopenic purpura associated with rheumatoid arthritis

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Conflict of interest: None

The patient was a 59-year-old woman. Rheumatoid arthritis (RA) was diagnosed and treatment started with gold sodium thiomalate (GST). In 2000, treatment was changed from GST to bucillamine (BCL) due to insufficient control of RA. This improved RA control, but rash and marked thrombocytopenia (8,000/μl) were seen, and BCL was therefore discontinued. Rash subsequently improved, but thrombocytopenia did not, and autoimmune thrombocytopenic purpura (AITP) was diagnosed based on normal megakaryocytes, PAimmunoglobulin (Ig) G positivity, and other factors. Even with a combination of prednisolone 1 mg/kg/day, high-dose Ig therapy, *Helicobacter pylori* eradication therapy, and cyclosporine for AITP, platelets remained at around 20,000/μl. Splenectomy was considered, but consent was not obtained. Etanercept (ETN) for RA and AITP was started in April 2007. RA control was good, but platelet count was unimproved. ETN was changed to abatacept (ABA) in March 2012. Platelets rose to >100,000/μl from August 2013 and have since remained at that level. This patient showed RA complicated by refractory AITP. Conventional treatments were inadequate and no improvement was seen in AITP, even with ETN administration. However, AITP improved when pharmacotherapy was changed from ETN to ABA.

P2-142

Efficacy and safety of abatacept with rheumatoid arthritis

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Conflict of interest: None

[Objectives] To assess the efficacy and safety of treatment for rheumatoid arthritis (RA) patients with abatacept (ABT) mostly in elderly people, case with underlying diseases, and no responder to the other biologics products (switch). [Methods] The study population consisted of 31 patients (men, 7; women, 24) until November 2013. The mean age was 66.1 years (44~88 years). The efficacy of ABT was evaluated using desease activity score (DAS)-28 for 12 months. [Results] The study population included number of 14 patiens with methotrexate (MTX) (12.9%) and 11 patients who hadn't take the other biologics (naïve) (35.4%). As for the underlying disease, there were old tuberculosis, colon cancer, heart failure, prostatic carcinoma, diabetes by one case. The mean DAS28 was decreased significantly from an average value of 4.01±1.37 at the base line, to 2.55±1.55 after 6 months ($P<0.05$), and 2.88±1.10 after 12 months. The DAS28 significantly decreased in the naive than the switch after 6 months (naive/switch baseline 3.53±0.99/4.25±1.44; after 6 months 1.53±1.21/3.00±1.48) ($P<0.05$). Adverse reactions were one osteomyelitis, one skin rash and one respiratory infection. [Conclusion] The results suggest that ABT is a safe and effective drug therapy option for RA patients espetially in naïve patients.

P2-143

The modulation of the T cell CD80/CD86: CD28 co-stimulatory signal does not suppress CD8-positive subpopulation in the course of the treatment for rheumatoid arthritis

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Conflict of interest: Yes

[OBJECTIVE] To clarify the influence of Abatacept (ABA) on CD8+ T lymphocyte subsets, the PBMC from Biologic-naive patients with active RA in ABROAD trial were analyzed using FACS. [RATIONALE] The post marketing surveillance of ABA revealed that the serious infections were less frequent compared with the treatment using other biologic agents (ACR 2013). However, the mechanism responsible for this safety profile has not been cleared yet. CD8+T cells play important roles in the immune surveillance system. In spite of the less dependency to the co-stimulatory signal through CD28, CD8+T cells could be influenced by ABA because of expression of CD28 on their surface. [METHODS] PBMCs were obtained from 30 patients enrolled in ABROAD study at baseline, 24 and 48 weeks of ABA treatment. The proportion of CD8+Tcells and CD25+ in CD8+ T cells were analyzed with flow cytometer. [RESULTS] Any significant reduction in the CD8+ T cell proportions (19.7±11.0% at baseline, 19.0±7.8% at 24 weeks and 20.8±9.0% at 48 weeks), as well as in CD25+ cell proportions in CD8+Tcells (3.29±2.5% at baseline, 3.50±2.5% at 24 weeks and 2.93±1.8% at 48weeks) were not observed. [CONCLUSION] The CD80/CD86: CD28 co-stimulatory signal inhibition does not alter the activation status of CD8+ lymphocytes through 48 weeks.

P2-144

Clinical evaluation of abatacept in our Department and related clinic

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Conflict of interest: Yes

[Objectives] We reviewed the efficacy and safety of abatacept (ABT) therapy in patients with RA. [Patients] RA was diagnosed by ACR classification criteria (1987). Twenty-two RA (6 males), age 62.2±12.7 years old, and disease duration 8.3±2.1 years. Fourteen patients were switched from other biologics. Corticosteroids were administered to 21 patients (6.7±3.8 mg/day) and MTX was used in 13 (8.3±2.1 mg/wk). Overlapping diseases: SLE: 4, SSc: 1, SS: 1, MCTD: 1, MRA: 1, PM: 1. [Methods] Efficacy of ABT was evaluated by SDAI at 0, 12, 28, 52 and 84 wk after infusion of ABT. [Results] At 84 wk, overall, the proportion of either clinical remission or low disease activity (LDA) by SDAI increased from 18.2% to 45.4%. With MTX, the rate elevated from 30.8% to 53.9%, and without MTX 0% to 33.3%. In bio-switch cases, the rate was 0% to 28.6% and in bio-naive cases was 50% to 75%. Three of 10 cases with high disease activity and 5 of 8 with moderate disease activity (MDA) achieved LDA. Mean SDAI decreased gradually until 28wk. Overlapping diseases were not exacerbated. Discontinuation: 5 cases: no response; 3, infection and pneumothorax; 1, pulmonary tuberculosis; 1. [Conclusion] ABT seems more effective in RA patients with MDA at background or using concomitant MTX or bio-naive cases.

P2-145

The clinical outcome of abatacept treatment in biologic naïve patients with rheumatoid arthritis in the TBC registry

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Conflict of interest: None

[Objectives] The 2010 EULAR Recommendations have been updated this year, abatacept (ABT) has become available as the first biologic agent for patients with RA. We studied the clinical outcome of ABT treatment for 52 weeks in patients without prior biologics therapy. [Methods] Biologic naïve patients treated with ABT for longer than 52 weeks (n=132) were extracted from the multicenter study group for RA (TBCR). Disease activities were assessed by DAS28CRP and SDAI. Furthermore, EULAR response criteria and drug retention rate at 52 weeks were evaluated. To determine predictors of low disease activity state (LDAS) at week 52, we performed multivariate analysis. [Results] Disease activities were significantly decreased at 4 weeks and further decreasing were observed continuously. The percentage of the patients who achieved LDAS was 57.7%. At 52 weeks, EULAR response rate showed 74.6% (good 46.9%, moderate 27.7%) and Drug retention rate was 86.5%. Multivariate analysis confirmed that patient global assessment at baseline was independent factor for achieving LDAS at week 52. [Conclusion] Clinical trials demonstrated that ABT shows significant efficacy in biologic naïve patients. Our results suggest that ABT is useful for patients with RA as the first biologic agent in daily clinical practice.

P2-146

Investigation of Serological and Clinical Factors Affecting Outcome on Efficacy of Abatacept

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Conflict of interest: None

[Objectives] Investigating association between clinical responses by Abatacept (ABT) and serological and clinical factors. [Methods] 48 RA patients who started ABT treatment between Oct 2010 and Aug 2012 were divided in groups by means of RF, anti-CCP antibody, ANA positivity, γ-globulin, MMP-3, and disease activity. Following evaluations were performed among the groups: drug retention rate, DAS response, DAS remission rate at 24, 52, and 104 weeks, and ΔTSS at 52, and 104 weeks. [Results] There was no significant difference between patients by RF values. But, long-term analysis found that patients with high RF value tended to have better DAS response and remission rate. Analysis on anti-CCP antibodies found that DAS response at 52 weeks was significantly better and continued to be better at 104 weeks. Patients with high MMP-3 and high disease activity showed better DAS response. ΔTSS values were higher in patients with high RF, anti-CCP, and MMP-3, indicating a discrepancy between clinical response and ΔTSS progression. [Conclusion] It was indicated that ABT may be more effective on RA patients with auto-antibody positivity and high disease activity. However, it is important for those patients to introduce idea of "tight control" for protection from structural damage.

P2-147

Abatacept therapy with steroid may achieve both the prompt remission and the high maintenance rate of remission in rheumatoid arthritis patients

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Conflict of interest: None

[Objectives] We aimed to confirm the effect of treatment using CTLA-4 Ig abatacept with steroid for rheumatoid arthritis (RA). [Methods] Abatacept with 0.2mg/kg steroid were prescribed for 31 RA patients that were resistant to DMARDs including MTX and untreated by biological drugs or switched from other biological drugs. The amount of steroid was arbitrarily reduced in parallel with symptoms in 48 weeks. The disease activity indexes DAS28-ESR/-CRP, CDAI, SDAI, Boolean were evaluated and statistically compared between before and each 4, 12, 24, 48weeks after the therapy begins by t-test and Wilcoxon signed-rank test. [Results] After the therapy begins, 26% at 4 weeks, 45% at 12 weeks and 55% of patients at 48 weeks achieved the DAS28 remission. 55% and 52% of patients at 48 weeks achieved the SDAI remission and the Boolean remission, respectively. DAS28, CDAI and SDAI had been statistically decreased since 4weeks from the therapy begins. The amount of steroid at 48 weeks was taperd to 40% compared with the therapy begins. There were no differences between with and without MTX about the disease remission rate. [Conclusion] Abatacept therapy with steroid showed the possibility to achieve the prompt remission and the high maintenance rate of remission despite using MTX in RA patients.

P2-148

Examination of the effectiveness of abatacept in rheumatoid arthritis (RA) patients with autoimmune diseases

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Conflict of interest: None

(Background) Since the effectiveness of abatacept has been reported in RA patients with autoimmune disease (AU), we examined the usefulness of abatacept in RA patients with AU. **(Method)** 13 RA patients with AU (F:M=12:1, 53.5±14.9 years old, BMI 22.4±2.66) was investigated retrospectively among 18 RA patients under abatacept medication. We evaluated the disease activity using DAS28-CRP before medication, after-medication 1, 3, 6 months. **(Result)** The amount of average medication medicines, prednisolone 8.7 ± 4.6mg, MTX 6.9 ± 2.1mg (MTX combination were 6 cases). The average of anti-CCP antibody was 17.9 ± 47.1 (6 cases negative). Transitions of DAS28-CRP were 3.39±0.62, 2.75±0.80, 2.34±0.50, and 2.42±0.58, and MMP-3 were 156.9±44.8, 154.5±76.7, 127.58±34.9, and 134.18±34.8. **(Discussion)** 6 patients of disease activity have improved from moderate to low in one month, and DAS28-CRP had the tendency for revelation of the effect of abatacept to be effective earlier, compared with RA patients who do not have autoimmune disease. It is common for it to be difficult to increase the quantity of MTX in RA patients with AU and joint symptoms do not improve in many cases. **(Conclusion)** It was suggested that the abatacept could become first biological therapy to RA patients with AU.

P2-149

Efficacy of abatacept treatment on the progression of structural damage with rheumatoid arthritis

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Conflict of interest: None

[Objectives] Our objectives in this study were to determine the inhibitory effects of abatacept on joint damage in 42 patients with rheumatoid arthritis who started treatment between October 2010 and October 2012 at two centers. They continued treatment over one year and their joint damage score was assessed using the total Sharp score (TSS) at baseline and week 48. [Methods] 30 patients were females. Mean age was 69.4 years. Mean duration of illness was 9.2 years. Concomitant medications included MTX in 17 patients at mean doses of 6.5mg/week. Desease activity was assessed using DAS28-ESR. Progression in TSS (ΔTSS) was defined as yearly change. Chi-square test was used to elicit association between structual remission rate and several factors, including use of MTX, age (under65; over65), and ΔDAS28-ESR (change of DAS28-ESR between baseline and week 12 or 24). [Results] Mean DAS28-ESR at baseline was 5.24. Mean ΔDAS28-ESR was 0.96 and 1.26 at week 12 and 24, respectively. Mean TSS at baseline was 60.9. Mean ΔTSS was 0.59. Structual remission rate at week 48 were 69% (29 patients). [Conclusion] Examination of prognostic factors contributing to structural remission at year 1 revealed that ΔDAS28-ESR at week 24 was an independent prognostic factor, whereas MTX use, age, and ΔDAS28-ESR at week 12 were not.

P2-150

The usefulness of Tofacitinib in RA patients of our hospital

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Conflict of interest: None

[Purpose] The usefulness of Tofacitinib (TOF) in RA patients who prescribed TOF by the clinical trial for 1 year or more is examined. [Method] Objects are 22 RA cases that participated in the clinical trial (phase II, mono-therapy, global). Seventeen among 22 cases who medicated with TOF for 1 year or more, were evaluated the efficacy (DAS28, SDAI, HAQ-DI, mTSS) and the adverse event for 1 year using the medical record. [Result] After TOF treatment, DAS28-CRP was declined from 4.9 to 2.1, SDAI from 30.4 to 5.4, HAQ-DI from 0.8 to 0.4, significantly. After 1 year, clinical remission rate was 41% in SDAI and 53% in DAS28-CRP. The functional remission rate was 76%. Yearly progression of mTSS before and after TOF was 6.1 vs. 0.6, and the structural remission rate was 75%. Moreover, DAS28-CRP in biologics naïve cases (n=10) declined significantly from 4.9 to 2.3, SDAI from 31.2 to 6.1. DAS28-CRP in biologics used history cases (n=7) from 4.9 to 1.8, SDAI from 29.2 to 4.4. The main adverse event was upper respiratory infection, herpes, and urinary tract infection. Although 1 ovarian cancer occurred 5 years after medication, it recovered by the operation. [Conclusion] TOF is an effective irrespective of the biologics use history, but the cautions to infection and malignancy are required.

P2-151

Biological therapy for rheumatoid arthritis (RA) patients with renal dysfunction

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Conflict of interest: None

[Objectives] Methotrexate is a first-line medication for RA, but it is contraindicated in patients with end stage renal dysfunction. Treatment for RA patients with renal dysfunction is controversial. This objective is to confirm the effectiveness of biological therapy for RA patients with renal dysfunction. [Methods] All RA patients with renal dysfunction (eGFR 40 ml/min./1.73m2 or on dialysis) who received biological therapy from January 2006 were enrolled and their clinical course was investigated. 29 patients (8 male, 21 female; 10 on dialysis) were enrolled. Mean age is 66.6±9.6 years old. [Results] 21 patients were administered etanercept and 5 patients achieved CR (DAS28 criteria), 1 patients improved partially. 15 patients switched to tocilizumab. 21 patients were administered tocilizumab and 14 patients achieved CR, 2 patients improved partially. 5 patients switched to other bio-DMARDs. One patient died of severe cellulitis and 2 patients died of pneumonia and thoracic empyemapyothorax. [Conclusion] Most patients receiving biological therapy showed improvement of their symptoms. Biological therapy can be a first-line treatment for RA patients with renal dysfunction, however adverse event like infection should be observed carefully.

P2-152

Therapeutic efficacy of infusing 1ppm H_2-resolved saline on Rheumatoid arthritis (RA); a randomized, double blinded, and placebo-controlled pilot study

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Conflict of interest: None

[Objectives] To confirm the therapeutic potential of H_2 on RA, randomized, double blinded, and placebo-controlled investigation of the infusion of H_2-resolved saline was performed. [Methods] 20 patients with RA were enrolled. 500ml of 1ppm H_2-resolved saline (10 patients) or placebo saline (10 patients) was drop infused every day for 5days. DAS-28CRP of the 6^{th} day or 4weeks after the start, was estimated. 9 of 20 patients showed antibodies against cyclic citrullinated peptides. 4 patients had been treated with methotrexate, 5 with steroid hormones, and 13 had been treated with neither of them. 6 patients were with early RA. [Results] In the H_2-infused group, DAS28 was decreased from 5.49 to 4.19 on the 6^{th} day and was reached 3.86 after 4 weeks on average. 6 showed good response, 3 moderate, and 1 showed no response. In the placebo group, DAS28 showed no remarkable decrease (from 5.04 to 4.86) on the 6^{th} day and was remained 5.09 after 4 weeks on average. MMP3 after 4 weeks was reduced by 18.7% ($p<0.05$) in H_2 group on average, and increased by 23.9% in placebo group. Only in H_2 group, the synovitis was improved in 4 patients and the bone edema was also improved in 1 patient. [Conclusion] The results suggest that the drop infusion of H_2 effectively reduces disease activities of RA.

P2-153

A clinical remission case of rheumatoid arthritis with radiographical improvement treated by an inhibitor of DNA methyltransferase (Azacitidine)

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Conflict of interest: None

[Objectives] It has been reported that DNA methylatioin of synovial cells may play a important role in the progression of rheumatoid arthritis (RA). Here, we experienced a RA patients with AML with myelodysplasia-related change, who showed marked improvement of RA clinical and radiographical activity by an inhibitor of DNA methyltransferase (Azacitidine). [Methods] RA clinical activity was evaluated by DAS28-CRP, and radiographical change was evaluated by Sharp/ van der Heijde method and measuring a maximum length of hand bone cyst. [Results] DAS28-CRP was dramatically improved 4.01 to 2.17 after initiation of Azacitidine 70 mg/m^2 7 days (1 course). Radiographical improvement was also observed after 17 course of the treatment. The maximum length of bone cyst and Sharp score were improved from 14.8 x 7.9 → 10.9 x 6.6 mm and 77→71, respectively. [Conclusion] An inhibitor of DNA methyltransferase may improve disease activity of RA.

P2-154

Antioxidant and anti-inflammatory effects of water containing a high concentration of molecular hydrogen (5-7ppm H_2 water) on Rheumatoid arthritis (RA)

Toru Ishibashi, Yuji Naritomi
Haradoi Hospital

Conflict of interest: None

[Objectives] To find the therapeutic potential of H_2 on RA, the antioxidant effects of H_2 on non-RA volunteers as well as RA patients were investigated. Also anti-inflammatory effects of H_2 on RA were estimated by the disease activities. [Methods] 10 non-RA volunteers and 20 RA patients drank 530ml of 5-7ppm H_2 water every day for 4 weeks. After a 4-week wash-out period, they drank it for another 4 weeks. Urinary 8-OHdG from both groups was measured and DAS28CRP of RA patients was estimated. [Results] Urinary 8-OHdG was significantly reduced by 23.2% with volunteers and by 14.3% with RA patients. They reduced 31.2% and 15.1% at the end of the study, respectively. DAS28 also decreased from 3.83 to 3.02 ($p<0.01$) during the first period and further reduced from 2.83 to 2.26 ($p<0.01$) during the second period. 14 showed good response, 2 showed moderate, and 4 were non-responder. All the 5 patients with early RA (ACPAs negative) achieved remission. [Conclusion] The results suggest that the hydroxyl radical scavenger H_2 effectively reduces oxidative stress in patients with RA and in non-RA volunteers. The symptoms of RA were significantly improved with 5-7ppm H_2 water.

P2-155

Continuous consumption of molecular hydrogen (5-7ppm H_2 water) improved the disease activities of Rheumatoid arthritis (RA)

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Haradoi Hospital

Conflict of interest: None

[Objectives] To confirm the therapeutic potential of H_2 on RA, the effects of continuous consumption of water containing a high concentration of H_2 (5-7ppm H_2 water) were observed. [Methods] 43 patients with RA (involve patients who were enrolled in the study for H_2-resolved saline) continued to drink 5-7ppm H_2 water for more than 6 M. DAS28CRP during the periods was estimated. 14 of 43 patients showed antibodies against cyclic citrullinated peptides (ACPAs). 9 patients were with early RA. [Results] In the ACPAs positive group, DAS28 was decreased from 4.77 to 2.64 on average (duration=11.9M on average). 11 showed good response. 2 showed moderate, and 1 showed no response. 8 patients achieved remission (57.1%) and 3 of them became drug-free. In the ACPAs negative group, DAS28 was decreased from 4.24 to 1.70 on average (duration=11.4M on average). 28 showed good response and 1 showed moderate response. 25 patients achieved remission (86.2%) and 18 (72.0%) of them became drug-free. Side effects which seem to be caused by H_2 have not been observed. [Conclusion] 33 of 43 (76.7%) patients achieved remission and 21 of them (63.6%) became drug-free. The continuous consumption of 5-7ppm H_2 water was effective to reduce disease activities of RA, especially on the patients who did not show ACPAs.

P2-156

Evaluation of synovitis of finger IP joint using ring gauge before and after biological therapy

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Conflict of interest: None

[Objectives] In evaluating outcomes of drug therapy for the patients with rheumatoid arthritis (RA), scales with DAS, SDAI and CDAI are commonly used. However, Boolean data type of evaluation for the synovial swelling cannot be always true. The purpose of this study was to evaluate the synovitis of finger IP joint using ring gauge semi quantitatively. [Methods] Seven patients with RA, all female, age averaged 63 years old, who underwent induction of biological therapy after insufficient treatment with MTX enrolled in the study. Besides usual clinical evaluations, diameter of the IP joints of thumb and fingers were measured using ring gauge before and after the biological therapy. [Results] Diameter of the IP joints decreased significantly (20.5 to 20.0 gauge in average) in all patients soon after the first induction of biologics. [Conclusion] Semiquantitative evaluation of the synovitis of finger IP joint using ring gauge is easy to achieve, reliable and economical tool for the treatment of RA. By using this method, synovitis of PIPJ revealed to be diminishing soon after induction of biological agents.

P2-158

Re-operation after posterior atlantoaxial subluxation using a C2 laminar screw in a patient with RA

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Conflict of interest: None

A 70-years-old woman with 13-year history of rheumatoid arthritis (RA) had an atlantoaxial subluxation (AAS) with a unilateral high-riding vertebral artery. Posterior occipito-C2 fixation with a C2 laminar screw (LS) was performed. In spite of Halo best fixation, screws were back-outed and we re-operated posterior occipito-lower cervical spine fixation. Seven years after the re-operation, her neck pain disappeared and instability of cervical spines was not observed. Wright described a novel technique of screw fixation into the axis using LS. This technique could allow for immobilizations of the axis without risk to the spinal cord and vertebral artery. Many reports had been recently published that LS was almost equal to the biomechanical strength and surgical outcomes in comparison with a pedicle screw. But these studies were nearly performed by using cadavers excluded from severe osteoporosis and RA, and cadavers were not actually agreed with clinical patients. The surgical fixation range of RA spondylitis had continued to be discussed, and we performed minimum posterior occipito-C2 fixation because of no subaxial cervical lesions. We should have chosen the surgical fixation range of RA spondylitis according to disease severity, bone fragility and prognosis of

individuals.

P2-159

Clinical results of total elbow arthroplasty for rheumatoid patients

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Conflict of interest: None

[Objectives] In current study, we evaluated clinical results of TEA for rheumatoid patients especially in regard of the clinical features using semi-constrained system. [Methods] In our institute, from January 2006 to October 2013 fourteen primary TEA had been performed for 13 female rheumatoid patients. Of these 14 TEA, 13 who had been observed over 1 year were included in current study. The mean age was 63.2 years old, the disease duration was 22.7 years and the follow-up duration after TEA was 56.2 months. And the mean affected joint counts in lower extremities (hips, knees and ankles; total 6 joints) that treated by any joint surgeries previous to TEA was 2.5 joints. Non-constrained system was applied to 8 elbows; group K, semi-constrained system to 5; group D. [Results] Revision surgeries had been performed for 3 TEAs, in a TEA (group K) due to deep infection and 2 (both group D) due to aseptic loosening. The latter 2 TEAs had been performed the patients who have long disease durations over 25 years and previous surgeries in lower extremities over 3 joints. [Conclusion] In the patients such as have long disease duration and previous several surgeries in lower extremities, increasing loading stress to upper extremities cause early failure especially semi-constrained system.

P2-160

Recent implant selection and clinical results of total elbow arthroplasty (TEA) for the patients with rheumatoid arthritis in our institution

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Conflict of interest: None

[Objectives] In elbow severely involved by rheumatoid arthritis (RA), total elbow joint arthroplasty (TEA) is applied. There are two types of TEA currently available; unlinked (resurfacing) and linked (mostly semi-constrained) prostheses. This report describes recent selection of TEA and their outcomes in our department. [Methods] The subjects were 9 elbows in 7 RA patients who underwent TEA since 2006 in our department. The mean age was 76 y at the time of surgery, and mean follow-up period was 32.5 m. Clinical results were evaluated by Mayo Elbow Performance Score and joint destruction by Larsen grade. We used 5 K-elbows as unlinked TEA and 4 Discovery elbow systems as linked. [Results] Despite no obvious differences in preoperative pain and ROM between groups, stability and function were better in K-elbow group compared with Discovery. Larsen grades were also better in K-elbow. The final total evaluations were 83.0 in K-elbow and 86.3 in Discovery on average with little difference in each section. [Conclusion] K-elbow was applied to the cases with somewhat-preserved joint stability and relatively lower joint destruction. Good short-term clinical improvements were obtained in both groups. Implant loosening may occur for linked prosthesis in long term, which we should be careful.

P2-161

Short term results of Discovery total elbow arthroplasty in rheumatoid arthritis patients

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Conflict of interest: None

[Background] Total elbow arthroplasty (TEA) is an effective treatment for rheumatoid arthritis (RA) patients. Few reports were described about Discovery TEA system, newly modified linked type TEA from Coonrad-Morrey TEA. [Objectives] To investigate the short term results of Discovery TEA for RA patients. [Methods] Twelve RA patients, underwent Discovery TEA after September 2010 with minimal follow-up of 1 year were examined retrospectively. Patients characteristics, range of motion, Mayo elbow performance score (MEPS), radiographic change, complication were examined. [Results] The average age and disease duration at the surgery was 63 and 22 years, respectively. Preoperatively, 9 elbows were Larsen grade IV and 3 were V. The average follow-up was 1.6 years. Extension was changed from -35 to -29 degree, and flexion was from 112 to 139 degree. MEPS was improved from 36 to 93. Implant loosening and radiolucent line were not observed. One intraoperative fracture (lateral epicondyle), 4 postoperative fracture (3 medial, 1 lateral epicondyle), one delayed wound healing, one ulnar nerve palsy were observed. Infection was never observed. One nonunion was observed who had synthesized for old olecranon fracture. [Conclusion] Discovery TEA for RA patients demonstrated excellent short-term results.

P2-162

Revision TEA for failed arthroplasty in RA elbow

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Conflict of interest: None

[Objectives] We evaluated the results of revision total elbow arthroplasty (TEA) for Rheumatoid arthritis (RA). [Methods] Six revision TEA operated between 2005 and 2013 for rheumatoid elbow were evaluated. Patients were females with a mean age of 60.4 years (range, 32 to72). [Results] Causes of revision were loosening, instability (dislocation) and breakage of a component in 3, 2 and 1 cases, respectively. A mean duration from initial TEA to revision surgery was 10.3 years (range, 1 to 13). Semi-constrained type arthroplasty (5 Coonrad-Morrey, 1 Discovery) were used for revision surgery. Joints were developed with posterior approach, reflecting a triangular-shaped triceps flap. Fractures often occurred during removal of fixed component and they were treated by wiring successfully except a case that needed re-revision using plate after non-union. A mean JOA score improved from 59 to 81 point at the time of follow up. Whereas flexion was improved from 125 to 131 degrees, extension, pronation and supination were unchanged. [Conclusion] Revision TEA using a semi-constrained components provided good functional outcomes. Fractures during removal of component need attention.

P2-163

A case of long standing posto-operative deep infection after total elbow arthroplasty

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Conflict of interest: None

[Objectives] Development of medical treatment including biologics, DMARD makes it more easy to suppress disease activity of RA. Nevertheless, functional disability due to joint destruction requires surgical treatment. Because of improved implant designs and surgical technique, indication of total elbow replacement for RA have expanded. The rate of post-operative complications following TEA is higher than that of THA of TKA. Deep infection following TEA sometimes results in significant mobidity to the patients. [case report] Seventy-five year old man suffered recurrent deep infections and required multiple revision operations. The reconstruction was performed in two stages. At the first stage, all of infected tissues, necrotic bone, linked TEA and bone cement were remove. Antibiotics loaded cement rods were inserted into the medullary canal of humerus and ulna. At the second stage, antibiotics loaded cement rods were removed and reconstruction was performed. Seven days of intravenous antibiotic treatment and two months of oral administration was continued postoperatively. Postoperative course was uneventful. [Conclusion] Best efforts must be made to remove intramedullary cement and infected and administrate sufficient antibiotics depending on the sensitivity of preoperative culture.

P2-164

Clinical and radiographic evaluations of Sauvé-Kapandji procedure for rheumatoid arthritis

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Conflict of interest: None

[Objectives] Several operative procedures have been reported for repairing destruction of the distal radio ulnar joint (DRUJ) in patients with RA. In our hospital, we have been applying the S-K method to the most of cases with DRUJ disorders in RA. For severely damaged DRUJ, we have been applying the S-K method with some modification. [Methods] We report the clinical and radiographic results of two methods and compare the result of them. 54 wrists underwent the original S-K method and 16 wrists underwent the modified S-K method from 2006 to 2009. The mean follow up period was 35months. ROM, DAS-28 and DASH were evaluated for physical assessments before and after the surgery. The radiographic evaluation was performed by assessment of the carpal height ratio (CHR), the carpal translation index (CTI) and radioulnar width ratio (RWR). [Results] ROM of the wrist joint was increased postoperatively in cases of the original S-K method and modified S-K method. Radiographic examination revealed no significant change regarding to the original S-K method and modified S-K method. [Conclusion] There was no significant change between two groups in clinical and radiographic results. Both operation methods should consider whether it is suitable for RA patient.

P2-165

The clinical results of Sauvé-Kapandji procedure for reconstruction of rheumatoid arthritis

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Conflict of interest: None

[Objectives] The clinical results of Sauvé-Kapandji procedure for reconstruction of rheumatoid arthritis were reviewed. [Methods] Scince 2001, we performed Sauvé-Kapandji procedure on 27 wrists (24 patients). The biologics was administered to 6 patients. The mean age at the time of the operation was 58.0 years. The mean duration of follow-up was 4.3 years. Patients were evaluated in terms of wrist pain, condition of osseous union and range of motion. Radiographic evaluation was performed in terms of CHR, CTR and PCSR. [Results] Wrist pain resolved or decreased in all patients. Bone union was observed in all cases. The mean total range of motion of flexion / extension decreased from 74.3° to 63.9° postoperation. The mean total range of motion of supination / pronation increased from 126.0° to 156.3° postoperation. The mean CHR decreased significantly 0.45 to 0.41 at the time of the recent follow-up. The mean CTR and the PCSR did not change significantly. In 12 of 24 patients, ankylosis was observed. In 6 patients who administered the biologics, radiological progression was inhibited. [Conclusion] Although there is some deterioration radiologically, Sauvé-Kapandji procedure is an effective procedure for patients with rheumatoid arthritis.

P2-166

Flexor carpi ulnaris tendon transfer for multiple extensor tendon rupture in patients with rheumatoid arthritis

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Conflict of interest: None

[Objectives] We report the operative results of flexor carpi ulnaris tendon transfer for multiple tendon rupture of extensor with rheumatoid arthritis patients. [Methods] We present three cases of women affected with all four tendons rupture from index finger to the little finger of rheumatoid arthritis. Ages at operation were 52 to 70 years with an average of 59 years. More than two years has past from onset in all cases. As operative treatment, ipsilateral flexor carpi ulnaris tendon was transferred to the ruptured tendons with palmaris longus tendon as a bridging graft. Arthrodesis of the wrist were performed in two cases and Sauve-Kapandji's procedure in one case simultaneously. [Results] There was no case of re-rupture and full extension of the MP joint was obtained in all patients postoperatively. Patient pain VAS scale were reduced but mHAQ score was slightly exacerbated. Patient satisfaction revealed very high level due to improvement of their ADL. [Conclusion] Flexor carpi ulnaris tendon transfer is a very useful option for multiple extensor tendon rupture in patients with rheumatoid arthritis.

P2-167

Surgical reconstruction of the severely deformed fingers with Jaccoud arthropathy

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Conflict of interest: None

[Objectives] Jaccoud arthropathy is chronic, deformiting and no erosive arthropathy occurring in the joint disease other than rheumatoid arthritis. [Results] (Case 1) A 71-year-old man, SLE For advanced prehensile disorder of both hands, arthroplasty (Swanson) and fusion were performed at the thumb and the finger joints. (Case 2) A 49-year-old woman, MCTD, For the ulnar deviation at the MP joint of the right hand. Balanse restoration was performed in the another hospital. Soon after the operation, extension loss appeared. Ulnar stump stabilization and extensor tendon reconstruction were performed. (Case 3) A 45-year-old man, SLE For the severe swan-neck deformity of both hands, MP joint arthroplasty (Swanson) is scaduled after a systemic medical control. (Case 4) A 55-year-old man, MCTD, For the swan-neck deformity of the left hand. Balance restoration using radial lateral band and DIP joint fusion was performed. (Case 5) A 54-year-old woman, MCTD For the severe ulnar deviation of both hands. MP joint arthroplasty (Swanson) was performed. [Conclusion] In Jaccoud arthropathy, soft tissue structure was attenuated and ruputured despite no destructive change at the joint. Balance restoration using only soft tissue was not reliable. Arthroplasty and fesion with bone resection were recommended.

P2-168

Joint preserved sergery for the forefoot deformation of RA

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Conflict of interest: Yes

[Objectives] The patient was already progressed joint destruction with rheumatoid arthritis, The surgery for hands, fingers and toes that were significantly impaired ADL has been increasing in recent years. For the forefoot deformation of RA, underwent a first 2-5 metatarsal osteotomy and great toe, we had investigated. [Material and methods] 13 feet 10 cases between 2013-2012, surgery for the forefoot deformation at our hospital. We metatarsal osteotomy in all cases MTP joint preservation. At the time of surgery mean age, 56 years old. Disease duration was 16 years. The surgical procedure was For great toe: Mann technique (wedge on osteotomy of the metatarsal bone and the base, oblique shortening and derotation) all cases, the big toe, 2nd-5th went oblique shortening osteotomy (Hanyu method). The patient was walking full load normal shoes with sole plate use under from 3 weeks after surgery. [Results] The hallux valgus angle was improved to 12.5 from 45 degree average. Osteotomy section were all cases bone union. 2 foot second toe is (15.2 %) fibrous

union, Discussion: Conventional RA foot surgery was resection arthroplasty. However, the assumption that the disease activity before and after surgery is suppressed, toe MTP joint preserved surgery is performed most recently.

P2-169

The mid-term outcome of reconstruction for the rheumatoid forefoot deformity

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Conflict of interest: None

[Objectives] We investigate the radiological analysis of reconstruction for the forefoot deformity in patients with rheumatoid arthritis (RA). [Methods] 24 lower extremities in 17 female RA patients were examined. The average age at the time of surgery was 56.8 years (range: 37-76 years) and the average post-operative follow-up period was 8.0 years (range: 5-13 years). The first metatarsophalangeal joint was replaced with a Swanson flexible hinge toe implant with a grommet. Metatarsal head resection was performed for the lesser toes. [Results] The average hallux valgus angle was 43.2 before surgery, 7.9 immediately after surgery, and 19.4 at the final examination. [Conclusion] The loss of corrective and corrective examination of hallux valgus angles showed positive correlation in this cases.

P2-170

Influence of MTP resection arthroplasty on various parameters about local and general disease activity in patients with rheumatoid arthritis

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Conflict of interest: None

[Objectives] To determine influence of MTP resection arthroplasty (Ope) on various parameters about local and general disease activity and QOL in RA patients. [Methods] The subjects used were 12 RA patients (all females) undergoing ope, mean age was 62.4 years. RA disease activity and QOL were measured using DAS28, SDAI, and mHAQ. CRP, ESR, MMP-3 were used as a clinical outcome measure. We analyzed the change of the drug such as MTX, PSL and biologics before and after Ope. They were measured 3 months (M), 6M and 1year after Ope. [Results] mHAQ was improved after 3M and improvement of mean was found in 7 items except “meal” but statistical significant difference was found neither. An improvement trend was found after Ope in ESR (at 6M), CRP (3M to 1 year) and MMP-3 (3M to 1 year), but the statistical significant difference were not found. Mean VAS was improved after Ope. Only doctor VAS was significantly improved at 1 year, an improvement trend was found in disease activity from 3M but statistical significant difference was not found. Dosage of MTX and PSL was almost same. [Conclusion] In this study, Ope was effective in improvement in disease activity and QOL in patients with RA. Ope improve not only local but also general disease activity. Ope was useful in the “treat to target” concept

P2-171

A case of hallux valgus due to RA with MTP joint instability treated with the extensor hallucis longus tendon transfer

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Conflict of interest: None

【Case】 Sixty year-old female with rheumatoid arthritis (RA) complicated with progressive systemic sclerosis (PSS). Correction surgery for hallux valgus was planned for left hallux pain on gait, but open wound with discharge had been detected in dorsal region of MTP joint. Debridement was performed because of persistence of infection. Soft tissue realignment was performed by cutting adductor halluces tendons. Finally infection was settled. After 1 year, she felt pain in her hallux valgus on gait so correction surgery was planned again. Preoperative hallux valgus angle (HVA) was 42°, and the intermetatarsal angle (M1M2) was 18°. MTP joint capsule had been opened at primary surgery and it became thin, so lateral instability was detected. Hallux valgus was corrected with modified Mann’s procedure. Extensor hallucis longus tendon was longitudinally incised half and half and lateral slip was reflected distally and then passed through transverse bony holes of proximal phalanx and metatarsal bone. Finally MTP stability was achieved. After 1 year of the surgery, she felt no hallux pain on gait and HVA was 18°, and M1M2 was 11°. 【Clinical significance】 Tendon transfer using lateral slip of EHL tendon is one of useful method for MTP joint instability on hallux valgus.

P2-172

Effectivity and problem of arthrodesis for hindfoot deformity in rheumatoid arthritis

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Conflict of interest: None

We investigated the postoperative result of arthrodesis for hindfoot deformity in rheumatoid arthritis (RA). We examined 5 RA patients (6 foot) who took hindfoot arthrodesis after 2012. Their mean age was 64.9±13.1 years, and their mean disease duration was 16.7±12.1 years. We performed one arthroscopic arthrodesis for ankle, two tibio-talo-calcaneal fusions, one double arthrodesis, one triple arthrodesis and one pan talar fusion. The JSSF RA foot ankle scale was significantly improved to 71±10.2 points postoperatively from 44.7±21.9 points preoperatively. Especially, the score for pain, deformity and ability to walk significantly improved. They started full weight bearing on 59.9±20.2 postoperative day. There was no case with infection or skin trouble. Improvement of the alignment in the X-ray was admitted in all patients. It took 123.3±42.4 days for bone union (54-180 days). Arthrodesis for hindfoot deformity of RA can get pain relief, improvement of walking ability, and good alignment. However, it takes a long time to bone union and the risk of complications increases in severe deformity case. Therefore, we think it is desirable to perform arthrodesis earlier before the abnormal alignment progress.

P2-173

Subtalar Joint Changes Following Talocrural Joint Arthrodesis

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Conflict of interest: None

[Background] An ankle joint lesion of rheumatoid arthritis (RA) is often accompanied by subtalar joint degeneration. However, in the absence of abnormal alignment, we perform isolated talocrural joint arthrodesis. We examined subtalar joint changes following arthrodesis. [Subjects] Four cases were studied. X-ray examination and CT scan prior to surgery detected a subtalar joint lesion in all cases. Mean age at the time of surgery was 64 (52-77) years and average post-surgery follow-up was 2.5 years. Ankle joint fixation was performed with an Ilizarov external fixator with no non-weight bearing period. [Results] Ankle joint fusion was achieved in all cases. Though all patients had previously had difficulty walking, postoperatively, three were able to walk with a T-cane and one walked without assistance. None experienced exacerbation of subtalar joint lesions, and some even showed joint space opening. [Discussion] In osteoarthritis, the subtalar joint is often preserved during pro-

cedures, while in RA, fixation is often necessary. Our results show that even patients with subtalar joint lesions can achieve sufficient pain relief. With further pharmacologic advancements, inhibition of joint destruction can be anticipated. Therefore, subtalar joint preservation is meaningful.

P2-174

A comparison of perioperative complications after total knee arthroplasty in patients with rheumatoid arthritis

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Conflict of interest: None

[Objectives and Methods] To examine the relation between disease-modifying anti-rheumatic drugs (DMARDs) and perioperative complications after total knee arthrplasty (TKA) in patients with rheumatoid arthritis, 53 patients were divided into three groups according to DMARDs: group 1 (biologic DMARDs, n=17), group 2 (MTX, n=14) and group 3 (other DMARDs, n=22). [Results] Complications occurred in 12 patients: biologics 2 cases (12%), MTX 3 cases (21%), others 7 cases (32%). Infectious complicattions occurred in 6 cases and 5 of them were taken other DMARDs. A serious complication (skin ulcer) occurred in the patient with biologic DMARDs. [Conclusion] Perioperative complications after TKA were tended to occur in patients unable to take MTX or biologic DMARDs.

P2-175

Total Hip Arthroplasty with a three-dimensional bone model for a Rheumatoid Arthritis Mutilans patient

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Conflict of interest: None

[Purpose] One case which a three-dimensional bone model was manufactured for total hip arthroplasty (henceforth, THA) with advanced bone defect by Rheumatoid Arthritis Mutilance is reported. [Object] An 85 years old woman, with Steinblocker classification Stage4, Class3 was operated. The right hip joint was Larsen classification Grade5. Using a CAD software, STL data of pelvic 3D geometry was obtained from her CT scan DICOM data, then synthetic wood model was manufactured by CNC mashine. Prereaming was performed for preparation of the cup supporter on the model. Then cup supporter was processed to fit the model preopreratively. The surgery was performed with the processed cup supporter. The model was also sterilized and was reffered during surgery. [Results] The processed cup supporter was easily installed into the prearranged position without any modification. It was thought that this procedures led to shortening of the operative time and reduction of the bleeding. [Conclusion] Processing the device preopreratively reduced the time, labour and patient's damage. Accurate device shape could contribute to better result.

P2-176

Radiographic evaluation of total hip arthroplasty for patients with rheumatoid arthritis: minimum 10-year follow-up

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Conflict of interest: None

[Objectives] The purpose of this study was to assess the radiographic results of total hip arthroplasty (THA) for patients with rheumatoid arthritis (RA). [Methods] Ten hip joints of seven patients were available more than 10 years follow-up. The average age of the patients at the surgery was 40.3 years. The average duration of RA at the operation was 13.5 years. We evaluated radiographic changes and survivor rate of components. [Results] The average follow-up period was 15.7 years. Aseptic loosening and upper migration of acetabular component were confirmed in 2 patients. One patient had undergone revision THA at 21 years after primary surgery. However, upper migration has been confirmed in acetabular component 5 years after revision. Meanwhile, both aseptic loosening and sinking were not confirmed at femoral components. [Conclusion] It was thought that careful follow-up is necessary after THA for patients with RA.

P2-177

Thromboprophylaxis of venous thrombo embolism (VTE) after total hip and knee arthroplasty with the oral direct Factor Xa inhibitors, edoxaban-evaluation using computerized tomographic pulmonary angiography (CTPA) after a pretest of D-dimer –

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Conflict of interest: None

[Objective] The CTPA is a useful method with which diagnosis can do DVT and PTE simultaneously. We used the oral direct factor Xa inhibitor, edoxaban as VTE prevention, after arthroplasty, and preventive effect was evaluated using D-dimer and CTPA. [Methods] 107cases (58Knees, 49hips, 13casesRA, 94casesOA) who was performed arthroplasty in our institution between December, 2011 and August, 2013 were received same dose (15mg orally once daily) of edoxaban. Drugs were begun 42-48hours postoperatively and continued for 8days. When the value of D-dimer was 1 or more before operation, or 15 or more after operation, we performed CTPA for evaluation of VTE. [Results] No symptomatic VTE was detected, and 7 asymptomatic VTE was detected. Age, BMI, eGFR, the lower limbs swelling measured at a patella height comparing with preoperative circumference, postoperative bleeding, serum CRP did not indicate a significant difference for the prevention of VTE. In 12 cases both value's of D-dimer (preoperative and postoperative) were high, and in the 6 cases of them VTE was detected. [Conclusion] We evaluated the efficacy and safety of same dose (15mg once daily) edoxaban for the prevention of symptomatic VTE. When both value's of D-dimer (preoperative and postoperative) were high, risk of VTE increased.

P2-178

High-velocity exercise improves physical function in patients with rheumatoid arthritis

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Conflict of interest: None

[Objectives] The purpose of the present research was to investigate the effect of the high-velocity exercise on physical functions in patients with rheumatoid arthritis (RA). [Methods] Sixteen patients with RA were randomly allocated to high-velocity exercise group (HV group: N=9) or low-velocity exercise group (LV group: N=7) for an 8-week intervention. Lower limb exercise program consisted of resistance training using elastic band. In HV group, patients contrated as quickly as possible during the concentric phase, paused for 1 second, and contracted eccentrically for 2 seconds. In LV group exercises consisted of the concentric phase for 2 seconds, the pause phase for 1 second, and the eccentric phase for 2 seconds. Outcome measures included pain, lower limb muscle strength, Sit-to-Stand Test (SST) and Timed Up and Go (TUG) test. Wilcoxon test were used to compare values before and after intervention. [Results] Pain in both groups was not significantly worsened between before and after intervention. Lower limb muscle strengths in both groups significantly increased after intervention. In HV group, SST and TUG were significantly improved after intervention. [Conclusion] High-velocity exercise

was effective for improving both lower muscle strength and physical function in patients with RA.

P2-179

Physical Exercise in Patients With Rhumatoid Arthritis

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Conflict of interest: None

[Objectives] Regular exercise is associated with better physical and mental health, and is associated with prevention of cardiovascular disease and stroke, diabetes, falls and obesity. Similarly, the exercise is important to the patient with RA. Therefore we investigated the frequency of physical exercise in patient with RA and compared it with The Questionnaires in Standard Monitoring of Patients with RA (Quest-RA). [Methods] A survey was performed with 77 outpatients with RA using international standardization physical activity questionnaire (IPAQ). And, we evaluated DAS28, HAQ, Hospital Anxiety and Depression Scale (HADS). [Results] The patients background was as follows: mean age was 62years, 71% were women, mean disease duration was 8 years, and mean DAS28 was 3.38. In QUEST-RA, the international average of the patients with physical exercise≧1 times weekly was 29.1%, on the other hand, was 27.2% in our hospital. Only 14.3% reported physical exercise≧3 times a week, and 12.9%≧1-2 times week. Physical activity was associated with men sex, lower HAQ. [Conclusion] As well as other countries, a proportion of RA patients with physical exercise was low. We propose rheumatologists motivate their patients to increase physical activity levels, and cope with this problems as a hospital.

P2-180

Relationship between patient-based satisfaction and conventional objective measurements in the early stages after total knee arthroplasty-Difference between osteoarthritis and rheumatoid arthritis-

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Conflict of interest: None

[Objectives] We investigated whether the relationship between patient's satisfaction and objective measurements in the early stages after total knee arthroplasty (TKA) differs between rheumatoid arthritis (RA) and osteoarthritis (OA) patients. [Methods] The subjects of this study were 79 who had undergone TKA for osteoarthritis (60 patients: OA group) or rheumatoid arthritis (19 patients: RA group). 2011 Knee society score were used to assess the patient's pain and satisfaction. The objective measures were femoro-tibial angle (FTA), range of motion (ROM), lower limb muscle strengths, timed up and go test (TUG) and one leg standing time. All patients were assessed at before surgery and 3 weeks after TKA. [Results] Patient's pain and satisfaction in both groups were significantly improved after TKA. FTA, ROM and one leg standing time in OA group were significantly improved at 3 weeks after TKA. In RA group, TUG was improved compared to before surgery, other measurements were not significantly between before surgery and postoperative phase [Conclusion] Our finding indicated that patient-based satisfaction in two groups improved after TKA, but conventional scales differ between RA and OA patients. Primary disease may be an important factor for the planning of effective rehabilitation.

P2-181

Making of self-help device for self-injection of teriparatide for rheumatoid arthritis patients

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Conflict of interest: None

[Objectives] Osteoporosis associated with rheumatoid arthritis (RA) causes decreases in activities of daily living. An osteoplastic agent, teriparatide, is administrated every day, using a pen type injector. However, in RA patients with severe finger deformities, both grip power and elaborateness of hand decrease, leading to the difficulty of self-injection. The purpose of this study is to make a self-help device for self-injection of teriparatide for rheumatoid arthritis patients. [Methods] Aiming at the independence of the self-injection of teriparatide, the self-help device was made. Since the circumference of the original injector is as thin as about 8 cm at the maximum, a cup-shaped holder was devised as a self-help device for the stable grip. [Results] This self-help device, the circumference of which is about 25 cm, has a large grip area, resulting in the reduction of load to finger joints and stable grip for RA patients. The visual analog scale level of the usability of the syringe was significantly decreased by the use of this device. [Conclusion] We successfully made a self-help device for self-injection of teriparatide for rheumatoid arthritis patients.

P2-182

Interventions to disabilities in the activities of daily living with treat to target strategy - A case report of an approach by physical therapist -

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Conflict of interest: None

[Introduction] The treatment of rheumatoid arthritis (RA) has improved significantly owing to treat to target strategy (T2T). T2T proposes the basic principle to "share" the decision with the patients, but be considered about the medication only. We had an experience that we could introduce the physical therapy following to T2T. [Case] 65-year-old woman, who developed RA in 1990, was performed total knee arthroplasty in 1998, but she had to remove arthroplasty due to late infection and had to accept an arthrodesis. Since then, she did not agree any suggestion of treatments. As a result, the right leg became longer than the left by 6.5 cm, but she declined to introduce the shoe lift. Her doctor changed from 2011 and applied T2T, she achieved the remission and became positive to the treatments. Left hip joint pain started to worsen from January in 2013, she decided to do left hip joint arthroplasty. However the leg length discrepancy increased after the surgery, we could introduce an optimal brace with shoe lift by asking for opinions to the patient following with T2T. [Discussion] T2T basically includes all surroundings of RA patients, then "share" the decision should not mean only medication. We considered that T2T should be applied to the treatments by other specialists.

P2-183

Examination of changes in physical function of rheumatoid arthritis patients treated by biologic disease modifiers

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Conflict of interest: None

[Objectives] Examination of changes in physical functions of rheu-

matoid arthritis (RA) patients treated by biologic disease modifiers (Bio) [Methods] 23 RA patients who were treated with Bio for 1 year were enrolled for evaluation of physical functions. Patient background showed mean age 68.4, disease duration 15.0 years, and baseline DAS/ESR 4.03. Following comparisons were performed between patients with or without moderate response in DAS/ESR (responsive group vs no efficacy group): DAS/ESR for disease activity, mHAQ and mFIM, TUG, and time for 10m walking. [Results] DAS/ESR was improved to 3.18 and 15 patients showed above moderate response. The mHAQ reduced from 0.69 to 0.40 and mHAQ improvement was significantly higher in the responsive group. For those in the responsive group, however, 10m walking and mFIM for 1 year, were worsening. While mHAQ had no correlation with mFIM, 10m walking, and TUG, mFIM showed significant correlation with 10m walking (p=0.02, rs = - 0.51) and TUG (p=0.03, rs = - 0.49) [Conclusion] Although HAQ has been widely used for evaluation of physical function in clinical practice of RA, it might be not appropriate for patients, especially with extended disease duration and relatively older age who has established joint damages and degenerative changes.

P2-184

A case report of the refractory skin ulcer in RA patient treated with our novel transcutanous application of Carbon dioxide

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Conflict of interest: Yes

[Objective] Transcutaneous CO2 therapy, such as artificial CO2 bathing, is one of the physio-therapy, and it has been used to ischemic disease and skin ulcer. We have already reported that our novel transcutaneous application of CO2 using hydro-gel and pure CO2 gas had the effect of angiogenesis in rat muscle. We applied this system for refractory skin ulcer in RA patient. [Case] 75 years old female with RA. She suffered refractory skin ulcer in the lateral side of her left lower leg from 15 years ago. The ulcer size was 15 cm x 5cm, and the depth was reached to almost her fibula bone. We applied our novel transcutaneous application of CO2 with the written informed consent under the approval of ethics committee. The duration and frequency of the application was 20 minute and twice in a week. The ulcer was reduced after 4 weeks. However, the ulcer had not healed after 8 months. Therefore, we increased the frequency of application to everyday. Then the healing of the ulcer was accelerated, and completely healed after 12months. The skin perfusion pressure was recovered from 56mmHg to 92mmHg in her left foot. [Discussion] Although we have to optimize the frequency and duration, our novel transcutaneous application might be effective treatment for refractory skin ulcer in RA patients.

P2-185

The effects of combination therapy with alendronate and eldecalcitol for glucocorticoid-induced osteoporosis –switch from alfacalcidol to eldecalcitol-

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Conflict of interest: None

[Objectives] To clarify the efficacy and safety in patients with glucocorticoid-induced osteoporosis (GIOP) undergoing combination therapy with alendronate (ALN) and alfacalcidol (ALF) by switching from ALF to eldecalcitol (ELD). [Methods] GIOP patients who received glucocorticoid therapy, alendronate and alfacalcidol were radamized into the two groups, combination ELD (0.75μg/day) and ALN (35mg/week) group (Group EA) and combination ALF (0.5-1.0μg/day) and ALN (35mg/week) group (Group AA). After treated for 6 months, lumbar spine BMD, hip BMD and bone turnover markers for efficacy, and the value of serum calcium (Ca), serum creatinine and urine Ca/creatinine ratio for safety were evaluated. [Results] Among 26 patients in Group EA and 34 patients in Group AA, two patients of Group EA dropped out within 6 months. The difference in lumbar spine BMD change between two groups was not significant. (EA 0.02% vs. AA 0.55% p=0.40). Hip BMD and bone turnover markers are also not different in two groups. The change of serum Ca is not significant in both Group EA (9.7→9.5mg/dL) and Group AA (9.8→9.6mg/dL). [Conclusion] We could not detect the effect of switching treatment from ALF to ELD at 6 months. However, both Group EA and Group AA are well tolerated. We continue this trial for 12 months.

P2-186

Changes in serum soluble RANKL and osteoprotegerin levels after teriparatide administration in rheumatic disease patients with glucocorticoid-induced osteoporosis

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Conflict of interest: None

[Objectives] The purpose of this study is to evaluate the effect of teriparatide (TPTD) on serum soluble receptor activator for nuclear factor kB ligand (sRANKL) and osteoprotegerin (OPG) levels in patients with glucocorticoid (GC)-induced osteoporosis (GIOP). [Methods] Twenty postmenopausal women with rheumatic diseases were included in this study. All the patients were changed from oral bisphosphonates to daily s.c. injections of TPTD (20 μg) for treatment of GIOP. We measured serum sRANKL, OPG, and bone turnover markers before and 6 months after TPTD treatment. The bone mineral density (BMD) was measured before and 6 months after TPTD treatment. [Results] 1. Mean serum sRANKL level was significantly decreased after TPTD treatment. In contrast, mean serum OPG level was not changed after the treatment. 2. Both of serum bone formation markers (OC, ucOC, BAP, and P1NP) and resorption markers (TRACP-5b and NTX) were significantly increased after TPTD treatment. 3. Mean BMD between before and after TPTD treatment was significantly increased compared to that of pretreatment value. [Conclusion] TPTD induced osteogenesis by activation of bone turnover. It is suggested that decreased serum sRANKL level might play an important role in mechanisms of action of TPTD in GIOP.

P2-187

Evaluation of Guidelines on the management and treatment of glucocorticoid-induced osteoporosis- Validation of American College of Rheumatology 2010 Recommendation in Japanese population –

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Conflict of interest: None

[Objectives] To validate ACR Recommenndation 2010 in Japanese population. [Methods] Subjects with connective tissue disease except rheumatoid arthritis were enrolled (18 males and 101 females). In this 2-year longitudinal study, an incident vertebral fracture was diagnosed with semiquantitative criteria by Genant (JBMR, 1993). Patients with bisphosphonate treatment (B-group) were compared with those without treatment (N-group). [Results] In low risk patients, incident vertebral fractures were observed in 67% of N-Group with less than 7.5mg PSL treatment, and in 100% of N-group and 33% of B-group with over 7.5mg PSL. In medium risk patients, 80% of N-group with less than 7.5mg PSL, and 100% of N-group and 50% of B-group with over 7.5mg PSL. In high risk patient, 88% of N-group and 42% of B-group with over 7.5mg PSL. In premenopausal female or male 50- years old, incident vertebral fractures were observed in 22% of N-group and 6% of B-group. [Conclusion] ACR 2010 was a useful indicator of bisphosphonate treatment for low

and medium risk patients. Monotherapy of bisphosphonate was insufficient and more intensive therapy should be required for most of patients with high dosage of PSL.

P2-188

Risk factors for incident vertebral fractures used Bisphosphonates (BP) in glucocorticaid-induced osteoporosis (GIO)

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Conflict of interest: None

Porpose) To clarify risk factors for incident fracrures in patients with BP in GIO. Patients and Methods) Patients (n = 137) with connective tissue disease other than RA were observed for 2 years. The means of age, disease duration, total predonisolone (PSL) dosage and daily PSL dosage during the study period were 61±15 (SD), 12 ± 11 years, 34 ± 34g and 8 ± 6 mg/day, respectively. Prevalent vertebral fractures were seen in 44% of the patients. Agents used for treatments of GIO were BP (54%), active vitamin D3 (7%) and vitamin K2 (6%). BMD were measured with DXA at the distal radius. Results and conclusions) 1) Incident vertebral fractures were seen in 64 patients (47%). 2) Logistic regression analysis showed the age (1.43 (OR)/5yo), total PSL dosage (1.09/5g), daily PSL dosage (2.36/5mg) and BMD (1.25/5% decrease) as independent risk factors, and treatments with BP (0.02) and vitamin K2 (0.06) as preventing factors ($p<0.05$). 3) Analysis of 74 patients with BP, incident fractures, the age was higher and the BMD was lower than those without incident fractures. Multivariable analysis with logistic regression revealed the presence of prevalent fracture (3.6), ther higher daily PSL dosage during the study period (1.7/5mg) and ther lower BMD (1.6/5%) as independent risk factors.

P2-189

Risk factors associated with vertebral fractures in patients with rheumatoid arthritis

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Conflict of interest: None

[Objectives] To identify potential risk factors associated with vertebral fractures in patients with rheumatoid arthritis. [Methods] We studied 288 (female 240) patients with rheumatoid arthritis. Disease activity were evaluated by DAS-28 and clinical risk factors were evaluated by clinical questionnaire. Bone mineral density (BMD) at lumbar spine were performed in all participants. Patients were 61years old on average and had median disease duration of 7.2 years. [Results] During 1.3 year follow-up, 18 (6.2%) patients developed vertebral fractures. Patients with fractures had significantly lower spine BMD, and higher CRP level when compared to patients without fractures. [Conclusion] The risk of vertebral fractures is higher in patients with higher CRP, and lower values of BMD.

P2-190

6-month effect of treatment examination when we changed it from alendronate or risedronate to minodronate in osteoporosis treatment patients with rheumatoid arthritis

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Conflict of interest: Yes

[Objectives] It has been demonstrated that bone mineral density (BMD) is increased by the switching from alendronate (ALN) / risedronate (RIS) to minodronate (MIN) in post-menopausal osteoporosis patients. The mechanism of osteoporosis in RA is unlike that of post-menopausal osteoporosis, and the switching effect to MIN is unknown. [Methods] We performed 6-month prospective study in RA patients with osteoporosis (66 women / 8 men) switching from ALN / RIS to MIN: 65.7 years old, BMI 21.5kg/m2, disease duration 15.9 years, DAS28-CRP2.51, steroid / vitaminD / biologics using rate was 60.8%/50.0%/17.6%. We examined BMD (0, 6months), bone metabolism markers (0, 3, and 6 months), and new fracture rate. Combined osteoporosis drugs were not changed during this period. [Results] BMD was increased by +2.41% in lumbar spine and +2.08% in proximal femur. The changes of bone metabolism markers were 246.2→177.6→183.5 mU/dl in TRACP-5b and 30.4→25.6→24.9 ng/ml in P1NP. New fracture rate was 4.1%. Increase of BMD was greater in patients with switcting from RIS than ALN, and with biologics and vitamin D combination. [Conclusion] Switching ALN / RIS to MIN seems effective when assessed by BMD increase in the treatment of RA osteoporosis.

P2-191

Progranulin knockout mice show severe osteoporosis compared to wild type mice

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Conflict of interest: None

[Objectives] Glycolipid metabolic disorders and autoimmune disease patients frequently suffers from osteoporosis, but its mechanism remains unknown. It has been reported that growth factor Progranulin (PGRN) inhibits TNF - α signaling and PGRN knockout mouse shows severe hyperlipidemia and atherosclerosis, but its effects on bone metabolism remains unknown. [Methods] Femoral and forearm bones were obtained by 48-weeks old PGRN knockout mice (PGRNKO) (n=8) and wild type mice (WT) (n=8) fed with normal chaw. We examined 3D trabecular structure by μCT, TRAP staining of femoral bone, and determined RNA expression level of TNF – α extracted from forearm bone. [Results] PGRNKO v.s. WT showed significant difference in both BV/TV (5.78 v.s.16.58 %; $P <0.001$) and in trabecular number (1.57 v.s. 3.79/mm; $P <0.001$). Cv/Av and cortical thickness showed no significant difference between two groups. The number of osteoclasts was 8.13 v.s. 0/mm ($P <0.05$). Relative expression levels of TNF-α in forearm bone was 2.18 v.s. 1.41 ($P <0.05$). [Conclusion] PGRN may be one of crucial factor involved in osteoporosis of glycolipid metabolic disorders and autoimmune disease.

P2-192

The effect of eldecalcitol on serum undercarboxylated osteocalcin in patients with osteoporosis

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Conflict of interest: None

[Objectives] Undercarboxylated osteocalcin (ucOC) is considered a marker for bone vitamin K deficiency. In addition, ucOC reflects the bone metabolic turnover. Eldecalcitol (ED) has been reported to strongly influence bone metabolism as compared to the conventional vitamin D supplementation. We examined the effects of ED on ucOC levels. [Methods] We measured serum ucOC levels in 54 osteoporosis patients (average age 79.2 years). The use drug is A group: only as for alfacalcidol, it is 6 cases, B group: only as for VK, it is 7 cases, C group: alfacalcidol + VK 16 cases, D group: no treatment 25 cases. We analyzed ucOC, NTX, BAP, lumbar bone mineral density in these groups. After the first examination, the alfacalcidol dosage example changed it to ED 0.75μg/day dosage, and other examples gave ED 0.75μg/day addition and reexamined 6 months later. [Results] The average ucOC level was 6.89ng/mL. The ucOC levels in 32 patients (59.3%) was higher than the standard value. After 6 months, the average ucOC was 4.45ng/mL. The serum ucOC level was reduced in 90.7% of patients who received additional ED treatment. [Conclusion] We examined the effects of ED supplementation on ucOC levels, and found that ED supplementation decreased ucOC levels along

with a decrease in the bone metabolic turnover.

P2-193

Prospective examination of clinical efficacy of minodronate which is administrated in glucocorticoid-induced osteoporosis. (Follow-up data)

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Conflict of interest: None

[Objectives] Glucocorticoids (GC) are used in almost all rheumatic disease. The incidences of vertebral and non-vertebral fractures are elevated, therefore glucocorticoid-induced osteoporosis was treated with bisphosphonates (BPs) in all patients initiating or already on GC. We examined to evaluate the usefulness of minodronate in assessing treatment effects on glucocorticoid-induced osteoporosis. [Methods] The serum levels of BAP, TRAP-5b are measured on days 0, at 6 months and at 1 year after glucocorticoid treatment. Bone mineral density values are measured at the lumbar spine and femoral neck on day 0, at 6 months and 1year after glucocorticoid therapy. [Results] The serum levels of BAP, TRACP-5b are not significant difference in minodronate and other BPs therapy group after glucocorticoid treatment. Minodronate therapy group were significant increased bone mineral density values at femoral neck after glucocorticoid therapy, and remain effective for a period of 1 year. [Conclusion] We speculate that minodronate might be good response to bone turnover and glucocorcicoid-indused osteoporosis.

P2-194

Assessment of the treatment of glucocorticoid induced osteoporosis in antineutrophil cytoplasmic antibody-associated vasculitis

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Conflict of interest: None

[Objectives] To assess the efficacy of treatments of glucocorticoid-induced osteoporosis (GIO) in antineutrophil cytoplasmic antibody associated vasculitis (AAV). [Methods] Patients with AAV who were treated with high dose glucocorticoid from 2005 to 2013 were retrospectively included. We evaluated background of the patients who had symptomatic fracture. [Results] Forty seven patients (30 MPA, 9 GPA, 8 EGPA, 32 female, 15 male, Age 69±16) were included. Median of observation period was 26 (3-96) months. Eight patients (7 MPA, 1 GPA, all female, Age 73±11) had symptomatic fracture. The term to incidence of fracture was 9 (1-47) months. Every first time fracture was vertebral body fracture. In fracture group, 26 patients were treated with bisphosphonate (BP), 24 patients were treated with active vitamin D3 analogs (VD3). In non-fracture group, 3 patients were treated with BP, 1 patient were treated with VD3. The number of patients who were treated with VD3 or combination therapy with BP and VD3 was significantly lower in fracture group than in non-fracture group ($p<0.05$). [Conclusion] Almost symptomatic fracture in patients with AAV who were treated with high dose glucocorticoid was vertebral body fracture and occurred in female. Treatment with ViD3 might reduce fracture risk in AAV.

P2-195

A study on Glucocorticoid-induced osteoporosis in patients with collagen disease in our hospital

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Conflict of interest: None

[Objectives] Glucocorticoid-induced osteoporosis (GIOP) is a major complication affecting the prognosis of patients with collagen disease or other different refractory diseases whoreceive continuous steroid treatment. In this study, we investigated the association of GC usage with the bone mineral density (BMD) and bone metabolism markers in 193 patients with collagen disease who had regularly visited our hospital. [Methods] We examined changes in the BMD and bone metabolism markers (TRAP-5b, P1NP) with the oral administration of GC. [Results] The TRAP-5b and P1NPlevels increased with the oral administration of GC and decreased with that of bisphosphonate (BP). The percent change of the BMD at the femoral neck in the GC group did not increase even with the oral administration of BP. The percent change of TRAP-5b seemed to be different at the lumbar vertebra from that of the femoral neck in patients who were orally administered BP. [Conclusion] We need to regularly assess the therapeutic effects by measuring the BMD and bone metabolism markers also in patients with GIOP who are orally administered BP.

P2-196

Osteoporosis in Rheumatoid Arthritis

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Conflict of interest: None

[Objectives] Rheumatoid arthritis (RA) is a risk factor of secondary osteoporosis. This study was to investigate a ratio of osteoporosis in RA and an effect of bisphosphonates against biochemical markers of bone. [Methods] We measured the bone mineral density (BMD) of radial DXA and calculated cross-linked N-telopeptide of type I collagen (NTX) in urine and bone-type alkaline phosphatase (BAP) in serum. We investigated 98 women RA patients, 30 to 87 years old. We administered bisphosphonates at 52 patients. [Results] There were 69 patients (70.4%) less than 70% in t-score and 51 patients (52%) were less than 85% in z-score. There was outlier of NTX or/and BAP in 13 patients (28.3%) of non-bisphosphonates group and only 2 (4%) of bisphosphonates group. 5 patients who had abnormal results both of NTX and BAP were less than 85% in z-score. [Conclusion] 51 patients were less than 85% in z-score that mean morbid decrease of BMD in compared with same aged women. The result suggested that RA could be a high risk factor of secondary osteoporosis. The ratio of outlier of biochemical markers was significantly reduced by giving bisphosphonates. To prevent secondary osteoporosis in RA, it is not only important to treat RA as good control but also to administer bisphosphonates early in same time.

P2-197

Bone morphometry with head of femur in the rheumatoid arthritis

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Conflict of interest: None

[Objectives] There are few bone morphometric reports with the load bone including head of femur in human. 7 heads of femur in 6 patients with rheumatoid arthritis who underwent a hip surgery were examined. [Methods] Femoral head was made vertical structure in a median plane and a non-decalcification slice specimen from central part. Villanueva bone stain was performed and bone morphometry with static parameter was analyzed. [Results] The average age is 71 years old (57-87). The bone mass-related parameter was high, and, as for the absorption-related parameter, it became a low value in comparison with ilium of the same age. When we investigate whether it possesses bone buds or not, which represent minimodeling, an osteoid-related parameter and the absorption-related parameter are high in the group possessing bone buds. [Conclusion] The possibility that it could become one index to express a bone kinetics to have bone buds was suggested.

P2-198

A case of systemic lupus erythematosus who showed lupus peritonitis and proteinlosing gastroenteropathy as the initial symptom successfully treated with intravenous cyclophosphamide pulse therapy

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Conflict of interest: None

The patient, a 50-year-old male, developed ascites and was admitted to a previous hospital. In the hospital he had been diagnosed as SLE since he developed photodermatosis, thrombocytopenia with positive antinuclear antibody, anti-DNA antibody, and treated with methylprednisolon pulse therapy (1000 mg/day) for 3 days and after with predonisolon 80mg/day. But his ascites was not improved. He was transffered to our hospital. Laboratory examination revealed a high level of C-reactive protein and thrombocytopenia and exudative ascites. CT revealed a large amount of ascites. Abdominal scintigraphy with 99mTc-DTPA-HSA showed proteinlosing gastroenteropathy. After plasmapheresis added, thrombocytopenia was improved, but ascites was not improved. On the 50th day in our hospital suddenly asites was developed and changed to hemorrhagic ascites and severe anemia was developed. Contrast-enhanced CT did not revealed a bleeding part. Because we thought that lupus peritonitis was developed, monthly intravenous cyclophosuphamide pulse therapy was started. With this therapy, his asites improved, and then abdominal scintigraphy showed no leak. Intravenous cyclophosuphamide pulse therapy was useful for Lupus peritonitis and proteinlosing gastroenteropathy.

P2-199

A case of a girl with SLE complicated with pneumatosis cystoides intestinalis (PCI) after methyl prednisolone pulse therapy

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Conflict of interest: None

Background: Although PCI is a rare condition, it may result from corticosteroid therapy for patients who have poor intestinal motility. **Case**: A 16-year-old girl was diagnosed as having SLE with photo hypersensitivity, hypocomplementemia, positive antinuclear antibody, and lupus nephritis. She had been suffered from continuous abdominal distention, disturbing her daily life. Her abdominal CT showed pseudo-obstruction. She was hospitalized for mPSL pulse therapy. Her abdominal distension was not serious at the day of admission. During the therapy, she got strong abdominal pain and distention. X-ray showed significant colon air. The symptoms quickly subsided by fasting, but the symptoms smoldered. After the pulse therapy, she got stronger abdominal symptoms than before. CT showed emphysema between intestinal serosa and mucosa. She was diagnosed as having PCI, and was conservatively treated with fasting and antibiotics. The treatment improved her abdominal symptoms, and the findings on X-ray disappeared. **Discussion**: In this case, increased intestinal pressure, maybe due to poor intestinal motility and bacterial over growth, and intestinal vulnerability caused by steroid therapy might have resulted in PCI. PCI should be considered during steroid therapy for autoimmune diseases.

P2-200

Successful treatment for a case of both SLE and progressive hepatitis C with immunosuppressive therapy and interferon beta

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Conflict of interest: None

Case description: A 53-year-old woman having existing SLE and insidious hepatitis C (HCV) infection was admitted to our hospital because of flared pulmonary arterial hypertension (PAH) and manifested hepatitis. She was diagnosed with SLE and PAH at the age of 35, and with asymptomatic HCV-genotype 1B infection. After initial treatment by full dose prednisolone (PSL), her SLE had been maintained on 9 mg/d of PSL and 3 mg/d of tacrolimus. In February 2013, SLE and PAH were exacerbated and hepatitis C developed slowly. In the course of successful treatment for SLE-PAH by 40 mg/d of PSL and one session of intravenous cyclophosphamide, hepatitis C progressed with elevation of serum HCV-RNA levels. In June 2013, total-bilirubin 3.9 mg/dl and ALT 226 U/l indicated imminent liver failure. After beginning a short acting interferon (IFN) beta therapy plus ribavirin, both SLE and hepatitis C resolved and normal levels of liver enzymes were accomplished. Type I-IFN, especially IFN-alpha is a putative pathogen in SLE. Both of SLE-PAH and HCV-liver failure in this case might have been lethal, and respective therapy appeared incompatible. The successful outcome in this case may be informative for treating similar disease conditions.

P2-201

A case of drug-induced lupus related with minocycline

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Conflict of interest: None

An 18-year-old Japanese girl had received oral minocycline 200mg daily for the treatment of acne since 16 years old. She had a fever three months before admission, and joint pain developed in her both knees and several PIP joints one month before. She was referred to our hospital because of a high serum level of anti-DNA antibody. She had already discontinued oral minocycline by the referral, on her own account. Because anti-nuclear antibody and anti-ds-DNA antibody were found positive, she was admitted to our department as having possible SLE. On admission, arthralgia and fever spontaneously resolved, and hypocomplementemia and cytopenia were not observed. She did not have erythema, nephritis or serositis. Autoantibodies other than anti-ds-DNA antibody were negative. Because symptoms subsided after the cessation of minocycline, she was diagnosed with drug-induced lupus. During the follow-up without treatment, arthralgia and fever did not relapse, and anti-ds-DNA antibody returned to normal. There are few reports of drug-induced lupus related with minocycline in Japan. We present this case along with a review of literature.

P2-202

Intravascular lymphoma in a patient with systemic lupus erythematosus (SLE)

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Conflict of interest: None

A 78-year-old man admitted to our hospital for acute laryngyal edema one year before. He was diagnosed as SLE, for pleural effusion, lymphopenia, serositis, elevated anti-nuclear antibody and anti-DNA antibody. After taking prednisolone (PSL) 40mg per day, pleural effusion was diminished. Azathioprine and intravenous pulse methylpredonisolone (mPSL) were administerated, because of elevated anti-DNA antibody and CRP. Intravenous pulse cyclophosphamide therapy results in decreasing PSL untill 15mg per day. On April 2011, he admitted to our hospital with dizziness, then turned out to have cerebral infarction. On the 54th day after admission, consciousness disturbance has developped. Even though intravenous pulse mPSL, cyclophosphamide and rituximab were administrated, consciousness disturbance and elevated anti-DNA and anti-dsDNA antibody remained. At last, pleural effusion and ascites increased, he died for respiratory failure. Autopsy revealed dilated cerebral capillaries containing large, atypical cells positive for CD79. This was consistent with intravascular large B cell lymphoma (IVLBL). Although it was standard clinical course as IVLBL, this case was hard to diagnose. When we

see SLE patient, we have to take IVLBL into consideration as differential diagnosis of CNS lupus.

P2-203

Acqired haemophilia A and suspected acquired von Willebrand's syndrome in a woman with systemic lupus erythematosus

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Conflict of interest: None

A 20-year-old Japanese woman was admitted to our department for fever, rash, and multiple oral ulcers. She had malar rash and her laboratory tests showed low white blood cell counts, and elevated erythrocyte sedimentation rate. Antinuclear antibody and anti-double stranded DNA antibody were positive and she was diagnosed as systemic lupus erhthematosus (SLE). On the second day of admission, she presented with uncontrollable bleeding from her nose and oral ulcer. Laboratory examination revealed prolongation of the activated partial thromboplastin time, reduced factor VIII (FVIII) activity and the present of FVIII inhibitor. In addition, her von Willebrand factor (vWF) activity was also markedly reduced. We diagnosed the patient as having acqired haemophilia A and suspected acquired von Willebrand's syndrome. Transfusion of recombinant human factor FVII and recombinant activated FVIII along with administration of prednisolone successfully stopped her mucocutaneous hemorrhage. Acquired hemophilia A and acquired von Willebrand's syndrome are both rare but lethal diseases. Therefore, when a patient with SLE complains about uncontrollable bleeding, physicians should carefully estimate coagulation function test.

P2-204

A case of recurrent lupus enteritis treated with rituximab

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Conflict of interest: None

[Case] A 22-year-old female was diagnosed with systemic lupus erythematosus (SLE) in 2010. In September 2012, she was admitted to our hospital because of diarrhea, nausea, vomiting and abdominal pain. She was diagnosed with lupus enteritis on the basis of enhanced CT which showed diffuse bowel wall thickening involving the small and large intestine. She was treated with two cycles of intravenous (IV) methylprednisolone (mPSL) pulse therapy followed by high-dose IV mPSL, but gastrointestinal (GI) symptoms remained. She was administered with monthly pulsed IV cyclophosphamide (IVCY) therapy and her symptoms recovered. After 6 months of IVCY therapy, azathioprine or tacrolimus were added as maintenance therapy. However she experienced four more episodes of recurrent lupus enteritis. In September 2013, she was admitted to our hospital on fifth recurrence of lupus enteritis. IV mPSL induced remission of symptoms but a more definitive treatment was needed to maintain clinical improvement and prevent a further relapse of GI symptoms. Therefore we decided to administer two cycles rituximab 500mg per week. She had no relapse of GI symptoms after rituximab therapy. [Conclusion] Rituximab can be useful agent for recurrent lupus enteritis that is resistant to conventional therapy.

P2-205

Colonoscopy was useful for the diagnosis and assessment of treatment in a patient with lupus enteritis

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Conflict of interest: None

[Case] A woman in her thirties was diagnosed with SLE 15 years ago and was treated with prednisolone (PSL) 17.5 mg/day before this episode. She was admitted to our hospital due to intermittent abdominal pain, diarrhea, and bloody feces. The enhanced CT showed nonspecific inflammation of colonic mucosa. The colonoscopy revealed solitary rectal ulcer and the biopsy showed lymphocytes and plasma cells infiltration into the lamina propria. She was diagnosed with lupus enteritis and her PSL was increased to 30 mg/day and azathioprine was initiated. Her symptoms ameliorated and she was discharged. However, abdominal pain and bloody feces relapsed one week later and she was readmitted. Repeated colonoscopy revealed new mucous edema and erosion in the sigmoid colon, although rectal colon ulcer was cured. She received pulse methylprednisolone and her PSL was increased to 50 mg/day. Subsequently, her symptoms and colonoscopic findings completely ameliorated, and she was discharged again. **[Clinical Significance]** In literature, lupus enteritis is described as abdominal vasculitis. However, typical findings of vasculitis were not always obtained by angiography or biopsy even in clinically suspected cases. Colonoscopy can be useful for the diagnosis and assessment of treatment in those cases.

P2-206

Successful treatment of severe thrombocytopenia with Eltrombopag in a patient with SLE

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Conflict of interest: None

We report a case of a 29-year-old woman, who was complicated with SLE and thrombocytopenia 9 years ago. Despite mPSL pulse, PSL, splenectomy and cyclosporine, she repeated severe thrombocytopenia several times, and PSL could not be tapered below 15mg/d. On September 2012, she was complicated with abnormal vaginal bleeding, and she immediately admitted. Laboratory data showed severe anemia (Hb 5.5g/dl) and thrombocytopenia (2.1 $X10^4/mm^3$). She recovered with mPSL pulse therapy and intravenous immunoglobulin (IVIG), and cyclosporine was switched to intravenous cyclophosphamide (IVCY). Because of nausea, IVCY was withdrawn after third administration. After getting informed consent, she was administered 12.5mg/d of eltrombopag. She responded to eltrombopag with increase of thrombocyte, and PSL was tapered from 25mg/d to 19mg/d. However her thrombocyte count has been very fluctuating sharply. In her menstrual period, she showed severe thrombocytopenia below 1.0 $X10^4/mm^3$. Other period, her platelet count increase over 20 $X10^4/mm^3$. After one year, she was administered eltrombopag between 37.5mg/d to 50mg/d. Further studies are warranted in order to determine the efficacy and adverse effect of elrtombopag to SLE patient.

P2-207

Effectiveness of intensive therapy including plasma exchange in 3 cases of systemic lupus erythematosus/lupus nephritis with thrombotic microangiopathy

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Conflict of interest: None

[Case1] A 19-year-old woman with a 7-year history of SLE/APS showed renal dysfunction and was diagnosed as LN (class IIIA/C+IV). Soon after the intravenous methylprednisolone (mPSL) was initiated, hemolytic anemia and thrombocytopenia developed. Thrombotic microangiopathy (TMA) was supposed and 12 times of plasma exchange (PE) with IVCY was effective and she achieved remission. **[Case 2]** A 57-year-old woman with a 21-year history of SLE presented with fever, disturbed consciousness, and renal dysfunction. After mPSL pulse therapy, thrombocytopenia with hemolytic anemia developed, and TMA was suspected. Ten times of PE combined with IVCY improved TMA and NPSLE completely. **[Case 3]** A 43-year-old woman with a 7-year history

of SLE showed a relapse of LN (Class IV-G (A/C)). TAC and MZR were not effective. TMA became progressed soon after intravenous mPSL pulse therapy. Nine times of PE combined with micophenolate mofetil (MMF) led to remission of TMA. **[Discussion]** We experienced 3 cases of SLE/LN with TMA, which became evident after steroid pulse therapy. PE combined with IVCY/MMF led to remission.

P2-208

Three cases of patients with systemic lupus erythematosus complicated with peripheral neuropathy (PN)

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Conflict of interest: None

[Objectives] We examined the clinical characteristics of SLE with PN. [Methods] The subjects were 3 SLE patients who were suspected of PN. We investigated autoantibody, complement value, immune complex, remote organ failure, and treatment-treatment reaction. [Results] **1:** A 24-y.o. man with 10 years of disease duration (dd) developed skin ulcer, and mononeuritis multiplex in both legs. **2:** A 29-y.o. woman who developed mononeuritis multiplex in legs. **3:** A 53-y.o. woman with 14 years of dd who developed mononeuritis multiplex in both legs while tapering PSL. All the cases were treated with a combination of PSL and the immunosuppressive drug. As for case 1, the patient developed lumbar abscess concomitantly during the IVCY, showed a recovery with the antimicrobial administration and surgical treatment, but didn't recover from the neuropathy. As for case 2 and 3, neuropathy of patients improved by a concomitant use of TAC/MZR and IVCY. [Conclusion] The patients had no obviously common characteristics. If the disease occurs to the long-term patients, incipient patients, and low disease activity patients under treatment, and if these patients complain about numbness or mobility disorder regardless of the duration of the disease or activity, it is necessary to continue the investigation with PN.

P2-209

Successful treatment with apheresis therapy in patient with transverse myelitis associated with SLE

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Conflict of interest: None

[case1] A 57-year-old woman presented with brain infarction internal capsule at January 2013. She was diagnosed with antiphospholipid syndrome, had anti-coagulation therapy with warfarin. After two months, she presented with sensory loss and Th2-7 level of spinal cord revealed long T2 signal on MRI. Based on neuropathy, leukopenia, anti-nuclear antibody, we diagnosed transverse myelitis associated with SLE. She received methylprednisolone (mPSL) pulse therapy, apheresis therapy and cyclophosphamide pulse (IVCY) therapy. Symptoms improved, PSL doses was tapered. [case2] A 38-year-old woman was diagnosed with SLE at the age of 13, was treated with PSL. In August 2013, she presented with paresthesiaon upper extremity, and C2 level of spinal cord revealed long T2 signal on MRI. She was diagnosed with transverse myelitis associated with SLE, received mPSL pulse therapy. After a month, she presented with brain infarction medial medulla. She received mPSL pulse therapy, apheresis therapy and IVCY therapy. Symptoms improved, PSL doses were reduced. Transverse myelitis was reported in 1-1.5% of patients with SLE, relapses are common 50% during corticosteroid dose reduction. Our case indicates apheresis therapy may be an effective treatment for transverse myelitis associated with SLE.

P2-210

Two cases of myelitis with positive anti-neuronal and anti-NR2 antibodies in systemic lupus erythematosus

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Conflict of interest: None

[Case 1] A-38-year-old woman was admitted to the hospital because of bowel and bladder dysfunction, weakness and sensory disturbance in legs of 4 days duration. She was diagnosed with SLE at 18 year old. Spinal MRI showed increased signal intensity in T2WI. CSF study showed pleocytosis, elevated anti-neuronal and anti-NR2 antibodies. She was treated with 6 sessions of plasma exchanges (PE), 6 times of pulses cyclophosphamide and 3 courses of pulse mPSL. PE sharply improved her strength, which was followed by gradual recovery. Normal spinal MRI was obtained at the day of 32 and anti-neuronal and anti-NR2 antibodies were observed at the day of 137. [Case 2] A 35 year-old woman was admitted to the hospital with 3 weeks history of bowel and bladder dysfunction, weakness and sensory disturbance in legs. She was diagnosed with SLE at 26 year old. CSF showed pleocytosis, anti-neuronal and anti-NR2 antibodies. Her symptoms resolved partially with a course of pulse mPSL. CSF revealed negative anti-neuronal and anti-NR2 antibodies at the day of 25. [Conclusion] Increased anti-neuronal and anti-NR2 antibodies were observed along with symptom of myelitis in these 2 cases. Further research is required for confirming the relationship of these antibodies and myelitis in SLE.

P2-211

Clinical study of neuropsychiatric SLE (NPSLE) in our hospital

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Conflict of interest: None

[Objectives] NPSLE is one of the important organ damage which is affected by prognosis in SLE. We have investigated the clinical appearance, activity, laboratory data, treatment and prognosis of NPSLE onset time. [Patients and methods] We investigated 27 patients (male4, female23) with NPSLE who had diagnosed in our hospital, during March 2000 to June 2013, retrospectively. [Results] The average age was 35.9, SLEDAI was 8 to 43. The Clinical manifestation was the following; Aseptic meningitis 15caces, Cerebrovascular disease 4 cases, Headache 12 cases, Myelopathy 1case, Seizure disorders 4cases, Diffuse neuropsychological syndrome 7cases and Cranial neuropathy 1case. Ten cases showed abnormal appearance in brain MRI. Labolatry data revealed significant high anti-sm antibodies and low complement. All cases had received steroid therapy and 19cases had combined steroid pulse therapy. Twenty four cases had treated with apheresis (7cases had combined IVCY therapy). The high anti-ds-DNA antibodies and low complement had improved after treatment. There was no recurrence for one year. The death was 1 case on onset. [Conclusion] There is not shown the optimum management of NPSLE at this time. Our data indicated the possibility that apheresis is one of the effective therapy for them.

P2-212

A case of central nervous system lupus complicated with various neuropsychiatric manifestation including limbic encephalitis

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Conflict of interest: None

Patient: A 42-year-old woman presented with pyrexia and abnormal behavior. **History of present illness**: In December 200X-1, exacerbated rash and oral apthae emerged during treatment for central nervous system lupus (CNS) lupus. Prednisolone (PSL) dose was increased from 10 to 20 mg/day. In January 200X, the patient was admitted with fever ³38°C, abnormal behavior, and disorientation. Limbic encephalitis was suspected due to symptoms such as increased protein in cerebrospinal fluid and extensive signal abnormalities in the left temporal lobe on magnetic resonance imaging. Tests for viral encephalitis and paraneoplastic syndrome yielded negative results. Limbic encephalitis associated with CNS lupus was diagnosed; therefore, steroid pulse therapy and aftertreatment of PSL 60 mg/day were initiated. During the clinical course, concomitant posterior reversible encephalopathy syndrome (PRES) was observed and supplementary treatment with intravenous cyclophosphamide (IVCY) was initiated. Cerebrospinal fluid and MRI findings subsequently resolved. **Discussion**: In this case, diverse CNS manifestations of limbic encephalitis and PRES appeared during treatment for psychiatric symptoms associated with CNS lupus. Favorable outcomes were achieved with steroid therapy and IVCY.

P2-213

Post-steroid neuropsychiatric manifestations in systemic lupus erythematosus

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Conflict of interest: None

[Objective] To clarify the characteristics of post-steroid neuropsychiatric disease (PSNP) in patients with SLE. [Methods] This retrospective observation study comprised 128 patients with SLE who did not present any neuropsychological manifestations on admission. One hundred and thirty patients with other autoimmune diseases were served as a control group. All patients were treated with high-dose corticosteroids (prednisolone ≧ 40mg/day) in Hokkaido University hospital, between April 2002 and December 2012. The prevalence and characteristics of PSNP were reviewed on medical records. Neuropsychiatric events were classified according to the American College of Rheumatology criteria for NPSLE (1999). [Results] The prevalence of PSNP was significantly higher in patients with SLE (25%, 32/128) than those with other autoimmune diseases (5%, 8/130) ($p<0.01$, OR 5.08, 95%CI [2.24-11.54]). Diffuse psychiatric / neuropsychological syndromes occurred in 30 patients, neurologic syndromes of the central nervous system in 5 patients. In 70 % of lupus patients with PSNP, one or more abnormal findings in spinal fluid, electroencephalogram, MRI or SPECT were observed. [Conclusion] PSNP was more frequent in patients with SLE, thus could be classified as one of the features of NPSLE.

P2-214

Study on clinical aspects of neuropsychiatric SLE

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Conflict of interest: None

[Objectives] To assess clinical aspects of NPSLE. [Patients] Thirty seven NPSLE patients (15.5%) of all 238 SLE patients treated at our department. [Results] All SLE (male 18: female 220): Age of SLE onset 31.9 ± 13.5 (male 38.1 ± 18.0, female 31.4 ±12.9 $p=0.043$), 71 cases at 20s, 58 at 30s and 44 at 10s. NPSLE (male 2: female 35): age of SLE onset 34.1±11.9 (male 35.5, female 34.0), 11 cases at 20s, 10 at 30s and 10at 10s. NPSLE symptoms occurred before more than 1 year of diagnosis of SLE in 3 cases, within 1 year in 17 and after more than 1 year in 17 (45.9%). Neuropsychiatric syndromes observed: Central nervous system 29 cases (cerebrovascular disease 11, psychosis 8, seizure disorders 7, cognitive disfunction 2 and aseptic meningitis 1) and peripheral nervous system 8 cases (neuropathy 5, acute inflammatory demyelinating polyradiculoneuropathy 2 and myasthenia gravis 1). Magnetic resonance imaging showed positive findings in 7 of 13 cases of central nervous system NPSLE excluded cerebrovascular cases. Central nervous system manifestations varied with serum LDH in 2 cases. Steroid pulse therapy was done in 25 cases of NPSLE, in which, intravenous cyclophophamide therapy was added in 10 cases. NPSLE was primary cause of death in 3 cases of 25 SLE death.

P2-215

Etanercept-associated SLE with Neuropsychiatric Syndromes

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Conflict of interest: None

A 71-year-old woman with rheumatoid arthritis (RA) had been treated with etanercept (ETN) and MTX due to inadequate responder of abatacept. Eleven month later, she developed face erythema, so ETN and MTX were discontinued. However, the rush got worse 2 weeks later. She was diagnosed with SLE according to face erythema, positive antinuclear antibody, positive anti-double strand DNA antibody, positive anti-cardiolipin IgG, hypocomplementemia, and pleuritis. She was treated with prednisolone 0.5mg/kg/day. One and half month later, she was admitted to our hospital with high fever, then she presented with loss of consciousness. After various examinations includingcranial MRI (magnetic resonance imaging) and cerebral spinal fluid testing, she was diagnosed with-Neuropsychiatric SLE (NPSLE). She underwent intravenous methylprednisolone pulse therapy followed by high dose steroids andcyclophosphamide therapy with successful recovery. This is the rare case of etanercept-associated NPSLE.

P2-216

Hiccups and gait disturbance in a systemic lupus erythematosus patient

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Conflict of interest: None

Neuropsychiatric systemic lupus erythematosus (NPSLE) presents diverse symptoms and its diagnosis is often difficult. Thirty four year-old female who had fifteen-year history of SLE admitted to the emergency department because of headache, vomiting and fever. Initial cerebrospinal fluid analysis and brain CT revealed normal. Five days later, nystagmus, double vision, hiccups, gait disturbance and positive meningeal irritation sign gradually appeared. T2 weighted MRI image showed that new high intensity lesions appeared from lateral medulla oblongata to periaqueductal gray. Her anti SS-A antibody, lupus anticoagulant and anti prothrombin antibody were all positive, and anti aquaporine 4 antibody was negative. IL-6 level in CSF was high (330 pg/ml). We diagnosed her as NPSLE and her symptoms completely disappeared after high dose corticosteroid therapy. The etiologies of NPSLE were supposed to be vascular involvements, autoantibody-related injury, overexpression of inflammatory mediators, such as cytokines, and their combination. Brainstem involvement in NPSLE is rarely reported and it is difficult to distinguish brainstem NPSLE from neuromyelitis optica spectrum disorder. We report this case with a review of the literature.

P2-217

Bilateral phrenic neuropathy observed in a patient with systemic lupus erythematosus

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Conflict of interest: None

【Case】A 67-year-old woman has developed progressive exertional dyspnea, pleural effusion and ascites since 2009, and was diagnosed as having serositis due to overlap syndrome (systemic lupus erythematosus (SLE), Sjogren syndrome, systemic scleroderma). We started oral administration of prednisolone (PSL, 40 mg/day) for the serositis, which improved. PSL was successfully decreased to 5.5mg/day. However, she developed progressive dyspnea and bilateral edema on lower extremities since April 2013, was admitted to our hospital. Chest Xp revealed no respiratory movement of bilateral diagram, suggesting of phrenic paralysis. The nerve conduction velocity test on bilateral phrenic nerves showed slight extension of latency and significant reduction of amplitude, suggesting of the presence of axonopathy. Moreover, anti-neuron antibody and anti-NR2 antibody were positive both in serum and cerebrospinal fluid. Taken together, we diagnosed this case as phrenic neuropathy, presumably related to NP-SLE. She received high dose PSL and intravenous cyclophosphamide therapy with non-invasive positive pressure ventilation (NPPV). The neuropathy has gradually improved at the present. 【Conclusion】we reported a rare case with NP-SLE having bilateral phrenic neuropathy.

P2-218

Two cases of NPSLE

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Conflict of interest: None

Introduction: NPSLE is a prognostic factor is one organ lesions severe SLE. But to predict its development it is difficult. Case: one disease to SLE onset woman 42 years old, about 10 years ago, lupus nephritis was seen then. It was during treatment steroid and mizoribine. She was hospitalized with kidney biopsy. 11th hospital day aphasia, tremor appeared, MRI to go again, was diagnosed with NPSLE is recognized findings in cerebrospinal fluid examination. Steroid pulse was performed, remission of symptoms, relapse was observed. Case 2 was 34 female outpatients, lower leg edema, general malaise appeared. She was diagnosed as SLE with anti- dsDNA antibody 153.5 U / ml. It was positive and 30.2 U / ml MPO-ANCA also. 38th hospital day disturbance of consciousness, convulsions appeared, the diagnosis of NPSLE in head MRI is performed steroid pulse, the endoxan pulse therapy, showed an improvement of symptoms. There is renal failure consideration, both two cases, NPSLE was developed to steroid treatment. It is said that the activities of the NPSLE is not necessarily related to the activity of other organs. However, I was considered when symptoms SLE fever, and rash is not suppressed was observed, that there is a need falls on treatment in mind always the NPSLE.

P2-219

Successful combined treatment with prednisolone, cyclosporine, IVCY and high-dose IVIg for anti-MDA5 antibody positive ADM associated with rapidly progressive interstitial pneumonitis

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Conflict of interest: None

【Case】A 62 year-old Japanese man was admitted to our hospital with shortness of breath, Heliotrope rash, Gottron's papules, arthralgia and fatigue. Laboratory investigations revealed that levels of serum LDH, KL-6, and ferritin were 400 IU/l, 1880 U/ml and 1393 ng/ml, respectively. MRI demonstrated no evidence of myositis. HRCT scans showed diffuse ground-glass opacities from the upper to lower lung fields. Anti-MDA5 antibody was positive. Therefore, he was diagnosed with ADM associated with rapidly progressive interstitial pneumonitis (RPIP). We initiated combination therapies including PSL, CyA and IVCY. Additionally, PMX-DHP was also carried out for 2 days. A few months later, 5-times IVCY was switched to high-dose intravenous immunoglobulin therapy (IVIg) because of the reactivation of IP shadow and serum ferritin (peak: 2599 ng/ml). The additional treatment with IVIg improved ADM associated with RPIP (ferritin: 437 ng/ml). 11 months after admission, he was discharged with maintenance therapy of PSL and CyA. 【Conclusion】Herein we report a case of successful combined treatment with PSL, CyA, IVCY and high-dose IVIg for anti-MDA5 antibody positive ADM associated with RPIP. IVIg might be considered as a new treatment for anti-MDA5 antibody positive ADM associated with RPIP.

P2-220

A case of systemic lupus erythematosus developed into dermatomyositis associated with rapidly progressive interstitial pneumonia

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Conflict of interest: None

Cyclosporin (CyA) combined with PSL is a standard treatment for dermatomyositis (DM) associated with interstitial pneumonia (IP). Here we report a case of systemic lupus erythematosus (SLE) developed into DM associated with rapidly progressive IP (RP-IP) even under the treatment with PSL and CyA. A 32 years-old woman was affected with SLE with lupus nephritis (type IV) in 2006. She was treated with 2 course of M-PSL pulse therapy followed by PSL (0.8 mg/kg) and CyA (2 mg/kg). PSL had been tapered to 20 mg/alternate day, when generalized erythema and muscle pain developed in Aug. 2013. When she visited ER, widespread consolidation and GGO were recognized on chest CT images, and she was referred to us suspicious of RP-IP. On admission, heliotrope rash, Gottron's sign, muscle tenderness, erythema keratodes on extremities, elevation of aldolase, and images compatible with myositis on MRI were found. Serum ferritin level, a prognostic marker of RP-IP in DM, was 2973 ng/ml. She was diagnosed as DM with RP-IP, and 6 course of M-PSL pulse therapy, increase the dose of CyA and IVCY every 3 weeks were done resulting in good clinical course. Development of DM under the treatment with PSL and CyA is rare, and we think that early combination therapy with 3 drugs was life saving.

P2-221

Refractory polymyositis which was taken a long time to be diagnosed and effectively treated by steroid, immunosuppressive, and intravenous immunoglobuline therapy: a case report

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Conflict of interest: None

We present the case of 57-year-old Japanese female with chronic weakness involving her proximal muscle and elevated serum CPK level. She had been complaining of easy fatigability and palpitation 9 months before admission. Her symptoms were gradually worsened, and feeling of fatigue extended in her neck and shoulder 2 months before admission and in her proximal upper and lower extremities when climbing stairs 1 month prior to admission. She went to medical clinic, where she was pointed out to have weakness involving her proximal muscle and elevated CPK level, and came to our hospital for further investigation. She was diagnosed as polymyositis, and received steroid pulse therapy and started to take 60mg of daily prednisolone, which were insufficiently effective for her symptoms. Methotrexate, cyclosporine, and intravenous immunoglobuline were administered in addition to the prednisolone, which were partially effective, but after tapering the dose of prednisolone, her symptoms recurred. Second intravenous immunoglobuline was administered, which was effective dramatically with almost complete remission of her symptoms.

P2-222

A case of polymyositis associated with anti-SRP antibody which is difficult to distinguish lumbar spinal stenosis

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Conflict of interest: None

71-year-old man was diagnosed with polymyositis in another hospital at the age of 35. His condition was stable for more than 30 years in the administration of prednisolone (PSL) 5mg / day. Difficulty walking has progressed gradually from 68 years old, but it is also lumbar spinal canal stenosis, was not consistent in the symptoms associated with this, because CK was within the normal range. We consider the possibility of worsening of symptoms due to progression of polymyositis, to examine such as MRI also did not clearly. So, where it was reduced further maintenance dose of PSL, muscle weakness and rise in CK was observed. In addition, anti-SRP antibodies are also found to be positive image inflammation of the lower leg muscles and also observed in MRI and FDG-PET, and became able to walk by prednisolone increased.

P2-223

A case of osteomyelitis and aseptic necrosis in tibia with polymyositis

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Conflict of interest: None

A 63-year-old-woman whose polymyositis (PM) has been treated with prednisolone, methotrexate, and tacrolimus for 13 years, suffered from right ankle joint pain and swelling without any injury. Although plain X-ray was normal, MRI revealed bone edema and signal change like “fracture line” at right distal tibia. CT scan did not show definite fracture. Bone biopsy specimen showed osteomyelitis with aseptic necrosis. She was treated with joint aspiration and injection, and her symptoms were gradually improved. Follow-up MRI revealed edema and partial collapse of right distal tibia. Concomitant skeletal symptoms with PM are including multiple joint pain and/or polyarthritis without bone destruction; on the other hand, osteomyelitis with aseptic necrosis is very rare. Here, we report this interesting case, and make consideration as well.

P2-224

A case of rheumatoid arthritis and dermatomyositis who caught phlegmone of his bilateral elbow one after another

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Conflict of interest: None

[Case] This is a case of 44-year-old male. At the time to come to our hospital, pain and swelling were observed in PIP and MP joint of bilateral hand and wrist and shoulder and right knee joint. CRP and ANA were negative but RF, MMP-3 and ACPA were positive in the laboratory data. So we diagnosed that he had RA according to the 2010 Rheumatoid Arthritis Classification Criteria. He began to take 8mg of methotrexate (MTX) weekly and bucillamine. But a decrease of white blood cell (WBC) was occurred. So MTX had to stop taking. Then Tocilizumab therapy was started 3 monthes after. But again the decrease of WBC was occurred. So we changed to do Golimumab therapy (GLM) 9 monthes after. However, he caught phlegmone on his left elbow 10 monthes after. So we had to give up GLM. The phlegmone was rapidly improved after antibiotic therapy. At that time, he was diagnosed dermatomyositis because of his Gottron’s sign of his bilateral elbow and finger. Then he caught phlegmone on his right elbow after 1 year. We throught that the focus was Gottoron’s sign of his right elbow. We started Etenercept therapy (ETN) after 1 year and 6 monthes. But he caught phlegmone on right elbow again after 1 year and 7 monthes. Again ETN was stopped and antibiotics was taken. Now we restart the ETN and continue.

P2-225

A case of anti-PM-Scl100 antibody positive polymyositis associated with infliximab therapy for ulcerative colitis

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Conflict of interest: None

A 60-year-old man with a 2-year history of ulcerative colitis, intolerance to 5-aminosalicylic acid and liver injury induced by azathioprine was treated successfully with infliximab maintenance therapy. Four months after starting infliximab treatment, he developed muscle pain in his upper and lower limbs. His serum creatine kinase (CK) increased to 1,100 U/L and infliximab treatment was stopped. However, he experienced hemorrhagic diarrhea and was admitted to our hospital. Based on muscle biopsy and electromyography, he was diagnosed with polymyositis. He was negative for myositis-associated antibodies against Mi-2, Ku, PM-Scl75, SRP, Jo-1, PL-7, PL-12, OJ, and EJ, but was positive for anti-PM-Scl100 antibody. He was treated with 60 mg/day intravenous prednisolone and tacrolimus was added. The muscle pain and diarrhea disappeared and CK was normalized. Several case reports have described myositis and other autoimmune diseases resulting from treatment with anti-tumor necrosis factor-α antibody. Despite the resolution of our patient’s underlying disease, clinicians should be aware of these complications.

P2-226

A case of the anti-CADM-140/MDA5 antibody-positive rapidly progressive interstitial pneumonia associated with dermatomyositis in which tacrolimus and the cyclophosphamide pulse therapy were effective

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Conflict of interest: None

A 45-year-old man noticed erythema on his fingers. The erythema appeared also in the face and the front neck gradually. Slight fever, sore throat, and myalgia emerged. He was diagnosed as dermatomyositis (DM) from the skin and muscle symptoms in a neighboring hospital. Treatment with prednisolone (PSL) was initiated and symptoms gradually improved. However his condition worsened after tapering of PSL. He was introduced our hospital, and admitted. There was the progression of respiratory symptoms from just before the hospitalization, and chest CT revealed ground-glass opacity images. We diagnosed as Clinically-Amyopathic DM complicated by a rapidly progressive interstitial pneumonia (RPIP). Anti-CADM-140/MDA5 antibody was also positive. We enforced steroid pulse therapy and used 7mg/day tacrolimus (TAC) with cyclophosphamide pulse therapy (IVCY). Additionally, we provided the direct hemoperfusion method using a polymyxin-B fixed fiber column. The erythema resolved and the serum markers such as ferritin and CT remark improved. In the RPIP with DM, it is required that multidrug should be used and maintained the effective blood concentration. This case was successful by providing IVCY and the enough use of TAC. We will report with bibliographic considerations.

P2-227

Three cases of inflammatory myositis-associated interstitial lung disease treated with polymixin B-immobilized fiber column direct hemopefusion (PMX-DHP)

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Conflict of interest: None

We report three cases of IM-associated ILD treated with PMX-DHP as well as predonisolone and immunosuppressants. Case 1 is a 46-year-old male diagnosed as clinically amyopathic dermatomyositis (CADM). Although we started treatment with methylprednisolone (mPSL) pulse therapy followed by oral prednisolone (PSL), tacrolimus (Tac) and intravenous cyclophosphamide pulse therapy (IVCY), respiratory failure got worse. However, his symptoms and findings of ILD gradually improved after the initiation of PMX-DHP. Case 2 is a 51-year-old female diagnosed as dermatomyositis in 2008. In 2012, her ILD had deteriorated regardless of administration of PSL, Tac and IVCY. After treatment with mPSL pulse therapy and PMX-DHP, the clinical symptoms and findings have gradually improved. Case 3 is a 74-year-old female diagnosed as polymyositis with positivity of anti-Ro antibody. She suffered from acute deterioration of ILD. We found her prompt recovery from ILD after initiation of PMX-DHP as well as mPSL pulse therapy. Increased evidences have been shown that PMX-DHP makes effects on acute exacerbation of ILD as well as ARDS, regardless of their etiology, although reasons for the efficacy remains to be clarified. We'll here report these three cases in addition to bliographic consideration.

P2-228

A case of clinically amyopathic dermatomyositis with Interstitial pneumonia complicated with sigmoid colon cancer

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Conflict of interest: None

A 59-year old woman was reffered to our hospital with complaints of cough, breathlessness, joint stiffness and skin rash. She showed heliotrope eyelids, periungual erythema, mechanic's hands and interstitial pneumonia (IP) by computed tomography. Although loss of muscle weakness and elevating serum skeletal muscle enzymes level, magnetic resonance imaging revealed abnormal high signal changes on her peroneus longus muscle. She was diagnosed of clinically amyopathic dermatomyositis (CADM). Intravenous steroid pulse therapy (mPSL pulse), oral cyclosporine and intravenous cyclophosphamide pulse therapy were not effective. Since colonoscopy revealed advanced sigmoid colon cancer, sigmoidectomy and colostomy were performed. For several postoperative days, her respiratory condition was improved significantly. However she developed pulmonary thromboembolism and cytomegalovirus infection. Although she was treated with ganciclovir, mPSL pulse and intravenous immunoglobulin therapy, she died of respiratory failure due to acute exacerbation of IP. IP with CADM is frequently resistant to immunosuppressive therapy, and there are very few examples of the complication with malignancy. We discussed treatment of the acute exacerbation of IP with CADM and malignancy with a review of the literature.

P2-229

An atypical case of MPO-ANCA positive granulomatosis with polyangiitis (GPA) in which an orbital mass led to the final diagnosis

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Conflict of interest: None

[Case] A 70's woman was tentatively diagnosed with microscopic polyangiitis (MPA) based on fever, polyarthritis, elevation of CRP level, positive MPO-ANCA and interstitial pneumonia 3 years ago. There was no significant renal disorder, neuropathy or rash. She was treated with daily dose of 0.8mg/kg prednisolone (PSL), and her symptoms and laboratory data ameliorated. 3 months before admission, she had a headache and pain around her right eye. Hypertrophy of soft tissue in her right orbit and nasal cavity was shown on CT. However, the biopsy of the soft tissue in her nasal cavity was negative for vasculitis or granuloma. Then, she suddenly went blind in her right eye. CT and MRI showed the mass pressing the optic nerve. Steroid pulse therapy was initiated and her visual impairment started to recover next day. Subsequent oral PSL (1.0 mg/kg and then tapered) and pulsed intravenous cyclophosphamide were administered. Her right eye visual acuity recoverd to 20/20, and the mass almost disappeared on MRI. **[Clinical Significance]** In this case, although MPO-ANCA, not PR3-ANCA was positive and the biopsy did not confirm the diagnosis, the final diagnosis was GPA based on the orbital mass formation for which steroid was effective. This case illustrated the difficulty in diagnosing GPA.

P2-230

A case of Eosinophilic Granulomatosis with Polyangitis (EGPA) with serum IgG4 elevation

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Conflict of interest: None

A 56-year-old man who developed bronchial asthma in 2010 was referred to hospital for anorexia and abdominal distension in 2013. Blood examination showed leukocytosis and eosinophilia (WBC 18000 cells/μL, Eosinocytes 55.8%), and he was admitted to hospital. Eosinophilic gastroenteritis was suspected but the upper and lower gastrointestinal endoscopy including a rectal biopsy was normal. The antinuclear antibody, MPO-ANCA and PR3-ANCA were negative. There was only the eosinophil infiltration in the skin biopsy, and no atypical cells were found in the bone marrow. Stomachache and eosinophilia worsened, further a pain and numbness appeared in the legs. Then he was suspected of EGPA and treated with methylprednisolone pulse (1g/day) followed by 60mg/day of prednisolone (PSL). Although eosinophilia and gastrointestinal symptoms were improved, neurologic symptoms were unchanged. He was transferred to our hospital. ANCAs were also negative but serum IgE and IgG4 levels were elevated. A nerve conduction study showed peripheral neuropathy. Neurologic symptoms were also ameliorated by IVIG. EGPA often complicates serum IgG4 elevation, but histopathological finding is unfulfilled with the criteria of IgG4-related disease. We report this case with histopathological investigation.

P2-231

A Case of ANCA-associated Vasculitis presented non-infectious Mitral Vegetation

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Conflict of interest: None

【Case】 A 72-year-old male was admitted in October 2012 with a 1-month history of otitis media, high fever, and headache. The echocardiography showed verrucous vegetations and mitral regurgitation. Laboratory values at the time of referral are as follows: CRP 14.96 mg/dl, MPO-ANCA 94 EU. Urinalysis showed hematuria (2+): sediment red blood cells 5-9/high power field and proteinuria. Chest CT scan revealed cavitary disease in right inferior lobe. His renal biopsy found glomerular crescentic formation. In addition, his temporal arteritis biopsy showed fibrinoid necrosis. Transoesophageal echocardiographic findings showed

mitral valve vegetation up to 11mm. Multiple blood culture remained negative. We diagnosed non-infective vegetation affecting the mitral valve in ANCA-associated vasculitis.【Conclusion】ANCA-associated vasculitis is an autoimmune necrotizing vasculitis that can affect many organ systems. Cardiac involvement is rare. Valves seem to be more frequently affected. Cardiologic investigations should have an important place at diagnosis and supervision.

P2-232

Granulomatosis with Polyangiitis Accompanied with Multinucleated Giant Cells in the Right Temporal Artery: a Case Report

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Conflict of interest: None

Vasculitides are classified by the size of the vessel involved, the pathological features and the clinical symptoms. Here, we report a case of granulomatosis with polyangiitis (GPA) who presented with pathological features of giant cell arteritis (GCA). [Case] 76 year-old woman, with low grade fever, loss of appetite and weight loss for six months was referred to our hospital. Physical examination revealed dilatation and attenuated pulsation in the right temporal artery, and livedo racemosa in both lower extremities. Laboratory data showed macrocytic anemia, elevated erythrocyte sedimentation rate and CRP, high titer of MPO-ANCA, estimated urine protein 0.6g/day, urine occult blood+/-. Computed tomography (CT) and chest X-ray showed multiple pulmonary nodules with cavitations. CT-guided lung nodule biopsy revealed granuloma, so she was diagnosed GPA. Temporal artery biopsy showed multinucleated giant cells and rupture of the inner elastic lamina.

P2-233

Clinical analysis of 9 patients with giant cell arteritis in our department

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Conflict of interest: None

[Objectives] Presentation of manifestations and analysis of treatment responses in giant cell arteritis (GCA). [Methods] 9 patients were collected from 2008 to 2013. Clinical manifestations and treatment responses were investigated, retrospectively. [Results] Among 9 cases of GCA (female 5, male 4, age 65.5±8.2 years), initial symptoms were fever (78%), malaise (78%), headache (56%), jaw claudication (11%), visual disturbances (44%), visual loss (11%), swelling of temporal artery (TA) (56%), and pulseless of TA (33%). Laboratory data were CRP 7.15±4.89 mg/dl, ESR 88.8±33.55 mm/hr, WBC 7240±1350/μl, Hb 10.9±2.1g/dl. Carotid artery wall thickening were found in 77%, aortic wall thickening in 44% and internal carotid artery stricture in 22%. Five patients (56%) were confirmed as GCA by TA biopsy. All patients were treated with steroid. All patients went into remission with CRP negativity. However, 4 patients were relapsed. There ware significant differences in duration of CRP positivity between non-relapse group and relapse group (5.6±0.5 vs 14.3±6.8 days, p=0.023). [Conclusion] Although GCA showed heterogeneous clinical manifestations, our study revealed that longer duration of CRP positivity might be a risk factor for relapse in GCA patients.

P2-234

A case of orbital apex syndrome due to exacerbation of granulomatosis with polyangiitis (GPA)

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Conflict of interest: None

Case: A 29-y.o. man **Present illness:** In Mar 2012, he started to receive prednisolone (PSL) 60 mg/d and monthly pulse therapy of cyclophosphamide (IVCY) 6 cycles to induce remission of GPA involving the upper airways and lungs. During PSL dose reduction, left temporal headache and left eye pain developed in Sep 2012. Trigeminal neuralgia was suspected but disappeared spontaneously. When PSL was decreased to 10 mg/d, left frontal headache, left eye pain, and a reduction of visual acuity in his left eye developed in Jun 2013. Contrast head MRI revealed abnormalities in the left orbital apex, sinus cavernosus, and the lesser wing of the left sphenoid bone, and he was diagnosed as orbital apex syndrome due to exacerbation of GPA. As IVCY was considered ineffective, he started PSL 40 mg/d, rituximab 375 mg/m^2/wk for 4 weeks. His left frontal headache disappeared, and contrast head MRI showed improvement. **Discussion**: Orbital apex syndrome is a symptom complex by affection of the nerves passing through the superior orbital fissure and optic canal, and is associated with an infection or injury, among others. Although this is rare among patients with ANCA-related angiitis, physicians should be aware of its possibility as this may significantly affect QOL and need prompt intervention.

P2-235

A case of granulomatosis with polyangiitis that presented with toe gangrene and complete atrioventricular block

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Conflict of interest: None

This is a case of a 48-year-old man who developed arthralgia in legs over the course of several weeks and did not improve despite analgesics. At the presentation to our hospital, in addition to persistment arthralgia, serum C-reactive proteins was elevated and chest X-ray showed a nodular shadow in the right middle lobe. Within several days after presentation, purpura developed from his right toe to his dorsal foot, turning into blood blister, and blood blister gradually spreaded in all extremities, and turning into gangrene on several toes. Vasculitis was doubted from pathological findings of TBLB. After admission the complete atrioventricular block developed, so an external cardiac pacemaker was inserted. The abnormality was not seen in upper respiratory tract. He had nephritis and his level of PR3-ANCA was high, so he was diagnosised with granulomatosis with polyangiitis. The steroid pluse treatment started and then complete AV block disappeared. After the steroid pluse treatment he was continued with oral prednisolone and cyclophosphamide. And a nodule shadow of his lung was reduced, his gangrene didn't spread. Gangren and complete AV block as a symptom of GPA are relatively rare. We present a case of valuable GPA that developed arthralgia at first, complicated by gangrene and complete AV block.

P2-236

A case of cutaneous polyarteritis nodosa with subcutaneous nodules on the trunk following polyarthritis

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Conflict of interest: None

[Background] Cutaneous polyarteritis nodosa (CPN) is characterized by a benign course and rarely progresses to polyarteritis nodosa (PN). Few CPN patients develop PN if associated symptoms were on the same area as skin lesions. The new draft of diagnostic criteria (new CPN) devised recently and it can be a distinct entity from PN. And CPN patients, but not new, without risk factors such as recurrent ulcers has also demonstrate a good prognosis. We report a case of CPN with arthritis to show this kind of patients have low risk for PN. [Case] A 51-year-old woman presented with seronegative polyarthritis 44 months ago and continued for 1 year. Arthritis relapsed 9 months ago and intraarticular injections were performed. She developed subcutaneous nodules on abdomen and back 6 months ago. Laboratory findings showed elevation of CRP and ESR, and normal IgG level. ANA was weakly positive, but ANCAs were negative. Skin biopsy revealed vasculitis in a small vessel of dermis. She was diagnosed as CPN and treatment with 30 mg/day of prednisolone was initiated, then symptoms had disappeared. There have been no new

lesions thereafter. [Clinical significance] This CPN patient without bad prognostic factors has not developed PN yet, but careful monitoring will be necessary for a long time.

P2-237

A male patient of cranial nerve palsy complicated with rheumatoid vasculitis (RV)

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Japanese Red Cross Center

Conflict of interest: None

A 47-year-old man, having 1-year history of seropositive RA with bone erosions, developed fever, numbness of palm, right pleural effusion and a variety of cranial neuropathy. When transferred to our hospital, his arthritis was well controlled by BUC, SASP. Dysphemia, dysphagia, left facial palsy, disturbed left eyeball movement, and tongue deviation were observed. Niether lumbar puncture nor encephalic and cervical MRI revealed abnormal findings. Peripheral nerve conduction study showed slight decrease of conduction velocity in left ulnar and median nerves. Although Bickerstaff`s brainstem encephalitis was a differential diagnosis, antineuric antibody was negative. Findings of pleural fluid and of lung specimen biopsied by VATS suggested rheumatoid pleuritis. CT-angiography revealed uneven distribution of right metacarpal artery, and thermography showed lowered temperature at the relevant region. With an assumption of RV, intravenous immunoglobulin (IVIg) was administered at dosage of 0.4mg/kg/day for 5 days. Soon he recovered well from neurological involvement. This case would be rare, but important in that rheumatoid vasculitis involved cranial nerves, and IVIg dramatically cured them.

P2-238

Two cases of necrotizing small arteritis at the uterus discovered by pathological examinations after panhysterectomy

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Conflict of interest: None

Case 1: A fifty-seven years old woman had a medical examination of gynecology because she had metrorrhagia June, 2008. The histrogical diagnosis was an atypical endometrial hyperplasia. The pathological examination showed necrotizing small arteritis, after she had the simple hysterectomy and bilateral salpingo-oophorectomy February, 2009. We had consultation for the pathological result but she had no significant foundings of angitis March, 2009. Case 2: A fifty years old woman had a medical examination of gynecology because she had hypermenorrhea June, 2009. She had a laparoscopic hysterectomy for the myoma of uterus and adenomyosis of uterus January, 2010. The pathological examination showed necrotizing small arteritis after the operation. We had consultation for the pathological result but she also had no significant founding of angitis February, 2009. They are the cases of the limited angitis of uterus. The limited polyangitis injuries one or several organs but the prognosis of them seems to be comparative good. They are comparative rare cases, so we present ours through the previous cases and the bibliographical studies.

P2-239

A case of single organ vasculitis with epididymis and spermatic cord

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Conflict of interest: None

A 69-year-old male presented to our emergency room with a complaint of fever and swelling scrotums for two days. He was diagnosed with epididymitis and funiculitis according to the contract CT findings. Antibiotics were given at the Urology outpatient department, but with little effect. He was admitted and introduced to our department on day 8. His temperature was 38.3℃. A cord like structure was palpable at his inguinal region. He had no tenderness of epididymis. The laboratory findings showed elevated WBC count and increased CRP level. Serologic test was negative. We suspected vasculitis, and performed a biopsy of his epididymis on day13. The result of biopsy showed invasion of inflammatory cells around the spermatic duct, indicating arteritis. Neither CT angiography nor gallium scintigraphy showed specific findings. On day 24 we started to prescribe prednisolone (PSL) at 60mg/day. He rapidly became afebrile, and the WBC count and CRP level decreased. He was discharged on day 30. Disease concept of Single Organ Vasculitis (SOV) was newly established at Chapel Hill Consensus Conference 2012. We herein report a rare case of SOV with epididymis and spermatic cord.

P2-240

Chronic peripheral arterial occulusive disease in a 12-year-old boy

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Conflict of interest: None

[Introduction] Chronic peripheral arterial occulusive disease (PAOD) is a rare. Most cases are adult. Buerger's disease is a one of PAOD and is a condition occurring in male smokers. We report the case of juvenile onset PAOD is a non-smoker. [Case] The case is a boy in twelve years old. Raynaud phenomenon was developed in both fingers and general fatigue from two years ago. His fingers were swollen, reddness and pricking. Digital ulcer on the second finger'stip in right hand was present, after eighteen months. His general condition is good without weight loss and fever. His features are absent pulses of peripheral arteries and Raynaud phenomenon in upper limb and digital gangrene on the fingertips of the second and middle finger in right hand. WBC 5900/μl, CRP <0.1 mg/dl, ESR 55 mm/h. Various antisera are negative. CTA shows Vessel occlusion and irregularity of the Branchial artery and the Popliteal artery. Vasodilators and antithrombotic and anticoagulant therapy were use together Hyperbaric Oxygenation (5-7 times in a week). These combination therapy improve Raynaud phenomenon. Hyperbaric Oxygenation persistent therapy has brought about good pain contorol, and inhibit to deteriorate in digital gangrene. [Conclusion] Clinical findings of Juvenile PAOD are different from adult PAOD.

P2-241

Two cases of Propylthiouracil induced MPO-ANCA-associated vasculitis

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Conflict of interest: None

[Objectives] Propylthiouracil (PTU) is one of the most common drugs that induce MPO-ANCA, but not all the cases develop MPO-ANCA associated vasculitis (AAV). We report two cases of PTU induced AAV with an atypical clinical course. [Case1] An 85-years-old woman with low-grade fever for two months transferred to our hospital because of elevated level of MPO-ANCA (>300 IU/L). No vasculitis symptom other than fever was seen on admission. Her fever once went down after PTU was withdrawn, but skin purpura, scleritis and jejunal ulcers appeared later. [Case2] A 55-years-old woman was admitted to our Hematological department for pancytopenia. Serum MPO-ANCA was positive and PTU was discontinued. No severe organ involvement other than fever, arthralgia and oral ulcers was present. Treatment with PSL 10mg/day once relieved her symptoms, but multiple hemorrhagic bullous lesions and skin ulcers were found one month later. She was histologically diagnosed AAV by skin biopsy. [Conclusion] We experienced two cases of AAV caused by PTU, whose organ symptoms appeared a little while after discontinuation of the drug. To avoid severe organ damage, careful observations are needed even if organ involvements are not present initially.

P2-242

Analyses of clinical feature and treatment in patients with ANCA-associated vasculitis

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Conflict of interest: None

[Objectives] We have examined clinical feature and treatment in patients with ANCA- associated vasculitis. [Methods] We have recruited 24 ANCA-associated vasculitis patients including 15 microscopic polyangitis (MPA), 4 granulomatosis with polyangitis (GPA) and 5 eosinophilic granulomatosis with polyangitis (EGPA) from 2005 to 2013. [Results] The average age was 65.3±2.9, 14 man and 10 woman. The average BVAS (Birminghan vasculitis activity score 2008 version 3) was 15.9±1.3 before treatment. These patients showed 7 interstitial pneumonia (5 UIP, 1 UIP possible, 1 non-UIP), 15 nephritis, 3 purpura, 7 multiple mononeuritis and 1 gastrointestinal perforation. Treatment for remission was 14 steroid alone, 10 steroid plus cyclophosphamide and 13 steroid pulse therapy. Two cases of MPA died and three cases of GPA recurred. Four cases had antinuclear antibody more than 160 times, and three cases of MPA showed positive anti-centromere antibody, but not showed symptoms and laboratory examnation for PSS and PBC. [Conclusion] We have examined clinical features and treatments in patients with ANCA- associated vasculitis. We recognized three cases of positive anti-centromere antibody, but the evidence of PSS was absent.

P2-243

A study to compare AZP and MTX about remission therapy for microscopic polyangiitis (MPA)

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Conflict of interest: None

Objective: We compared the therapeutic effects between azathioprine (AZP) and methotrexate (MTX) in microscopic polyangiitis (MPA). Patients and Methods: Of 50 patients with MPA admitted to our hospital from Jan. 2005 to Oct. 2013, 22 patients who were treated with AZP or MTX in addition to glucocorticosteroids (GC) were enrolled in this study. We evaluated the therapeutic effects and prognosis of AZP or MTX in addition to GC. The disease severity was assessed by the JMAAV protocol. Results: Of 22 patients, 17 was treated with AZP (group A) and 5 was treated with MTX (group B). The numbers of patients who achieved remission are 15 in group A and 5 in group B. There were no significant differences in the rate of steroid pulse therapy and IVCY therapy (p=0.9046, and p=0.4673, respectively), the initial dose of GC (p=0.5333), BVAS (p=0.7442) and the rate and duration of remission (p=0.4212, and p=0.5988, respectively) between group A and B. Conclusion: There was no significant difference in the therapeutic effects and prognosis between AZP and MTX in MPA.

P2-244

Mizoribin pulse therapy in angiitis syndrome

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Conflict of interest: None

【Objective 】To assess the efficacy and safety of mizoribin (MZR) pulse therapy in angiitis syndrome.【Method】The strategy of MZR pulse therapy (MZR-P) is 350~500mg/time of MZR, 2~3times/week. 7 patients with angiitis syndrome treated with MZR-P were enrolled in this study. We assessed laboratory findings, dose of steroid and immunosuppressants at 0, 6, 12 months after mizoribin initiation.【Results】The mean age was 59.3±35.3 (male:female was 2:5). 4 patient were microscopic polyangiitis, 2 were aortitis syndrome, and 1 was Henoch-Schoenlein purpura. 4 patients were initiated with MZR-P witin 2 weeks after steroid initiation (groupA: remission induction), and 3 patients refractory to steroid were treated with MZR-P additionally (groupB: remission meintenance). At the point of MZR-P initiation, the dose of PSL in the groupA and B were 35±10mg/day, 14±6mg/day, respectably. And in the groupB, mean steroid dosage was decreased to 8.3±1.7 mg/day 12 months after the treatment. Azathioprine dosage was reduced from 75mg/day to 25mg/day in a patient of the groupB. In the all patients, serious adverse event and revival of the angiitis did not appear for 12 month.【Conclusions】Mizoribin pulse therapy is possible to be one of the options of treating angiitis syndrome.

P2-245

Evaluation of the proportion of readmissionafter corticosteroid therapy initiation in elderly patients with ANCA-associated vasculitis

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Conflict of interest: None

[Background] In Japan, the incidence of ANCA-associated vasculitis (AAV) is increasing. AAV frequently requires treatment with high-dose corticosteroids and immunosuppressive drugs, which may cause severe adverse events, particularly in elderly patients. [Objectives] To evaluate the proportion of readmission and reasons for readmission after corticosteroid therapy in elderly AAV patients. [Methods] This retrospective cohort study included AAV patients aged ≥65 years who were diagnosed at Tenri hospital from 1994 to 2009. The primary and secondary outcomes were the proportion of readmission within 2 years after corticosteroid therapy initiation and reasons for readmission, respectively. [Results] Totally, 43 patients were included. Of these, 9 received steroid pulse therapy and 30 received immunosuppressive therapy. The proportion of readmission within 2 years after treatment initiation was 53% (23/43). The reasons for readmission included disease exacerbation (n = 4), infection (n = 13), fracture (n = 4), and others (n =2). [Conclusion] Readmission was attributed to infection and fracture, both possible adverse events of corticosteroid therapy, indicating that the risk of adverse events and disease control should be given equal consideration during the treatment of elderly AAV patients.

P2-246

A case of relapsing polychondritis associated with patulous Eustachian tube

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Conflict of interest: None

The patient, 67-year-old woman, was reffered to our department with several months of low-grade fever, swelling of both ears and fingers and generalized pain. Our investigation revealed bilateral auricular chondritis, non-erosive, seronegative polyarthritis, nasal chondritis, scleritis, carditis and aortitis. Although she showed positive urine occult blood test, she denied further evaluation. Antinuclear antibody was negative and anti-type II collagen antibody was 49.5 EU/ml. She was diagnosed as relapsing polychondritis. She was treated with prednisolone (1mg/kg/day) and her symptoms improved. After starting therapy, she became to perceive her own voice as abnormally loud and feel pressure in her left ear. Her left tympanic membrane vibration with every breath taken by her was observed and she was diagnosed as patulous Eustachian tube. Before treatment, FDG-PET scanning showed abnormal accumulation around her Eustachian tubes. We speculated that lumen of Eustachian tube dilated during the healing stage of Eustachian tube chondritis. Relapsing polychondritis is a rare autoimmune disease involving cartilage tissue of the

whole body. Eustachian tube chondritis is known to causes Eustachian tube stenosis, but rare to cause patulous Eustachian tube.

P2-247

Pulmonary parenchyma lesion with Relapsing Polychondritis combined with Myelodysplastic Syndrome

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Conflict of interest: None

[Case] 65 years, Male. In March, 2012, he had left auricular swelling, fever, arthralgia, scleritis, and superficial lymphadenopathy. He was diagnosed relapsing polychondritis (RP) combined with myelodysplastic syndrome (MDS) with auricular biopsy and bone marrow examination. In May, 2012, CT scans showed there were 3 small nodules in his lung. He was treated with PSL25mg (0.5mg/kg), and his symptoms got better and these nodules disappeared. In Apple, 2013, he repeated fever, and CRP got worse. He was treated with PSL27.5mg and AZP100mg, but CRP became 10.45mg/dl. CT scans showed there were diffuse ground-glass opacities and a few small nodules. Acid-fast bacilli smears (sputum, gastric fluid, bone marrow) were negative. Tuberculosis PCR of bone marrow was negative. QFT was unavailable. β-D glucan was 16.8pg/ml, CMV antigen wasn't detected. Bronchoscopy showed almost of cells were macrophages in BALF, tuberculosis PCR was negative, cytology was Class II. We didn't find meaningful bacteria with any culture. We diagnosed this lung lesion was caused by RP. [Conclusion] There were few reports about pulmonary parenchyma lesion with RP. This is an interesting case that CT scan shows diffuse ground-glass opacities and a few small nodules in RP combined with MDS.

P2-248

A case of Sweet syndrome associated with relapsing polychondritis and myelodysplastic syndrome

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Conflict of interest: None

We report a 63 year-old man with relapsing polychondritis (RP) and myelodysplastic syndrome (MDS), subsequently associated with Sweet syndrome. Before admission, he was diagnosed as relapsing polychondritis proven by ear cartilaginous biopsy and treated with steroid therapy. RP relapsed steroid-dependently. Therefore, he was admitted to our hospital. Laboratory data showed pancytopenia and bone marrow aspiration subsequently proved MDS. He presented with high fever. Physical examination revealed multiple, erythematous, pseudovesicular plaques on trunk, histopathological evaluation of which demonstrated diffuse neutrophilic infiltration with nuclear dust in the dermis without vasculitis. Chest computed tomography showed multiple pulmonary nodular lesions and histological findings of lung biopsy specimen revealed lymphocytic cluster at intraalveolar space. We diagnosed him as Sweet syndrome, and administrated 40mg/day of oral PSL. His symptoms improved. Based on these findings, our patient was diagnosed as Sweet syndrome associated with RP and MDS.

P2-249

Successful treatment of relapsing polychondritis with airway involvement by tocilizumab

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Conflict of interest: None

A 37-year-old female showed auricular pain in July 2011 and ocular pain with hyperemia, polyarthritis and saddle nose in August 2012. She was treated with betamethasone of 2mg/day by home doctor, and was referred to our hospital in December 2012. She felt airway obstruction. PET/CT showed the accumulation of FDG in the trachea and central bronchus. A biopsy of auricular cartilage showed infiltration of lymphocytes. She was diagnosed with relapsing polychondritis (RP). Autoantibody against collagen type II was negative. She was treated with prednisolone (PSL) of 55mg/day, followed by methotrexate (MTX) of 10mg/week. On the 40th hospital day, her symptoms improved, but thickening of the central bronchus remained. Tocilizumab (TCZ) of 8mg/kg was intiated on the 48th hospital day with favorable response. Now, she is stable with no recurrence and PSL is tapering to 12.5mg/day. Airway involvement is a prognostic risk factor of RP and needed to be evaluated and controlled strictly. There are limited reports that biologic agents are effective for RP and we review the treatment with TCZ.

P2-250

A Case of Relapsing Polychondritis Presenting with Costochondritis in Which ^{99m}Tc scintigraphy, ^{67}Ga scintigraphy and Ultrasound examination Were of Great Value for Diagnosis and Management

Takashi Okada[1], Go Murayama[1], Keisuke Oda[2], Souichiro Nakano[2], Jun Suzuki[2], Michihiro Ogasawara[2], Ken Yamaji[2], Naoto Tamura[2], Yoshinari Takasaki[2]
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Conflict of interest: None

Relapsing polychondritis is a relatively uncommon disease manifesting various symptoms associated with inflammation and destruction of the cartilage. Early diagnosis can be difficult. Case. A 63-year-old man was admitted to our hospital with fever and chest pain after cerebral infarction treatment. He had a pain, swelling and rubefaction arouond the ribs. Whole-body CT showed edema of the thyroid cartilage, tracheal cartilage and costal cartilage. The accumulation of ^{99m}Tc scintigraphy was observed in tracheal cartilage, nasal cartilage and thyroid cartilage and that of ^{67}Ga scintigraphy was observed in costal cartilage. Ultrasound examination found increased blood flow level in nasal cartilage, thyroid cartilage and costal cartilage. Serum typeII collagen antibody was detected. Difinite diagnosis of Relapsing polychondritis was performed from a thyroid cartilage histologically. After starting treatment with prednisolone 55mg/day, the symptoms disappeared and abnormal observations on CT, ^{99m}Tc scintigraphy, ^{67}Ga scintigraphy and Ultrasound examination were normalized. Relapsing polychondritis should be promptly diagnosed and treated to prevent cartilage destruction. ^{99m}Tc scintigraphy, ^{67}Ga scintigraphy and Ultrasound examination was useful for diagnosis and management in Relapsing polychondritis.

P2-251

A case report of relapsing polychondritis preceding a transient unconsciousness with aseptic meningitis

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Conflict of interest: Yes

[Background] We report a patient of relapsing polychondritis (RP) with an unconsciousness which resolved spontaneously. We considered the cause of the unconsciousness was aseptic meningitis. [Case] A 64-year-old man admitted to our hospital with fever and pain of pinnas. He had been diagnosed as having RP since 2005 so we doubted that RP was flair up again at that time. After the admission, he lost consciousness

(JCS I-1). The examination revealed meningeal inflammation or encephalopathy because brain waves were slow and levels of cerebrospinal fluid (CSF) protein were risen, however numbers of CSF cells were normal. We treated with antibiotics and antiviral drug, but we couldn't detect the source of infection through the various cultures and antibody tests. After that, his consciousness had returned at once, so this disturbance of consciousness was temporary. But fever and levels of CRP were not improved in spite of the following treatment. We judged that RP was flair up and increased the dosage of prednisolone (PSL) - 30 mg / d. [Conclusion] In the past, RP complicated with aseptic meningitis was reported only ten cases in Japan and almost all cases were needed high dose PSL treatment. We received that aseptic meningitis of RP spontaneously resolved without PSL treatment.

P2-252

Efficacy of TNF inhibitors in patients with spondyloarthritis: a retrospective study

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Conflict of interest: None

[Objective] Recently, accumulating evidence indicated the efficacy of anti-TNF therapy on spondyloarthritides (SpA). The aim of this study was to evaluate the efficacy and safety of TNF inhibitors in the treatment of SpA. [Method] Patients with SpA who were treated with TNF inhibitors and were followed at least for 6 months were included in the study. Efficacy was evaluated using peripheral joint count, patients' pain VAS, ESR, CRP, BASDAI, BASFI and BASMI. Safety assessments were conducted based on clinical records. [Results] Nine patients with psoriatic arthritis, eight with ankylosing spondylitis and one with arthritis associated with inflammatory bowels disease were included in the study. At 24 weeks, the number of tender and swollen joints decreased compared with baseline. CRP levels significantly decreased at 4 weeks and 24 weeks. However, significant improvement was not detected in BASDAI, BASFI or BASMI. Two patients discontinued treatment owing to lack of efficacy. One patient withdrew anti-TNF therapy because of cutaneous malignancy. [Conclusion] In patients with SpA, TNF inhibitor was useful for improvement of peripheral arthritis and inflammatory reactions. However, no significant improvement was detected in indices for spinal involvement.

P2-253

Disease Characteristics and Treatment in 116 Patients with Psoriatic Arthritis

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Conflict of interest: None

[Objectives] This retrospective study assesses the epidemiology, clinical manifestations, and treatment of psoriatic arthritis (PsA) in a 520-bed tertiary-level hospital in Japan. [Methods] Physician-diagnosed PsA patient records from January 2003 through September 2013 were reviewed for clinical characteristics, serologies, complications, and treatment. Current diagnostic classification criteria were subsequently applied. [Results] Data from 116 patients (57 male; mean age, 47.5 years) were extracted. At diagnosis, 39.7%, 40.5%, and 19.8% of patients had asymmetric oligoarthritis, systemic polyarthritis, and DIP arthritis, respectively. 44.8% had axial joint involvement. Prevalence of dermatological manifestations was 84.5% for plaque psoriasis and 12.9% for pustular psoriasis. Classification criteria for psoriatic arthritis (CASPAR) positivity was 92.2%; assesment in ankylosing spondylitis (ASAS) criteria (peripheral joint involved type) was 100%. [Conclusion] There is large overlap between PsA and other rheumatic diseases. This information helps further clarify an RA-mimicking disease.

P2-254

Combination therpy of Ustekinumab and GCAP for severe psoriatic arthritis: case report

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Conflict of interest: None

【case】We report on a 41 years-old woman. A pustule appeared at 24 age. She was diagnosed with pustular psoriasis, and treated with etretinate and PUVA, but rashes repeatedly improved and relapsed. At 29 age rashes were deteriorating and we combined CSA. At 34 age rashes were relapesed. In addition enthesitis and arthralgia appeared. We diagnosed PsA (3points of CASPAR). At 38 age we introduced IFX. It was effective for both rashes and artritis, but gradually attenuated. We switched to ADA from 40 age. (15th, CRP5.4) However, the effect was transient, the symptom recurred (19th). We used MTX together, but stopped in a nausea. The symptom turned worse and affected QOL. Therefore we introduced GCAP and UST, because disease severity was high. (PASI 17.2, CRP6.5, DAS28 6.5) The treatment was very effective. (12weeks time, PASI 4.5, DAS28 2.8, CRP 1.4) 48th week now, disease activity maintains low. (DAS28 2.6, CRP 0.9)【conclusion】PsA chronicity passes progressively and QOL is affected with bone destruction from an early stage. In this case GCAP and UST was effective. UST is an antibody for the p40 subunit of IL-12 and IL-23 and restrains both courses of Th1 and Th17. UST has different mechanism from the TNF inhibitor therapy. I report becase UST was effective, for resistant TNF inhibitor therapy and high disease activity.

P2-255

The result of joint replacement surgery for Psoriatic Arthritis

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Conflict of interest: None

[Objectives] The prevalence of psoriasis in the general population is 0.1% in Japan. Psoriatic arthritis (PsA) is a chronic inflammatory arthropathy that affects approximately 6% to 48% of patient with psoriasis. The aim of this paper is to evaluate the results of total hip and knee arthroplasty (THA and TKA) in patients with PsA. **[Methods]** Material included 4 patients, 1 female and 3 males, on whom 3 THAs and 3 TKAs were performed at Nagoya City University Hospital between 1992 and 2013. The mean age of patients was 43.8 years. The mean follow-up duration is 7.8 years. The patients were evaluated Japanese Orthopaedic Association (JOA) score, range of motion (ROM), surgical site infection (SSI), postoperative psoriatic skin lesion and loosening of joint prosthesis. **[Results]** The average of JOA score increased from 60 to 82.7 points in the THA group and that increased from 37.3 to 74.0 points in the TKA group. In all patients, there is no evidence of loosening of the implant and SSI at the latest examination. Skin lesions were well controlled. **[Conclusion]** Our study did not show SSI and deterioration of skin lesions in joint replacement surgery for PsA. All patients had improved clinical joint score and ROM.

P2-256

A case of ulcerative colitis with positive HLA-B27 associated with bamboo spine like lesions

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Conflict of interest: None

[Case] An UC male patient, who was 69, was introduced our hospital with his complains of limping gait due to back pain. His back pain and

diarrhea had recurred since his 30s. In his 50s, his arthritis were worsened; however, the cause were unidentified. NSAIDs did not effect, but PSL (5 mg daily) was effective, thus he was suspected having RA. UC was detected by colonoscopy at his 61, because the recurrent melena had been noted. Then, 5-ASA 1500 mg daily was added, soon its dose was increased 2250 mg daily. At the same time, palmoplantar pustulosis was present, but sternoclavicularitis had been absent in all his course. His data of the first arrival were below: WBC, 10,000 /μL; Hb, 10.9 g/dL; CRP, 6.7 mg/dL; RF, negative; HLA-B27, positive; Schober's test, expanding 1.5 cm; no ocular lesions; X-ray, no peripheral but some axial arthritis (syndesmophyte like lesions). When UC was worsened in 2013, sacroiliitis was absent from X-ray and MRI. The ASAS criteria (2009) was fulfilled with over 3 months' back pain occurred under his 45, positive HLA-B27, active UC, back-pain, and arthritis in large joints. [Clinical significance] We experienced an UC patient followed to SpA fulfilled by ASAS criteria (2009). HLA-B27 might be very important, when arthritis detected in patients with UC.

P2-257

A case of dermatofiblosarcoma protuberans that was administrated Adalimumab for the treatment of ankylosing spondylitis, and that was increased rapidly

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Conflict of interest: Yes

A 74-year-old man had neck pain and stiffness of systemic joints in October 2010. He was given diagnosis of ossification of posterior longitudinal ligament and was treated. But he did not improve, so he was referred to our hospital in January 2012. His physical findings were mobility limitation of chest and lumbar region. Bamboo spine was present on radiographs. The C-reactive protein level and erythrocyte sedimentation rate ware elevated. HLA B27 was positive. We diagnosed with ankylosing spondylitis. We treated him with adalimumab and it improved his symptoms and inflammatory reaction rapidly. But surgical wound on left elbow was swelled in June 2012. (Before 10 years, He was given diagnosis of sarcoma on left elbow and excised it.) We stopped this treatment and biopsied this lesion. We diagnosed with dermatofiblosarcoma protuberans. Adalimumab dosen't increase incidence of malignancy in statistically. But some report shows drug-associated malignancy after adalimumab treatment. In this case, adalimumab caused relapse of skin tumor, so we shoud be noted marignancy.

P2-258

A bilateral carpal tunnel syndrome following calcium pyrophosphate deposition of the bilateral wrists

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Conflict of interest: None

[Objectives] Calcium pyrophosphate deposition (CPPD) is a disease which deposit calcium pyrophosphate in articular tissues. We report a case of bilateral carpal tunnel syndrome following CPPD of the bilateral wrists. [Methods] A 71 year old man with X-ray finding of calcification in the both wrists was operated for a carpal tunnel syndrome of the left wrist. Gritty chalky deposits, perforating the palmar articular capsule of the left wrist, were observed in the floor of the carpal tunnel. Synovial tissues with papillary proliferation and calcium deposition were histopathologically found in the resected deposits from the wrist and the carpal tunnel. Furthermore, rhombus-shaped crystals were identified by a polarized light microscopy. Seven months after the operation of the left wrist, the operation of the right wrist was performed, and the findings of the right wrist both during the operation and by a microscopy were similar to the left wrist. [Conclusion] This is the first case report of bilateral carpal tunnel syndrome of the patient with chronic CPPD of the both wrists. Chronic CPPD brings damage of articular and periarticular tissue and reduce the function of the limb. It might be necessary to make a careful observation of chondrocalcinosis, even if it is asymptomatic.

P2-259

A case of relapsing polychondritis developed during the course of gout treatment

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Conflict of interest: None

A 64 year-old male had been treated for gout since 2002 without apparent gouty attacks. He had hoarseness in October 2010, and an otorhinolaryngologist (ENT) diagnosed as vocal code polyp. In May 2012, he found swelling and pain in his right auricle. While it looked like a gouty tophus, swelling developed into whole ear and closed an external acoustic meatus. Swelling and pain appeared later also in left, and his ENT had continued antibiotic therapy with no effect. When he visited us in October 2012, he suffered from polyarthralgia and hard of hearing as well with elevated CRP level. Since his symptoms strongly suggested relapsing polychondritis (RP), detailed examinations were performed. Histology of auricular cartilage showed perichondral invasion of white blood cells and destruction of cartilage. Bronchoscopy revealed redness and vascular swelling in bronchial mucosa, and CT disclosed soft tissue swelling around bronchi. He had a positive anti-type II collagen antibody, while other autoantibodies were negative except for anti-TPO. Based on these findings, he was diagnosed as RP, and predonisolone therapy exhibited remarkable effects. Auricular chondritis is characteristic of RP, and physicians should be aware of this particular finding to make an early diagnosis.

P2-260

A case of Castleman disease [CD] with high IL-6 level in ascites

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Conflict of interest: None

A 65 years old woman was admitted because of anasarca, and body weight gain. Laboratory test showed as follow: WBC5700/μl, Hb10.4/dl, PLT2.4×10^4/μ, CRP7.0mg/dl, Cre1.2mg/dl. Whereas antoantibodies examined were all negative, dysfunction of endocrinesystem was revealed as follow LH<0.1mIU/ml, FSH<0.05mIU/ml, PRL126ng/ml, FT4 0.64ng/dl, TSH13.1μIU/ml. CT scan showed pleural effusion and ascites, multiple lymphadenopathy. Lyphonode biopsy revealed that mixed type of hyaline vascular and plasma cell variant which was shown in CD. Plasma IL-6 level was 10.8pg/mL and plasma VEGF level was 9430pg/mL, IL-6 level in ascites was 1080pg/dL. As uric protein had been persisted, we diagnosed MPGN by biopsy. She also realized numbness and muscle weakness, which was revealed that polyneuropathy, thus various organopathy were complicated. M protein wasn't identified. We tried steroid therapy including pulse therapy, however response to the therapy was insufficient. Therefore Tocilizumab therapy (0.8mg/kg/day) was administrated and it decreased IL-6 level in ascites. Recently, unique clinicopathologic variant of CD, like POEMS syndrome and TAFRO syndrome, which are complicated various organopathy including pleura effusion and ascites has been identified. We'll report unique case of CD with high IL-6 level in ascites.

P2-261

Clinical study in two facilities for Polymyalgia Rheumatica and Giant Cell Arteritis

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Conflict of interest: None

[Objectives] To evaluate the clinical characteristics of polymyalgia rheumatica (PMR) and giant cell arteritis (GCA). [Methods] We retrospectively analyzed 85 patients with PMR and 28 patients with GCA. We checked the erythrocyte sedimentation rate (ESR), CRP, MMP-3, hemoglobin (Hb), ferritin, creatinine (Cr), dosages of glucocorticoids (GC), follow-up period, discontinuation of the GC, and concomitant medications. [Results] The median age was 76.2 years in PMR and 75.8 years in GCA. ESR was 88.4 ± 30.6mm/hr in PMR and 112.6 ± 28.7mm/hr in GCA ($p = 0.0006$). MMP-3 was 216.5 ± 194.8ng/ml in PMR and 113.5 ± 96.7ng/ml in GCA ($p = 0.003$). Dosage of GC was 14.6mg in PMR and 39.2mg in GCA. Follow-up period was 2.9 years in PMR and 2.3 years in GCA. There were no significant differences in CRP, Hb, ferritin, and Cr. There were 8 patients with PMR who could discontinue GC, and the mean period before discontinuation was 2.1 years. There was no factor significantly associated with the discontinuation of GC. Methotrexate was used as a concomitant medication in 11 cases of PMR and in three cases of GCA. [Conclusion] Because MMP-3 in PMR is higher than in GCA, MMP-3 may be useful to distinguish the two diseases. GC treatment can be discontinued in only about 10% cases with PMR.

P2-262

Presence of distal musculoskeletal symptoms predicts treatment response to glucocortcoid in polymyalgia rheumatica

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Conflict of interest: None

[Objectives] To elucidate the significance of distal musculoskeletal symptoms (DMS) in patients with polymyalgia rheumatica (PMR). [Methods] This retrospective single center study included patients diagnosed with PMR according to the 1982 Chuang criteria. [Results] 34 of the 49 patients (69%) have DMS. Relapse rate was higher in PMR with DMS (P/D) than PMR without DMS (P) (53 and 13%, respectively, $p<0.05$). The mean lag time between symptom onset and starting treatment (treatment delay: TD) was significant different between P/D and P (74.5 and 40.8days, respectively, $p<0.05$). Glucocorticoid survival rate was 78% in P after 18 months during the same time period in which survival rate fell to 58% in P/D. In P/D, TD was not different between relapse patients and non-relapse patients (74.0 and 70.2days). Distal tenosinovitis was more frequent in non-relapse patients than relapse patients (62.5 and 38.9%, respectively, $p=0.17$). 50.0% of patients in relapse have RS3PE, whereas 31.3% of patients in non-relapse have RS3PE. [Conclusion] Our findings show that treatment response is different between P/D and P. Findings of RS3PE or tenosinovitis may help predict relapse risk among patients in PMR with DMS.

P2-263

Polymyalgia Rheumatica: The Impact of the Period of Time to Start Treatment on Outcome

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Conflict of interest: None

[Objectives] PMR has been on the increase to be introduced to our hospital. However, there are a large number of cases difficult to distinguish from other diseases. It varied widely in period that a patient develops and is diagnosed of PMR, and then, starts treatment. We examined how the period of time from the development of PMR to the start of treatment influenced outcome. **[Methods]** We studied 44 cases those who met Bird's criteria and were followed up more than a year. They were classified into 3 groups depending on the period of time from the onset of disease to the start of treatment: A-Group (the period is within a month): B (one to 2 months): and C (over 3 months). Then, we made a comparison of onset age, PSL induction dose, and the rate of dose reduction in one year among the groups. **[Results]** Each group's average of the dose amount of PLS is 12.8/ 14.2/14.1mg in A/ B/ C. Likewise, the average onset age is 71.3/ 71.1/ 75.8. The dose amount of PSL and the reduction rate in a year did not show a significant difference among the groups. **[Conclusion]** It is unlikely that the period of time from the onset of disease to the initiation of treatment significantly influences the outcome. It suggests a possible beneficial effect that it has time to distinguish PMR from other diseases.

P2-264

A case of polymyalgia rheumatica disease serum procalcitonin, CEA high lasts

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Conflict of interest: None

【Case】The patient was 86-year-old woman. Fever, bilateral shoulder and buttock pain appeared. Serum procalcitonin level was high, but we thought that bacterial infection was negative. Serum CEA level was high, and tumor was pointed out in left lobe of thyroid gland. It was class II in fine- needle aspiration cytology. So we considered adenomatous goiter. She met all the diagnostic criteria of Bird et al. Contrast MRI showed bilateral scapulohumeral periarthritis and subacromial bursitis. So we considered that his diagnosis was polymyalgia rheumatic, and gave low dose of adrenocorticosteroid to her. Her symptom disappeared immediately, and CRP level decreased to negative range. Serum procalcitonin and CEA level remained high.【Consideration】It is a case that is consistent as the course of polymyalgia rheumatica disease. But bacterial infection could not be ruled out because of high serum procalcitonin and, malignancy could not be ruled out because of high serum CEA. The only goiter was pointed out by whole body screening, but malignancy cells were detected by fine-needle aspiration cytology of twice. Possibility of medullary thyroid cancer can be considered for serum procalcitonin, CEA high is sustained. Follow-up by the otolaryngology is needed continuously.

P2-265

Clinical consideration of polymyalgia rheumatica

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Conflict of interest: None

【Objectives】We consider the clinical presentation of polymyalgia rheumatica (PMR).【Methods】We investigate 25 patients background of PMR from April 2012.【Results】We collected clinical data of 25 PMR patients from April 2012 in our hospital. The 25 patients included 9 males and 16 females aged 73.8±9.5 years, initially they were treated with steroids (prednisone 15.4±4.1 mg/day). The refractory 5 patients treated steroids combined with disease-modifying anti-rheumatic drugs. They included 2 patients with methotrexate, 2 patients with tacrolimus, and 1 patient with mizoribine. Initially 10 patients had diabetes mellitus (DM), 5 patients (3 males and 2 females) of them associated with cancer. Each 3 Male patients had gastric cancer, colon cancer and lung cancer, and both 2 female patients had breast cancer. The case of colon cancer complicated multiple livers meta died from hepatic failure. The 20 PMR patients did not develop a new cancer in the clinical course.【Conclusions】It is uncertain of frequency associated with cancer in PMR patient. In a total of 25 PMR patients, 5 patients (20%) had cancer, which were all complicated with DM. Moreover in 10 PMR patients with DM, 5 patients (50%) had cancer. In conclusion, we must examine a cancer in

new-onset PMR patient with DM.

P2-266

Protein profiles of peripheral blood mononuclear cells as a candidate biomarker for Behcet's disease

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Conflict of interest: None

[Objectives] To investigate the pathophysiology of Behcet's disease (BD) and find biomarkers for the disease. [Methods] Proteins, extracted from peripheral blood mononuclear cells (PBMC), were comprehensively analyzed in 16 patients with BD, 16 patients with rheumatoid arthritis (RA), 12 patients with Crohn's disease (CD), and 16 healthy control subjects (HC) by 2-dimensional differential gel electrophoresis. Differently expressed proteins were identified by mass spectrometry. [Results] 563 protein spots were detected. We completely discriminated between the BD and HC groups, between the BD and RA groups, and between the BD and CD groups by multivariate analysis of intensity of 23, 35, and 1 spots, respectively. The spots contributing to the differences included proteins related to cytoskeleton, transcription/translation, T cell activation, bone turnover, regulating apoptosis, and microbial infection. Intensity of 3 spots provided AUROC of 0.889 for discrimination between the BD group and the non-BD groups. Intensity of the above 1 spot completely discriminated the CD group from the other groups. [Conclusion] PBMC protein profiles, especially the profile of 3 spots, would be candidate biomarkers for BD. The identified proteins may play important roles in the pathophysiology of BD.

P2-267

Vasculo-Behçet's disease: a clinical study of seven cases

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Conflict of interest: None

OBJECTIVE: The aim of the present study was to analyze clinical features of Behçet's disease (BD) with vascular involvement. METHODS: Seven vasculo-BD patients, diagnosed and treated in our hospital, were retrospectively studied. The median follow-up period was 7 years (7 months – 12 years). RESULTS They were 3 men and 4 women. Mean age at the diagnosis of BD was 40.9 years (28-54 years), and age at the onset of vascular lesion was 41.1 years. Arterial and cardiac lesion was observed in 4 cases (aortic regurgitation 2, thoracic aorta aneurysm 1, renal artery aneurysm 1), and venous lesion was observed in 6 (superior vena cava occlusion 2, inferior vena cava occlusion 1, deep vein thrombosis 5). The surgery was performed in 4 cases (aortic valve replacement 2, AC bypass 1, vascular prosthesis implantation 1, nephrectomy 1). Two cases were complicated with entero-BD; both showed perforation of the ileum. Immunosuppressive drugs were given in 4 patients, an anti-TNF agent in one patient, and warfarin in 6 patients. Two patients died; one from septic shock following perforation of the ileum and another from infection. CONCLUSION: Vasculo-BD patients showed more venous lesions rather than arterial lesions, and a half of the patients underwent surgery.

P2-268

The clinical course and treatment in patients with Beçhet's disease; a single center experience of current 14 cases

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Conflict of interest: None

[Objectives] We examined the clinical characteristics, features of intestinal lesions, treatment in 14 patients with the Beçhet's disease followed at the Juntendo University Urayasu Hospital currently. [Methods] Two patients were male, 12 were female. The mean age at onset of Beçhet's disease was 36 years. [Results] Two patients were HLA-B51 positive and the rest 12 were not tested. Seven cases showed the complete phenotype of the Beçhet's and 7 were incomplete and one was not determined. All patients have aphta and 10 cases have cutaneous lesion. Twelve patients involved arthritis. Two patients involved in vascular, 3 in central nervous system. Anti- TNF-α antibody therapy used to 10 cases for uveitis and 3 cases for intestinal Beçhet's. Twelve patients were treated and well-controlled by steroid, 1 case ASA, and 10 cases colchicine. Three case with cyclosporine. [Conclusion] Anti- TNF-α antibody therapy was well tolerated for Beçhet's disease in our hospital.

P2-269

Behcet's disease with refractory skin rash, gingivitis and stomatitis: a case report

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Conflict of interest: None

A 37 years-old female was admitted our hospital for suspected Behcet's disease because of arthralgia, stomatitis, low grade fever, and genital ulcer. She had no optical abnormality, and HLA-B51 was negative. Skin biopsy was not helpful for definitive diagnosis. Oral prednisolone and steroid pulse therapy were not effective, and Colchicine was stopped because of liver dysfunction. Combination therapy with methotrexate and tacrolimus had only limited efficacy. Stomatitis and gingivitis worsened gradually, and she was unable to eat because of oral pain. Biologics was not used because of suspected fungal infection. For lesions of the mucous membranes and skin, Granulocyte/ Monocyte Adsorption Apheresis (GMA, once a week, a total of five times) was performed. Partial efficacies were shown in oral pain, cavity lasts and gingival atrophies. Second course of GMA and 3 times of Infliximab (IFX) showed additional improvement. Clinical significance: Efficacy of IFX has been reported for refractory ocular lesions of Behcet's disease, and it may be useful for mucosal lesion or skin rash. In addition, IFX was also effective for rare clinical conditions such as refractory gingivitis.

P2-270

One case of attack of acute neuro-Behcet's disease during the course of chronic progressive neuro-Behcet's disease

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Conflict of interest: None

[Objectives] Chronic progressive neuro-Behcet's disease (NBD) is characterized by intractable, slowly progressive neuropsychiatric behavior, and ataxia. This time, we report a case of attack of acute NBD during the course of chronic progressive NBD. [Case & Clinical Course] A 22-year-old female had an onset with high fever, unconsciousness and

convulsion six years ago. She gradually developed urinary incontinence, dementia-like mental symptoms, and spastic gait. Her MRI brain image showed progressive atrophy of brain stem, cerebellum and cerebral hemisphere, and then she was diagnosed with chronic progressive NBD in March 2013. And mini pulse therapy of methotrexate (MTX) was started. In late August 2013, she suddenly had left handgrip weakness, developed left hemiparesis and urgently went into the hospital. By MRI brain image with contrast-enhanced lesions in the white matter at right hemisphere, she was diagnosed with attack of acute NBD. She resolved following steroid pulse therapy with moderate doses of prednisolone. Later, her mental symptoms got worse, we initiated infliximab therapy with MTX therapy. [Conclusion] We experienced a case of attack of acute NBD during the course of chronic progressive NBD.

P2-271

Twenty-four cases of Behçet's disease with recto-anal lesion in Japan

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Conflict of interest: None

[Objectives] The typical gastro-intestinal lesion of Behçet's disease is found in ileum; however, some cases show lesions in large intestine, rectum and anus. We experienced two cases with Behçet's disease, who had severe intestinal lesions including rectum and anus. Bothe cases did not respond steroid therapy and died. This experience prompted us to investigate similar cases. [Methods] By the investigation using ICHUSHI (Japan Medical Abstracts Society) and PUBMED, we found 24 cases with Behçet's disease with recto-anal lesion in Japan including our cases. [Results] Fourteen cases were men and 10 are women, and their mean age was 44 years old. The ulcerative lesions were found in 96% in rectum, 92% in large intestine, 75% in ileo-cecal region, 33% in small intestine and 21% in anus. Two cases (8%) showed the lesions only in the rectum and anus. Ten of 14 cases (71%) were treated using prednisolone. Salazosulfapyridine, tacrolimus, and inliximab were commonly used in together. The surgical treatment was required in 7/17 (41%) and the mortality rate was high (24%). [Conclusion] These data suggested that recto-anal lesion indicates the severe and difficult to be treated Behçet's disease.

P2-272

Adalimumab was effective in treating intestinal disorder like Behçet`s disease with myelodysplastic syndrome

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Conflict of interest: None

Various autoimmune diseases have been reported to be associated with myelodysplastic syndrome (MDS). Recently, the coexistence of MDS with trisomy 8 and rare disorders of the immune system like Behçet`s disease has been described. A 62-year-old man with aortitis syndrome and MDS with chromosome 1 abnormality was transferred to our hospital with alveolar hemorrhage. After the treatment with glucocorticoid and cyclophosphamide, bloody diarrhea and hypotension suddenly developed. Colonoscopy found a large deep ulcer in the descending colon, but it was unable to perform endoscopic hemostasis or transcatheter embolization because of no present bleeding. The ulcer was thought to be caused by intestinal Behçet`s disease with myelodysplastic syndrome, then adalimumab was given to treat his bleeding. Bleeding was temporarily improved in 3 days and colonoscopy on the 13-th day found the regeneration of epithelial cells around the edge of the ulcer. In a later day, the appearance of trisomy 8 was observed on chromosome analysis. To our knowledge, this is the first case of intestinal Behçet`s disease with myelodysplastic syndrome treated with adalimumab.

P2-273

A case of Behcet disease with past history of three-times of Aortic valve replacement

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Conflict of interest: None

A 38 year old man was admitted to our hospital because of suspicion of aortitis. He have had 3 times pasthistory of aortic valve regurgitation and 3 times aortic valve replacement. Pathological findings of aorta indicated aortitis. As other past history, he have had genital ulcer. He had acne like lesion on his back on admission. He did't have uveitis and other ocular lesion. Behcet disease was diagnosed. He was treated with PSL and MTX and Colchicine. After treatment, AR was not ditected by Ultrasoud Cardio Graphy.

P2-274

Usefulness of observation over time of serum βD glucan level and usage of Sulfamethoxazole Trimethoprim in our hospital

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Conflict of interest: None

[Objectives] We examine the effectiveness and side effects of Sulfamethoxazole Trimethoprim, and the effectiveness of evaluating the serum βD glucan levels over time. [Methods] We extract the collagen disease patients who were prescribed Sulfamethoxazole Trimethoprim within the period of October 2013 from September 2012, and examined for prevention of PCP prophylaxis and side effects of Sulfamethoxazole Trimethoprim used. We also examined changes in serum βD glucan levels. [Results] The patients who were prescribed Sulfamethoxazole Trimethoprim for prevention of PCP prophylaxis were 60 cases, and the average βD glucan level was 17.8 ± 37.9pg/ml. On the other hand the average βD glucan level was 108.8 ± 87.0pg/ml in the six cases with a diagnosis of PCP. Patients with PCP had not been prescribed Sulfamethoxazole Trimethoprim. 6 patients had developed side effects of Sulfamethoxazole Trimethoprim, 2 patients had cytopenia, 2 had rash, 1 had eosinophilia, and 1 had liver enzyme elevation. [Conclusion] Sulfamethoxazole Trimethoprim is effective for prevention of PCP prophylaxis, but it is necessary to consider the expression of side effects of Sulfamethoxazole Trimethoprim. It is possibly to catch and prevent early onset of PCP, by observation over time of serum βD glucan level.

P2-275

Clinical significance of cytomegalovirus (CMV) antigenemia in the prediction and diagnosis of CMV gastrointestinal disease in Rheumatology field

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Conflict of interest: None

[Objectives] Although pre-emptive prophylaxis based on cytomegalovirus (CMV) antigenemia test has been employed for CMV prevention following hematopoietic cell transplantation, the efficacy of CMV antigenemia test in the rheumatic disease field is uncertain. Therefore, we evaluated its efficacy in the rheumatic disease field. [Methods] We studied all patients who had admitted for the treatment of rheumatic disease in our department and who also had been underwent CMV antigenemia screening test on admission from August 2008 to September 2013. [Results] We identified 135 patients and 153 admissions. Nine admissions (5.9%) became positive for CMV antigenemia screening tests. Moreover, three cases had diagnosed as having CMV infection by gastrointestinal tract pathology and treated with antivirus agents. The rest of 6 cases did not receive antiviral treatment, and 5 cases discharged home and one case died due to cerebral infarction. [Conclusion] CMV antigenemia scrreen-

ing test seems to be effective as our study showed that its sensitivity 100% and specificity 96%.

P2-276

Two SLE and overlap syndrome cases of intestinal perforation with cytomegalovirus (CMV) related colitis leaded to emergency colectomy

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Conflict of interest: None

<Case1> A 31-year-old woman suffered with SLE and lupus nephritis (LN) had been treated using prednisone (PSL) and immunosuppressants. When LN was aggravated, steroid and cyclophosphamide pulse therapy were performed. After these treatments, intestinal perforation occurred and laparoscopic Hartmann's operation was performed. The serum CMVC7HRP was detected and the pathological diagnosis of resected colon showed CMV-colitis. Severe melena was continued despite ganciclovir therapy and laparoscopy total colectomy and ileostomy were carried out. <Case2> A 49-year old woman with MCTD and RA overlap syndrome had been treated with PSL for more than 20 years. After we increased PSL dose for adrenal insufficiency triggered by urinary tract infection, ganciclovir were started because of the serum CMVC7HRP-positive. However intestinal perforation occurred and Hartmann's operation was performed. The pathological diagnosis of resected colon showed CMV positive cells. If patients treated with PSL and immunosuppressants complained of abdominal pain and melena, CMV-colitis should be considered. Because the intestinal perforation caused by CMV-colitis has a poor prognosis in patients received immunosuppressant therapy. We will report two cases with bibliographic considerations.

P2-277

Serological profile of hepatitis B virus (HBV) and clinical features of reactivated HBV hepatitis patients with rheumatoid arthritis (RA)

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Conflict of interest: None

Recently, reactivation of HBV infection is a serious problem in the treatment of RA. Prospective study reported that the reactivation of HBV hepatitis was found in 6 out of 121 patients. However the risk factor in municipal hospitals was not examined yet. Objective: To analyze the serological profile of HBV and to find the risk factor of reactivation in RA patients treated with immunosuppressant. Methods: 669 sets of HBsAg, HBsAb and HBcAb titer were retrospectively collected. Serological prevalence were classified according to age and analyzed by stratified data. RA patients who took entecavir and other RA patients were compared and risk factors were estimated. Results: Median age was 68.6 (19-94) and sex ratio was 1:3.9. Median disease duration was 2.0 year (0.1-37.5). Prevalences of HBsAg, HBsAb and HBcAb were 1.47%, 19.7% and 17.4% respectively. Stratified prevalence rates were as follows; HBsAg (0/0/0/1.6/1.7/1.6/2.0%), HBsAb (0/7.1/9.5/19.7/18.3/23.4/25%), and HBcAb (0/0/0/19.0/16.9/20.6/23.1%). 7 RA patients were treated with entecavir due to the reactivation of HBV hepatitis. 6 patients were treated RA with MTX and 3 patients were treated with PSL. Conclusion: Serological prevalence was increased with advancing age. Not all patients who treated with entecavir were taken MTX.

P2-278

The prevalence of hepatitis B virus reactivation in patients with autoimmune diseases

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Conflict of interest: None

[Objective] To evaluate the prevalence of past hepatitis B virus (HBV) infection and the incidence of its reactivation under immunosuppressive therapy in autoimmune diseases. [Methods] Three hundred thirty-six patients were evaluated for HBV markers, including hepatitis B surface antigen (HBsAg), and antihepatitis B core antibody (HBcAb) and antihepatitis B surface antibody (HBsAb). We retrospectively collected the clinical data and investigated the incidence rate of reactivation of HBV. [Results] Five patients (1.4%) were HBV carriers at baseline. One hundred thirty-seven patients (40.8%) were diagnosed with resolved hepatitis B based on HBsAg negative and HBcAb/HBsAb positive. Respectively, 52.9% and 56.6% of the patients in their 60s and 70s were diagnosed with resolved hepatitis B. Five patients (3.6%) developed reactivation of HBV. The patients were 56-88 years old. One patient with polymyositis was administrated high dose PSL and MTX. Four patients with RA were treated with MTX, MTX, tacrolimus, and etanercept, respectively. Two out of 82 (2.4%) treated with MTX vs one out of 32 (2.7%) treated with biologics in RA patients with resolved hepatitis B, developed HBV reactivation. [Conclusion] There is no difference of the HBV reactivation rate between MTX and biologics in this study.

P2-279

Reactivation of hepatitis B virus in patients with rheumatoid arthritis

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Conflict of interest: None

[Objectives] The danger of the HBV reactivation in patients who receive immunosuprressive therapy was pointed out these days. HBV-DNA monitoring situation in our department was examined this time. [Methods] We enrolled 22 patients (8 was men and 14 women) with RA who had antibodies against hepatitis B core antigen (anti-HBc) and who had received treatment with anti rheumatic drugs, including biological drugs. The average age was 64 years old. The monitoring span of HBV-DNA quantity and the generating situation of HBV reactivation were examined. [Results] In the first-time inspection, HBV-DNA had not detected in all patients and monitoring was performed in every 4-8 weeks. Although very-small-quantity of HBV-DNA was observed twice in one patient medicated with methotrexate (MTX) and mizoribine (MZB) and infliximab (IFX). But after entecavir medication started, HBV-DNA was undetected promptly, and re-detectation was not seen and did not show the rise of AST and ALT, either. [Conclusion] We experienced one patient who developed reactivation of HBV-DNA during HBV-DNA monitoring. RA patients with resolver hepatitis B virus should be monitored based on guideline.

P2-280

Study of HBV reactivation in patients with rheumatoid arthritis in our department

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Conflict of interest: None

[Objectives] We investigated the reactivation of HBV in our department. [Methods] 213 RA patients were administered immunosuppressive agent between September 2013 from July 2012. Biologics was administered for 71 patients, MTX 187, tacrolimus 42, mizoribine 6, prednisolone more 5mg/Kg/day none. We measured HBsAg, anti-HBs, anti-HBc. The mean observation period was 12 months (6-15 months) [Results] One HBV career existed. 22 patients were resolved infection state, biologics was administered for 5 patients, MTX 18, tacrolimus 7. HBV reactivation occurred in two (9%) of 22 patients. Case 1: 81-year-old woman, anti-HBs positive, anti-HBc negative. HBV-DNA was less than 2.1 log copies/ml during administration of MTX 4mg/week and TAC 1mg/3 days, but increased to 2.5 five months after. Case 2: 76 -year-old woman, anti-HBs, anti-HBc positive. HBV-DNA was negative for three weeks after starting golimumab 50mg / month on MTX10mg/week, but 7 weeks after administration became positive HBV-DNA less than 2.1. [Conclu-

sion] We observed two HBV reactivation. It has been reported that the risk of reactivation is high with RA patients using biologics and occult infected. Given that the mortality rate due to fulminant of de novo hepatitis is high, it was considered a HBV screening test is important.

P2-281

Analysis of hepatitis B surface antibody titers in rheumatoid disease patients under immunosuppressive therapies

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Conflict of interest: None

Background) Hepatitis B virus (HBV) reactivation is a rare but a severe complication of immunosuppressive therapy. Patients and Methods) Anti-HBs titration before and after, or under, each therapy were compared. Results) Twenty-eight patients with rheumatoid diseases, who were positive for anti-HBs before or under immunosuppressive therapy, were included. Their underlying diseases were RA: 12, SLE: 4 and others: 14. The administered immunosuppressive agents were glucocorticoid (prednisolone: PSL) in 14, methotrexate (MTX) in 9, no immunosuppressive therapy in 5 patients. The median baseline HBsAb was 402.7 mIU/mL (7.0-1000.0) mIU/mL. The following period was 19.0±18.3 months. The latest HBsAb titer was 140.3 (1.5-1000). Variation of anti-HBs titer in patients under PSL therapy were significantly higher than in those under methotrexate therapy and non-immunosuppressive therapy ($P<0.01$). None of the 28 patients developed HBsAg seroreversion, or HBV reactivation. Conclusion) HBsAb titer decreased significantly ($p<0.01$) after or under PSL therapy. On the other hand, methotrexate therapy is less likely to decrease HBsAb titer. None of the 28 patients developed HBsAg seroreversion and HBV reactivation.

P2-282

Assessment of rapid turnover proteins in patients with rheumatoid arthritis receiving biologic agents

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Conflict of interest: None

[Objectives] Patients with rheumatoid arthritis (RA) are considered to be at nutritional risk. We evaluated nutritional state with rapid turnover proteins (RTP) and change of RTP after administering biologic agents. [Methods] 6 active RA patients were enrolled. We assessed CDAI, CRP, ESR, transthyretin (TTR), transferrin (Tf), retinol-binding protein (RBP) at baseline and 2 weeks after giving biologic agents. [Results] Baseline characteristics were as follows: 2 males, 4 females, mean age 56.8 y/o, mean disease durations 50 months, mean BMI was 21.0, mean serum albumin (ALB) 3.8 mg/dl, 3 treated with MTX (13.3 mg/w), 5 treated with PSL (6.50 mg/day). TCZ were administered to 3 patients, ADA to 1, GLM to 1, and IFX to 1. CDAI tended to be lowered (19.5±5.81 vs 1.2±3.20, $p=0.08$), and CRP and ESR were significantly decreased (2.52±2.26 vs 0.05±0.04 mg/dl, $p<0.05$, 51.5±31.9 vs 13.5±7.66 mm/hr, $p<0.05$, respectively). TTR, Tf and RBP were significantly elevated (19.0±4.24 vs 27.8±6.37 mg/dl, $p<0.05$, 186±42.9 vs 214±48.3 mg/dl, $p<0.05$, 2.88±1.42 vs 4.10±1.98 mg/dl, $p<0.05$, respectively). [Conclusion] Although baseline BMI and ALB were normal, active RA patients showed low RTP. Rapid elevation of RTP after treatment suggests biologic agents could improve nutritional state of RA patients.

P2-283

3 cases of multicentric Castleman's disease treated with Tocilizumab

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Conflict of interest: None

Castleman's disease is a rare but important lymphoproliferative disorder. Here, we report three case of multicentric Castleman's disease (MCD) treated with Tocilizumab. Case 1: 44 year-old, female. She had skin lesions, lymphadenopathy in 1999. High dose glucocorticoid and multi drug chemotherapy were not effective. MCD was diagnosed by lymph node biopsy in 2010, and Tocilizumab was begun. Laboratory data before treatment; IL-6 12.1 pg/dL, CRP 10.3 mg/dL, IgG 6017 mg/dL. Case 2: 41 year-old male. He had lung lesion 1999. Rituximab, glucocorticoid, and chemotherapy were not effective. MCD was diagnosed by bone marrow biopsy in 2010, and Tocilizumab was begun. Labo data; IL-6 35.7 pg/dL, CRP 10.3 mg/dL, IgG 6017 mg/dL. Case 3: 56 year-old male. He had IgA nephritis 1999, and started glucocorticoid therapy and hemodialysis. MCD was diagnosed by lymph node biopsy in 2013, and Tocilizumab was begun. Labo data; IL-6 19.6 pg/dL, CRP 7.6 mg/dL, IgG 6017 mg/dL. Symptoms and laboratory data were improved in all cases with Tocilizumab. Patients with MCD is likely to develop amyloidosis unless adequately treated. Treatment needs to be started as early as possible to minimize complication, however, MCD is difficult to be diagnosed. We discuss our cases with literature review.

P2-284

Research or substance-P, glutamic acid, GABA and glycine evaluationin serum of Fibromyalgia case (FM)

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Conflict of interest: None

[Objectives] The cause of FM was discussed many years, however, it was not yet identified. In of FM, recognition of pain can be considered participation of pain-ascending path-way in the cord and pain suppressing descending pathway in the cord. In ascending path way, substance-P and glutamic acid participation can be considered. On the other hand, subordinate portion of the cord will be considered connection with glycine. Then, in upper portion of central nerve, GABA will be connected with working in pain control. [Results] The mean values of substance-P in FM are 24.0 pg/ml, and that of healthy cases is 15.4 pg/ml. $t=23$, $\gamma=0.05$. About mean glutamic acid titer, that of FM is 73.2 n mol/ml, that of healthy cases is 47.6 n mol/ml. $t=4.8$, $\gamma=0.01$. The relative relation index between substance-P and glutamic acid was $\gamma=-0.07$. About of GABA in serum, the mean value of FM cases showed 145 p mol/ml. That titer is maller than that of healthy persons. $t=1.74$, $\gamma=1.0$. The mean value of glycine in FM, showed 335 n mol/ml. There is significant difference, $t=2.7$, $\gamma=0.02$. [Conclusion] In FM cases, the mean value of substance-P and Glycine showed significant higher titers. The mean titer of GABA in FM cases is lower titer than healthy persons. The mean value of Glycine is higher.

P2-285

A case of gouty arthritis presented spondylodiscitis and Achilles tendonitis

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Conflict of interest: None

【Case】 The patient, a 62-year-old man with a 3-year history of hyperuricemia, presented with severe neck pain, Achilles enthesopathy and polyarthralgia. He consumed alcohol heavily. The biochemical profile showed elevated levels of CRP (3.6 mg/dl), uric acid (UA) (10.9 mg/dl) and creatinine (1.7 mg/dl). Bone scintigraphy showed polyarthritis including first MTP joints. Notably, bone scintigraphy with CT also revealed spondylodiscitis of C5-6, which was confirmed by MRI, and left Achilles tendonitis. Moreover, left Achilles tendonitis was also confirmed by ultrasonography, indicating enthesitis with low-echoic lesion and calcification. Needle aspiration yielded a white viscous liquid, with numerous urate crystals identified on polarized light microscopy. He was diag-

nosed with gouty arthritis associated with spondylodiscitis and Achilles tendonitis. After the treatment with allopurinol, colchicine and prednisolone, his symptoms were improved. 【Conclusion】 The cervical spine and Achilles tendon are rare and notable sites of involvements in gout, and differential diagnosis of gouty arthritis from spondyloarthritis, RA, tumor, pseudogout, and infection is necessary. When the patient was noted to have neck pain and Achilles enthesopathy, we should always recognize gouty arthritis.

P2-286

A case of macrophage activation syndrome induced by agranulocytosis caused by salazosulfapiridine

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Conflict of interest: None

[Objectives] We report a case of macrophage activation syndrome (MAS) induced by agranulocytosis caused by salazosulfapiridine (SASP). [Case] A 60-year-old man was diagnosed as rheumatoid arthritis (RA). SASP was started due to exacerbation of RA. He got fever 24 days after the initiation of SASP. His number of leucocytes showed 180/ml (segment cell 0%) and he was admitted under diagnosed of agranulocytosis. [Clinical course] We discontinued SASP and treated him with G-CSF and antibiotics. In spite of the improvement of the number of granulocytes, he showed dyspnea on the 5th day. On the 6th day, he showed systemic inflammatory response syndrome and his laboratory data showed as following; WBC 30230/μl, RBC 285×10^4/μl, Plt 0.6×10^4//μl, PT-INR 1.82, FDP 356 μg/ml, AST 93 U/l, LDH 7724 U/L, ferritin > 8000 ng/ml, soluble IL-2 receptor 10215 U/ml and red cell fragment was seen. We suspected of disseminated intravascular coagulation or MAS and started plasma exchange (PE). He improved with steroid pulse therapy and PE. His laboratory data showed that neopterin was 50mmol/l and IL-6 was 24 pg/ml, by which we suspected MAS. [Conclusion] Agranulocytosis is a rare, but severe side effect of SASP and some cases are reported. This is the first report of a case of agranulocytosis with MAS.

P2-287

Case report of the patient who desires to become pregnant suffered severe inflammation two months after developing early Rheumatoid arthritis, but dramatically cured by initiation of treatment with adalimumab (ADA) and high dose MYX same timing

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Conflict of interest: None

Case report: The 38 years-old female patient developed RA in January 2013. In 2 months, her condition went worsen rapidly. At the first examination, she was suffering from Stage I and Class3, and her DAS28 (ESR) score was 6.9. She had shown dramatic decrease in activities of daily living (ADL). She desired to eliminate symptoms as early as possible for housekeeping and child-rearing; therefore, ADA treatment together with MTX (12mg) was initiated based on the guideline for usage of TNF inhibitors which modified in 2012. DAS28 (ESR) score decreased to 1.62 in 1 month and was maintained at lower level (1.44) even after seven months, which was striking improvement. **Clinical significance:** This treatment significantly decreased disease activity, and improved activity impairment (AI) based on the result of WPAI/RA questionnaire. Currently MTX was cut and ADA treatment is continued under careful observation because she hopes to become pregnant. It has not been long since the simultaneous administration of ADA+MTX in early RA patients was approved, so that this case is very rare. We also followed the disease course from the point of view of work productivity, and reported that initiating this treatment made her to live normal life, and this fact gives a great impact clinically.

P2-288

Differences of the responses to salivary stimulation test in autoimmune diseases

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Conflict of interest: None

[Objectives] We performed salivary stimulation tests using capsaicin and citrate to evaluate salivary secretion in autoimmune diseases. [Methods] This study included 149 patients, divided into three groups: patients with primary or secondary Sjögren syndrome (SjS group), patients with systemic sclerosis not complicated by SjS (SSc group), and patients with autoimmune diseases other than systemic sclerosis not complicated by SjS (non-SjS/non-SSc group). Three kinds of filter paper (simple, containing capsaicin, containing citrate) were used. [Results] Salivary flow by simple filter paper was decreased in the SjS and SSc groups, but was not decreased in the non-SjS/non-SSc group. In the salivary stimulation test using filter paper with capsaicin, salivary flow was still decreased in the SjS group. On the other hand, salivary flow was increased in the SSc and non-SjS/non-SSc groups. In the salivary stimulation test using filter paper with citrate, salivary flow was still decreased in the SjS group. On the other hand, salivary flow was increased in the SSc and non-SjS/non-SSc groups. [Conclusion] It was suggested that salivary secretion responses to stimulation might be difference in autoimmune diseases and xerostomia might be improved by using effective stimulant in SSc.

P2-289

A case with TAFRO syndrome, a variant of Castleman's disease

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Conflict of interest: None

A 46-year-old-woman was admitted to the hospital because of chest and back pain. Laboratory examination showed the increase of CRP value, liver dysfunction and hypoalbuminemia. CT scanning of chest and abdomen revealed hepatosplenomegaly, bilateral pleural effusion and ascites. PET/CT revealed abnormal accumulation of FDG in cervical, mediastinal and retroperitoneal lymph nodes. Pleural effusion was exudative, but no malignant cell was discovered. In spite of administration of various antibiotics, symptoms and laboratory data did not improve. The histological findings of cervical lymph node biopsy showed the infiltration of plasma cells between lymphatic follicles, which was consistent with multicentric Castleman's disease. She became in the condition of anasarca. Steroid pulse therapy was performed and then massive dose of steroid was administered. As a result, her symptoms and signs gradually improved, and the addition of cyclosporine A brought into successful decrease of pleural effusion and ascites as well as increase of thrombocyte counts. The patient's condition was considerably consistent with a variant of multicentric Castleman's disease, TAFRO (thrombocytopenia, anasarca, fever, reticulin fibrosis and organomegaly) syndrome.

P2-290

The meaning of living survey about rheumatoid arthritis (RA) patients

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Conflict of interest: None

[Purpose] We conducted the questionnaire survey in RA patients (pts) about past medical consciousness of mouth cleaning, smoking, other life habits and medical histories. [Method] We demanded the questionnaire sheet from May to June in 2013, and analyzed the questionnaire results (214 RA pts) from which consent and a reply were obtained. [Result] Wish of RA study meeting: 41.3% (86/208), consciousness of mouth-

cleaning: 73.6% (156/212), family dentist: 72.6% (130/179), alcoholic ingestion: 27.3% (58/212), smoking (male): 34.1% (15/44), smoking (female): 8.9% (15/169), cancer past: 30.7% (65/212), pneumonia past: 22.7% (48/211), herpes zoster past: 21.3% (42/213), hospitalization past: 73.4% (157/214), steroid internal use history: 58.1% (115/198) [Discussion] Many RA pts have consciousness of mouth-cleaning and visit the family dentist. Smoking rates of RA pts are almost same as compared with those of general population in Japan (or in Hiroshima). So, it is considered for much more pts education to be important from now on. There are some dissociation between oral consultation record collected at the time of the first medical examination and these questionnaire results. Therefore, we should check the medical and everyday life consultation carefully and periodically.

P2-291

Four cases of pneumatosis cystoides intestinalis complicated by connective tissue disease

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Conflict of interest: None

[Introduction] Pneumatosis cystoides intestinalis (PCI) is a rare disease characterized by gas within the intestinal submucosa or subserosa. We report 4 cases of PCI complicated by connective tissue disease (CTD). **[Case 1]** A 71-year-old woman with granulomatosis with polyangiitis and diabetes mellitus (DM) was treated with prednisolone (PSL) and α-glucosidase inhibitor (α-GI). Abdominal computed tomography (CT) showed gas in the intestinal wall. Images improved after stopping α-GI administration. **[Case 2]** A 70-year-old woman with rheumatoid arthritis and DM was treated with PSL and α-GI. Serum C-reactive protein levels were high; therefore, CT was performed, showing intraperitoneal free air and gas in the intestinal wall. Improvement was seen after stopping α-GI. **[Case 3]** A 70-year-old man with dermatomyositis was treated with PSL, but developed pneumonia. Imaging showed intraperitoneal free air and gas in the intestinal wall. He received high-dose oxygen, but died of infection. **[Case 4]** A 42-year-old woman with dermatomyositis and scleroderma was treated with PSL. She felt abdominal fullness, and abdominal CT suggested PCI. After taking antibiotics and high-dose oxygen, improvement was seen. **[Conclusion]** In CTD patients, PSL and α-GI raise the risk of PCI development.

P2-293

A case with adult onset Still disease developed macrophage activation syndrome associated with cytomegalovirus infection

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Conflict of interest: None

A 78-year-old woman with rheumatoid arthritis treated with predonisolone (PSL) developed wrist arthritis, generalized itchness, pharyngeal pain and fever. She was admitted to our hospital with the laboratory data of CRP 15.36 mg/dl, AST 100 IU/l, LDH 961 IU/l, serum ferritin 11000 ng/ml, and sIL-2R 2920 U/ml. Result of skin biopsy was compatible with adult onset Still disease (AOSD). Other examinations including culture tests and lymph node biopsy could not detect infection or malignancy. Under the diagnosis of AOSD, 1 mg/kg/day of PSL improved the symptoms and the laboratory data but tapering of PSL exacerbated them. Cytomegalovirus antigen was detected in her peripheral blood cells and she was treated with ganciclovir. Additionally, pancytopenia simultaneously occurred and she was diagnosed as macrophage activation syndrome (MAS). Steroid pulse therapy, cyclosporine and plasmaapheresis could not improve multiple organ failure and she died. Necropsy revealed lymphoma-like accumulation of CD45RO positive cells in the mediastinal lymph node. This is a case with AOSD developed MAS. Exacerbation of AOSD should be distinguished from infection or lymphoma against confusing conditions.

P2-294

Unmet educational needs for non-specialized physicians for RA working at non-teaching medical institutions in Nara: Prefecture-wide cross-sectional study

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Conflict of interest: None

Background: It is relevant to provide an optimal practice to RA patients by non-specialized physicians in the area where there are few teaching institutions and specialists concerning RA. ***Objective:*** To clarify unmet educational needs of non-specialized physicians for RA. ***Setting:*** Multi-hospitals and clinics without educational certification of RA by JCR in Nara prefecture. ***Participants:*** Non-specialized physicians currently engaging in RA practice. ***Method:*** Cross-sectional study. ***Primary outcome:*** Training contents for RA practice which they are hoping to receive. ***Results:*** We enrolled 31participants. What are the most often items among each category is thirties in age (n=13, 42%), less than 5years in duration of engaging in RA practice (n=20, 65%), orthopedist in certification (n=18, 58%), respectively. Among 35answers including duplication, the workshop contents they hope to receive as primary outcomes are treatments (n=19, 61%), diagnosis (n=5, 14%), complication or adverse events (n=3, 9%), respectively. As for treatments, they want to attend the workshop of how to use biologics (n=10) and MTX (n=3), criteria for drug selection (n=3), respectively. ***Conclusion:*** RA practitioners at non-teaching institutions in Nara have a tendency to be young orthopedist. They wish to learn RA treatments.

P2-295

Construction RA network in G Prefecture; GRN

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Conflict of interest: None

[Objectives and Methods] While the medical treatment for rheumatoid arthritis (RA) has been changed, evidences for performing better medical treatment is needed, and the multicenter clinical study needs to be accumulated for that purpose. In addition, we have to do the educational activity to RA patients and the general public. So, we established the multi-institution database with five RA clinics, one belongs to the University Hospital, three orthopedics hospital, and one rheumatism special clinic (non-floor). The name of this database was made as GRN. After the approval of the Ethics Committee, we established GRN and gathered information among these institutes. [Result] As a collection method of data, after anonymity of patient information, each institution scanned the view tables (a medical examination view, laboratory data, HAQ, etc.), and sent to a GRN secretariat via cloud service. Then, the collected data were inputted into forms which the GRN secretariat created using database management software. We analyzed the clinical data and gave the presentation in the previous JCR meeting. [Consideration] This database is used to collect the clinical data of multiple institutions, therefore the collected clinical data would be expected to be useful.

P2-296

The role of pharmacist in patient care with Reumatoid arthritis (RA) by the questionaire

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Conflict of interest: None

[Objectives] In the treatment of RA with biologics, patient's care, prevention of infection are very important. This study aimed to clarify the role of pharmacist in patient care with RA. [Methods] We executed the research for outpatient care RA 64 person in our hospital from March to May in 2013. We used questionnaire sheet about dairy activity, medication of RA, and psychological state. [Results] 64 patients (12 males and 52 females, age average: 60.3, duration: 9 years, DAS28: 2.64, CRP: 0.54mg/dl) were enrolled and 30% was influence of daily activity after onset of RA. Most painful joint was wrist, next was finger and knee. Over 50% of patients could medicate on their fingers. But they had gradually the difficulty to work and daily activity. 70% was good compliance of medication. 80% of patients wanted to know the effect and side effect of drug. [Conclusion] This finding suggest the importance of Pharmacist full understanding the psychological and financial of patients in order to keep the motivation of medication.

P2-297

Value of a pen-type etanercept injection (Patient questionnaire/ self-injection guidance)

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Conflict of interest: None

Objective: The advantages and disadvantages of the pen-type injection were analyzed based on the results of a questionnaire survey administered to investigate the usefulness of this method. Methods: Subjects were 54 patients who self-injected ETN (7 using vial-type, 47 using syringe-type); 17 of these patients switched to the pen-type. Each device was evaluated on a five-point scale from 1 (good) to 5 (poor). Results: The scores for the pen-type were lower than those for the vial- and syringe-type in three categories: 2.0 points for appearance, 1.8 for ease of disposal, and 2.6 for social activities. No difference was noted among the three types in other categories, the patients switched to using pen-type showed that significant differed from those of the conventional devices was pain during needle sticking. No difference was noted in the scores for age, grip, radiographic stage, or disease activity. Discussion: Pen-type injections reduced pain during needle sticking. Pen-type injections are safer, and the lack of differences in retention and injection procedure may have stemmed from the use of injection aids with conventional devices, as well as the fact that many patients were accustomed to giving themselves injections. Pen-type injections may not be easy to use for all patients.

P2-298

Introduction and operation of team medical care system enables to quickly respond to needs of patients in outpatient care

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Conflict of interest: None

[Objectives] In our hospital, we operate outpatient service of Rheumatology by team medical care system, which is composed of medical doctor, nurse, pharmacist, physical therapist, clinical laboratory technologist, social worker, and managerial dietician. In order to give patients better medical care and find out complaint and demand of patients, we carried out questionnaire survey to all patients. [Methods] 1) Length of waiting time and response and behavior of stuff. 2) Query or anxiety for therapy. 3) Whether patient has key person (s) or not. 【Results】 1) Because 67% of patients felt waiting time was long, we provide patient a chance to take physiotherapy course and are asking regional clinic for taking care some patients to shorten waiting time. 2) Because 40% of patients had anxiety adverse effect and cost of medical care, we prepared original booklet and started to perform seminar to them. 3) Because we realized 6 % of patient had no key person to support them, nurses and social worker are considering how to develop way to support those patient as the stuff of outpatient care. [Conclusion] We could cope with each other and quickly responded

P2-299

The validity of team medical care in RA treatment

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Conflict of interest: None

[Objectives] To assess the validity of team medical care in RA treatment through two case reports [Case 1] 50-year-old female. She has already taken Methotrexate (MTX). But she couldn't take it because of being aware of the side effect of it. We considered that she had better taken MTX, so we (doctor and nurse) talked something with her. We were sure that she worried about the progress of RA because her mother and grandmother were also had RA and had severe RA deformity. So we explained that the progress of RA treatment and efficacy of early RA treatment. Then she could consider to treat of RA positively. We aimed to get a remission and to work. Finaly she can take MTX treatment. [Case 2] 35-year-old male. He has already taken the Adalimumab treatment. He tended to absent an appointment. We considered that if he could take the Adalimumab by himself, he could continue Adalimumab treatment. So we beban to teach him to take Adalimumab by himself. He got the technique through the twice of practice. Then he started to take Adalimumab by himself. Now he can continue to take the treatment. [Conclusion] This two case reports show that team medical care in RA treatment was useful.

P2-300

Successful therapy for refractory adult onset Still's disease (AOSD): a high-dose initial steroid followed by the rapid dose reduction combined with tocilizumab (TCZ)

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Conflict of interest: None

[Objective] To investigate the efficacy of high-dose prednisolone (PSL) followed by a rapid dose reduction combined with TCZ in AOSD. [Methods] The long-term effects of TCZ therapy were investigated in nine refractory AOSD patients, including eight reported previously and one new patient receiving induction therapy. Of these, the two most recent underwent rapid steroid dose reduction, while the others followed the traditional reduction schedule. [Results] The two patients who underwent rapid steroid reduction had macrophage activation syndrome (MAS) or active disease resistant to 1 mg/kg/day PSL. After attaining negative serum C-reactive protein (CRP) levels, the respective PSL doses in the two patients were reduced from 120 to 25mg and 80 to 35 mg in 1 month, combined with TCZ therapy. The traditional steroid schedule in the other patients was used because of our inexperience with rapid reduction or accompanying MAS. This retrospective study suggested that beginning TCZ therapy should be based on the serum CRP and ferritin levels. The nine AOSD patients did not relapse on maintenance TCZ therapy, including three steroid-free patients. [Conclusion] Initial high-dose steroids and combined tocilizumab might enable a rapid steroid-dose reduction for refractory Still's disease.

P2-301

Incidence of adverse events after systemic glucocorticoid therapy in our hospital

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Conflict of interest: None

[Objective] To investigate the incidence of adverse events (AEs) after systemic glucocorticoid (GC) therapy. [Methods] We retrospectively examined patients with connective tissue disease who were admitted to our hospital between 2008 and 2011 and were administered GC therapy (>=20 mg/day prednisolone), and investigated the incidence of major AEs during the 2-year follow-up period. [Results] One hundred and twenty-one patients were studied, including 24 patients with polymyalgia rheumatica, 21 with systemic lupus erythematosus, and 19 rheumatoid arthritis. Among them, 5 patients died (3 of infection, 1 of hemophagocytic syndrome, 1 of sudden death) and 15 completed treatment or were referred to other hospitals. The following AEs occurred during the follow-up period: severe infections in 15 patients, impaired glucose tolerance (IGT) in 23, vertebral fractures in 7, peptic ulcers in 3, femur head necrosis in 1, dyslipidemia in 34, and cataract in 4. Forty-seven percent of severe infection cases, 78% of IGT cases, and 88% of dyslipidemia cases developed in the first 6 months, whereas no vertebral fracture or cataract was noted during this period. [Discussion] The occurrence of AEs after GC therapy was relatively high with a prominent susceptible period.

P2-302

Nine cases with psoriatic arthritis and six cases with osteoarthropathy associated with palmoplantar pustulosis

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Conflict of interest: None

[Objectives] [Methods] We report nine cases with psoriatic arthritis (PsA) and six cases with osteoarthropathy associated with palmoplantar pustulosis (PPP). [Results] The mean age of the nine cases with PsA was 54.8 years (range: 29-75). Male to female ratio was 7-to-2. Two cases were controlled well with oral administration such as sulfasalazine or methotrexate. Four cases with severe arthritis responded well to adalimumab (ADA). One case responded well to ADA, however palmoplantar pustulosis developed. Two cases did not respond to ADA, and severe psoriasis developed. The mean age of the six cases with osteoarthropathy associated with PPP was 61.8 years (range: 53-71). All of them were female. Four cases were controlled well with oral and topical medications. One case responded well to ADA. Pustulosis and arthritis worsened in one case despite administration of etanercept. [Conclusion] Therapy with tumor necrosis factor alpha inhibitors may be associated with paradoxical arthritis or psoriasis. In such cases, other biologic agent such as ustekinumab or ixekizumab may be effective.

P2-303

Patient preference survey by intraoperative opioids using postoperative nausea and vomiting

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Conflict of interest: None

[Objectives] Reported in hospital surveys patients preference on postoperative nausea and vomiting by intraoperative opioids use weak opioid-induced nausea and vomiting related to drinking or smoking. Performed on postoperative nausea and vomiting in patients with intraoperative opioids this time. [Methods] Intraoperative opioid using artificial joints and spine surgery (92 cases Male 25, average 68 age. Female 67, average 71 age. OA: 40, RA: 18, ANFH: 8, spinal disorders: 13, osteoporosis: 13) underwent and investigated patient backgrounds and the presence or absence with nausea and vomiting, drinking, smoking. [Results] 27 in 92 being nausea and vomiting, 23 female, 21 without drinking, 16 without smoking, on their 65 without nausea and vomiting, 14 without drinking, 4 without smoking. In this study, no relation with age, BMI, diseases, surgical management. [Conclusion] Side effects risk for opioid demonstrated for the elderly, women, slimming, but from the results of this was related to drinking and smoking. PCA reduced at risk for perioperative pain is involved in not rehabilitation but surgical outcome in patients. For risked patient, opioids should be care for nausea and vomiting.

P2-304

Changes in the Treatment of Rheumatoid Arthritis by Orthopedics Practitioners in Osaka Prefecture Over a Decade: A Questionnaire Survey

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Conflict of interest: None

[Objectives] A questionnaire survey was conducted to determine the change in the treatment of rheumatoid arthritis (RA) by orthopedic practitioners in Osaka Prefecture over 10 years. [Methods] An anonymous survey on RA treatment, with a focus on pharmacotherapy, was conducted thrice, in 2003, 2008, and 2013. This survey was targeted to the members of the Osaka Clinical Orthopaedic Association. Questionnaires were sent to the members by mail, and the responses were summarized. [Results] The response rate was 34.7% (139/401) in 2003, 31.7% (145/459) in 2008, and 24.5% (115/469) in 2013. Regarding the therapeutic drugs, the use of methotrexate (MTX) as a first-line treatment and salazosulfapyridine (SASP) as a second-line treatment has increased. On the other hand, the use of steroids has decreased. In addition, the introduction rate of biological products (Bio) and the use of disease-modifying antirheumatic drug (DMARD) combination therapy have increased. [Conclusion] Bio have been launched successively over the past decade, resulting in active prescription in some clinics. The mostly prescribed DMARDs are MTX, SASP, bucillamine, and tacrolimus; the increases in evidence as well as medical expenditures are likely to have contributed to an increase in the combined use rate in each DMARD.

P2-305

The role of nurses in the treatment of rheumatoid arthritis as indicated by the medical treatment degree-of-satisfaction questionnaire

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Conflict of interest: None

[Objectives] We investigated the treatment satisfaction of patients with rheumatoid arthritis (RA), and examined the nursing support system required. [Methods] We surveyed 398 patients with RA consulted who consulted at our hospital from August to June 2013, with respect to treatment and daily life satisfaction and patient's concern. We divided them into two groups: Bio use patients and Bio unused patients. We compared our results with those of a questionnaire survey (370 persons) conducted in 2012. [Results] The incidence of arthritic pain relief, a reduction in joint swelling, and improved daily life was found to be 65.6%, 71.7%, 75.7% and 75.7%, respectively, in Bio use patients, and 58.8%, 58.7%, 63.1%, and 73.5%, respectively, in Bio unused patients. Bio use patients showed a higher degree of satisfaction. No significant difference in the results was noted between the 2013 survey and the 2012 survey. More than half the number of patients expressed desire for detailed information about the outcomes, side effects, and treatment method, and for the installation of a consultation system. [Conclusion] Many patients with RA

had anxiety due to lack of information. Thus, nurses should ensure information dissemination such as the installation of a consultation window.

P3-001

Study on clinical features of rheumatoid arthritis with hepatitis B virus carriers by Ninja cohort

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Conflict of interest: None

[Objectives] To reveal the clinical characteristic of patients with rheumatoid arthritis (RA) complicated by hepatitis b virus (HBV) carrier. [Methods] By using the largest database for Japanese RA (Ninja), we examined the differences of clinical features for 145 RA with HBV carrier patients and 145 RA patients without infection which matched for age, sex, duration, and renal function. [Results] Compared with RA with HBV carrier and without HBV, there were siginificant diffrens for distribution of Class classification (I, 19.6%; II, 44.1; III, 34.3: IV, 2.1, 2.1 vs 35.0, 51.8, 11.2), number of pain joints (68) (4.8 vs 2.4), number of pain joints (28) (3.5 vs 1.8), physician global assessment (20 vs 15), mHAQ (0.5 vs 0.4), HADS (D) (6.2 vs 4.8), DAS28ESR (3.6 vs 3.1), DAS28CRP (2.9 vs 2.4), SDAI (10.5 vs 7.7), CDAI (9.9 vs 7.2), rate of MTX use (51.7 vs 67.6), rate of biological agent discontinuation (6.9% vs 2.1) ($p < 0.05$). [Conclusion] A clinical feature of RA patients with HBV carrier is distinctly different from that of RA without HBV.

P3-003

Change over the years of QFT in the patients of rheumatoid arthritis

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Conflict of interest: None

[Objectives] Methotrexate (MTX) is known as an anchor drug to rheumatoid arthritis, use limit was up to 16 mg per week from 2011. Immunosuppressive activity of the patient is a problem by using a large amount of MTX. After increased the amount of MTX, they demand verifying quantiFERON-TB Gold test (QFT test) in the accompanying document of the medicine. We haven't gotten an answer that QFT test is useful to immunosuppressed patients with long-term use biologics and MTX yet. It hasn't shown what kind of change happen in arthritis patients for long years. To observe change over the years of rheumatic patients QFT test, we extracted elements. [Methods] We carried out the QFT test to 100 arthritis outpatients in 2011 at our hospital. The QFT test results were compared to those of 2013. [Results] QFT test positive patients were six at 2011 in arthritis patients out of the 100 patients. Four of six patients were examined for QFT test at 2013. Only one patient kept positive in QFT test. Three of four patients changed negative. Anti-TB drugs were administrated to QFT test positive persons from 2011 to 2013. No patient QFT test changed positive in 2011 to 2013. [Conclusion] It is estimated QFT test is good index to the activity of tuberculosis in patients with rheumatoid arthritis.

P3-004

Second to fourth digit ratio (2D/4D ratio) in systemic lupus erythematosus

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Conflict of interest: None

In human hands, the lengths of index and ring fingers (2D4D ratio) differ between males and females. In females, the length of index finger is equal or longer than that of ring finger. 2D4D ratio are stable over time. 2D4D ratio strongly correlate with exposure or sensitivity to prenatal testosterone. 2D4D ratio has reported to associate with incidence of sex-biased diseases and malignancies. This association implies exposure to prenatal sex hormone contributes to certain diseases susceptibility. Systemic lupus erythematosus (SLE) is a multisystemic autoimmune disease. The etiology of SLE is unknown, but SLE is prevalent in women and sex hormones may be importantly associated with pathogenesis of this disease. It was reported that patients with SLE had increased estrogen levels and E2 (17β-estradiol) increase the production of IgG and anti-dsDNA antibody in SLE. However, several reports have shown that Androgen deficiency has been also associated with the development of systemic lupus erythematosus (SLE). Therefore, precise roles of sex hormones in pathogenesis for SLE remain to be understood. Because there were no reports concerning 2D4D ratio in SLE, we conducted this study to clarify correlation between 2D4D ratio and SLE.

P3-005

Polyarthropathy in Type 2 Diabetes Patients Treated with DPP4 Inhibitors

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Conflict of interest: None

Objectives: Dipeptidyl peptidase 4 inhibitors (DPP4Is) inactivate incretin hormones while also affecting the immune system, since CD26/DPP4 is involved in T cell activation and chemokine action. Our objective is to evaluate for a potential association between DPP4Is and an increased risk of joint inflammation, and to identify possible underlying biomarkers in affected patients. ***Methods***: A study cohort included 741 patients with type 2 diabetes (T2DM) who were seen at the Kobari General Hospital, between February 2010 and January 2013. Plasma levels of various biomarkers were also assessed. ***Results***: Thirteen patients with polyarthropathy were identified among 385 DPP4I users. In DPP4I-treated patients diagnosed with polyarthropathy, plasma level of SDF-1α was significantly decreased compared to controls. Following cessation of DP-P4I treatment in patients with polyarthropathy, the joint symptoms disappeared, while SDF-1α plasma level was restored to the level of the control cohorts. ***Conclusion***: Our study indicates that the use of DPP4Is as therapy for T2DM may induce joint symptoms in a specific population. These patients were distinct from those with rheumatoid arthritis since the latter had been reported to have higher level of SDF-1α.

P3-006

Prevalence and features of spondyloarthritis associated with Crohn's disease: a single institute, cross sectional study

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Conflict of interest: None

[Objectives] In Japan Crohn's disease (CD) patients surpassed 30,000 people and it is supposed that spondyloarthritis (SpA) associated with CD increase. The prevalence of CD-SpA in Japan has not been reported. We aimed to clarify the prevalence and features of CD-SpA. [Methods] We performed questionnaire survey about SpA to CD patients from April to September 2013. We used the Assessment of SpondyloAr-

thritis international Society classification (ASAS) criteria. [Results] Nine (17.6%) patients have SpA among 51CD patients. The mean disease duration was 14.2 and 11.9 years in the SpA group and the non-SpA group, respectively (p=0.42). All SpA patients and 21 (50%) non-SpA patients had infliximab (IFX) treatment ($p < 0.01$). Multivariate analysis showed no clear association for gender, disease duration and IFX. All SpA patients were peripheral type: 7 (77.8%) patients with arthritis, 2 (22.8%) patients with dactylitis and 4 (45.6%) patients with enthesitis. Three patients were suspected to have sacroiliitis but MRI examination didn't reveal active inflammation. [Conclusion] The prevalence of CD-SpA was 17.6 %. When physicians see CD patients with arthralgia, sausage-shaped finger and heel pain, physicians should take SpA consideration. An early diagnosis may improve ADL and QOL.

P3-007

Prevalence and risk factor of spondyloarthritis associated with ulcerative colitis: a single institute, cross sectional study

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Conflict of interest: None

[Objectives] In Japan ulcerative colitis (UC) patients surpassed 100,000 people and it is supposed that spondyloarthritis (SpA) associated with UC increase. We aimed to clarify the prevalence and risk factor of UC-SpA. [Methods] We performed questionnaire survey about SpA to UC patients from April to September 2013. We conducted clinical examination, analysis of blood biochemistry and imaging test. We used the Assessment of SpondyloArthritis international Society (ASAS) classification criteria. [Results] This study included 93 patients with UC and 11 (11.8%) patients have SpA. The mean disease duration was 12 years in the SpA group and 8.6 years in the non-SpA group ($P<0.05$). Two (2.4%) non-SpA patients had infliximab treatment. In multivariate analysis long disease duration and men were significant dependent risk of SpA (OR 1.25, 95%CI 1.03-1.52, $P<0.05$). Axial SpA patients was diagnosed in 2 (18.1%) patients, peripheral SpA in 9 (81.8%) patients: 4 (44.4%) patients with arthritis, 2 (22.2%) patients with dactylitis and 7 (77.7%) patients with enthesitis. [Conclusion] The prevalence of UC-SpA was 11.8% in our hospital it was relatively higher than previously estimated. Long disease duration and men were significant dependent risk factor of SpA.

P3-008

The necessity of multi imaging examinations to diagnose polymyalgia rheumatic (PMR)

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Conflict of interest: None

[Objectives] It's not easy to distinguish rheumatoid arthritis (RA) with PMR-like onset. To diagnosis PMR-like RA with more precision, we investigated the imaging examinations conducted to diagnose PMR and the prognosis of the patient with PMR in our hospital. [Methods] We divided 49 patients with diagnosis of PMR from January 2009 to March 2013 into the three groups according to the latest diagnosis, PMR treated only PSL group, PMR needed other DMARDs group and RA changed from PMR group, and investigated the imaging examinations (Ga scintigraphy, US and MRI) were performed to diagnosis PMR. [Results] The numbers of each group were 35 patients (71.4%), 8 patients (16.3%) and 6 patient (12.2%). In the RA changed from PMR group, 4 patient took only Ga scintigraphy, one patient took Ga scintigraphy + MRI and one patient took Ga scintigraphy + US. Nobody took Ga scintigraphy+MRI +US beame RA. [Conclusion] Even if the symptom and progress are likely PMR, synovitis should be evaluated by US or MRI.

P3-009

Cytotoxic T lymphocyte is essential for the pathogenesis of immune glomerular injury by recognizing antigen presented as immune complex on target tissue

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Conflict of interest: None

Objectives: We have proposed a novel 'self-organized criticality theory' explaining the cause of SLE. Here we investigated the contribution of immune complex (IC) and cytotoxic T lymphocyte (CTL) to the pathogenesis of immune glomerular injury. **Methods:** Wild-type (WT) BALB/c mice, β_2-microglobulin (β_2m)-deficient mice lacking CD8 T cells or μMT mice lacking B cells were repeatedly immunized with ovalbumin (OVA). Splenocytes of WT mice were adoptively transferred into naïve WT mice. **Results:** After 12x immunization with OVA, WT mice developed glomerulonephritis accompanied by deposition of IC and an increase of IFNγ-producing CD8 T cell in spleen. In contrast, although deposition of IC was appeared in kidney, glomerular injury did not developed in β_2m-deficient mice. In μMT mice, 12x immunization with OVA induced CTLs but not IC deposition or glomerular injury. When CD8 T cells from mice immunized 12x with OVA were transferred into naïve WT recipients, glomerular injury was induced, but only when a single injection of OVA or sera of mice immunized 12x with OVA was also given simultaneously. **Conclusion:** Deposition of IC is required but insufficient to induce issue injury. CTLs that recognize antigen presented as IC on the renal tissue cause immune glomerular injury.

P3-010

Studies on the mechanism of antigen cross-presentation to generate cytotoxic T lymphocyte in the induction of lupus tissue injuries

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Conflict of interest: None

[Objectives] We found that SLE was induced experimentally by repeatedly immunizing the mice normally not prone to autoimmune diseases with the same antigen, and have then proposed a novel 'self-organized criticality theory' explaining the cause of SLE. Over-stimulated CD8 T cell *via* antigen cross-presentation fully differentiated into cytotoxic T lymphocyte (CTL) to induce lupus tissue injuries. Here we examine the molecular detail of antigen cross-presentation in relation to lupus nephritis. [Methods] BALB/c mice were repeatedly immunized with ovalbumin (OVA) to induce glomerular injury. Exotoxin A, MG132 or primaquine was repeatedly co-immunized with OVA to inhibit a translocon Sec61, proteasomal degradation or endosomal trafficking. Proteinuria and IFNγ-producing CD8 T cell in spleen were detected. [Results] Proteinuria were minute in mice treated with exotoxin A, MG132 or primaquine. Further, treatment of exotoxin A, MG132 or primaquine inhibited an increase of effector CTL. [Conclusion] Export of antigen from endosome to cytoplasm *via* Sec61, proteasomal degradation and endosomal trafficking are essential for not only antigen cross-presentation but also the development of immune glomerular injury.

P3-011

Analysis of immune cells for Ankylosing spondylitis patients

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Conflict of interest: None

[Objectives] Ankylosing spondylitis (AS) belongs to spondyloarthritis, mainly affects spine, sacroiliac joints, peripheral joints and entheses. There are several findings which suggest the involvement of immune system in the pathogenesis of AS. HLA-B27, the most important gene in AS, is present over 95% of AS patients. The efficacy of TNFa blockade against AS symptoms is well recognized. The fact that spontaneous arthritis in HLA-B27 transgenic rats does not develop under germ-free condition indicated the importance of mucosal immunity in AS. Although the increase of Th17 cells in AS patients has been reported, the role of other immune cells is largely unknown. In this study, we analyzed innate lymphocytes, B cells and Monocytes in AS. [Methods] Peripheral blood mononuclear cells (PBMC) of healthy subjects and AS patients were separated by using Lymphoprep. Innate lymphocytes (NK cells, MAIT cells, gd T cells, iNKT cells), Plasmablasts, B-1 cells and monocytes were analyzed by FACS. [Results] The frequency of MAIT cells was decreased in AS. However, there were no differences in the proportions of other innate lymphocytes, B cells and monocytes between AS patients and healthy controls. [Conclusion] These result suggested that MAIT cells may be involved in the pathogenesis of AS.

P3-012

The effects of antirheumatic drug on cell surface proteins in human synovial sarcoma cell line, SW982

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Conflict of interest: None

[Objectives] Sulfasalazine (SASP) is currently used as a disease-modifying antirheumatic drug, however, the action mechanism of SASP has not been fully understood. To promote understanding of the mechanism, we studied changes of protein profiles by SASP and its metabolites, sulfapyridine (SP) and 5-aminosalicylic acid (5ASA), focusing on cell surface proteins of a human synovial sarcoma cell line, SW982. [Methods] The isolated cell surface proteins were separated by 2-dimensional difference gel electrophoresis (2D-DIGE). Protein spot intensity of which was changed by the agents were detected by using Progenesis SameSpots software. [Results] A total of 576 protein spots were visualized by 2D-DIGE across all the gels. Compared to the non-treated cells, we found significant changes (more than 1.5 folds or less than 1/1.5 fold, $p<0.05$) in the expression levels of 11 protein spots in the cells treated with SASP, 22 spots in the cells treated with SP, and 2 spots in the cells treated with 5ASA. Five spots were overlapped among them. [Conclusion] We found that multiple cell surface proteins were affected by SASP. Identification of the affected cell surface proteins, which is on-going, would help understanding of the action mechanism of SASP.

P3-013

Regulation of CXCL10 by thymidine phosphorylase in rheumatoid arthritis fibroblast-like synoviocytes

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Conflict of interest: None

[Objectives] Thymidine phosphorylase (TP) plays an important role in angiogenesis, tumor growth, invasion, and metastasis, as we previously demonstrated. TP is induced in FLS of rheumatoid arthritis (RA) by TNF-α and some other cytokines reported to be major mediators in RA. In this study, we investigated how TP is involved in the pathogenesis of RA. [Methods] In FLS obtained from 2 RA patients, the expression of TP, CXCL10, and other cytokines was measured by quantitative real-time PCR, immunoblotting, and ELISA. Microarray analysis was performed using FLS transfected with *TP* cDNA and treated with a TP inhibitor (TPI). [Results] The expression of TP in FLS was up-regulated by TNF-α, IL-1β, IL-17, IFN-γ, and LPS. Microarray profiling in TP-overexpressing FLS identified CXCL10 as an inducible gene by TP. The expression of CXCL10 was induced by TNF-α, and suppressed by *TP* siRNA and TPI. Furthermore, the combination of TNF-α and IFN-γ synergistically augmented the expression of TP and CXCL10. The TP-induced CXCL10 expression was suppressed by antioxidant, EUK-8. [Conclusion] The concerted effect of TNF-α and IFN-γ strongly induced the expression of TP in FLS of RA. The induction of TP enhanced the expression of CXCL10, which may contribute to the Th1-phenotype and bone destruction in RA.

P3-014

Effects of methotrexate and salazosulfapyridine on protein profiles of exosomes derived from a human synovial cell line of SW982

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Conflict of interest: None

[Objectives] To assess effects of DMARDs on synovial cell line-derived exosomes. **[Methods]** We used human synovial sarcoma cell line of SW982 as a model for RA-derived synovial cells. SW982 were cultured in media containing IL-1β and/or DMARDs (methotrexate (MTX) and Salazosulfapyridine (SASP)). Exosomes were isolated from the conditioned culture media using Exoquick-TC. Then, exosomal proteins were comprehensively analyzed by 2-dimensional differential image gel electrophoresis (2D-DIGE). Protein spots intensity of which was significantly altered by the treatment with DMARDs were identified by mass spectrometic analysis. **[Results]** 294 protein spots were detected in the exosome preparations. Among them, 8, 10, and 21 spots showed more than ±2.0-fold expression with statistical significance in SASP-, MTX-, and SASP+MTX-treated groups respectively, as compared with the group without DMRAD. Similarly, 62 spots showed significantly different expression between the control and IL-1β groups. The IL-1β-induced change of 22 spots were suppressed by the simultaneous addition of DMARDs. **[Conclusion]** Exosomal proteins derived from synovial sarcoma cells are affected by DMARDs and IL-1β. A part of the effects of IL-1β on the exosomal proteome were suppressed by DMARDs.

P3-015

The expression of the oxytocin-monomeric red fluorescent protein 1 (mRFP1) fusion gene and the role of the oxytocin in the adjuvant-induced arthritic rats

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Conflict of interest: None

[Objectives] Several lines of evidence have suggested that Oxytocin (OXT) plays an important role in pain modulation and analgesia. The present study examined the effects of chronic inflammation on OXT-mRFP1 expression in the posterior pituitary (PP), the hypothalamus, and the spinal cords using the adjuvant arthritis (AA) model and determined whether OXT is involved in chronic pain pathway. [Methods] To induce AA, OXT-mRFP1 transgenic rats were i.c. injected heat-killed Mycobacterium butyricum at the base of their tails. We observed mRFP1 fluorescence intensity in the paraventricular (PVN), the supraoptic nuclei (SON), and the spinal cord, when AA was established, and the expression of the mRFP1, and the OXT mRNA levels in the hypothalamus were also measured by in situ hybridization histochemistry. Also changes in mechanical nociceptive threshold were measured, after OTR antagonist (i.p.) injections. [Results] OXT-mRFP1 fluorescent intensity in the PP, PVN, SON and dorsal horn of the spinal cord and OXT-mRFP1 mRNA levels in the

PVN and SON were significantly increased in AA rats. i.p. injection of OXR antagonist in AA rats caused decreases of its mechanical nociceptive threshold. [Conclusion] These results suggest that OXT may play an role in pain modulation and analgesia in AA rats.

P3-016

Effects of sulfasalazine and tofacitinib on the protein profile of articular chondrocytes

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Conflict of interest: None

[Objectives] Sulfasalazine (SSZ) and tofacitinib are effective for treating rheumatoid arthritis (RA), however, their effects on chondrocytes have not been fully understood. We here tried to elucidate their effects on chondrocyte proteins. [Methods] We treated chondrocytes from 5 osteoarthritis patients with IL-1β, IL-1β+SSZ, IL-1β+tofacitinib, SSZ alone, and tofacitinib alone. Then, we compared protein profiles of the chondrocytes using 2-dimensional differential gel electrophoresis. Further, we identified altered proteins by mass spectrometry. [Results] Out of 892 detected protein spots, the IL-1β stimulation changed intensity of 43 spots more than 1.3-fold or less than 1/1.3-fold significantly. SSZ suppressed the IL-1β-induced intensity alteration in 16 (37%) out of the 43 protein spots. Tofacitinib suppressed the IL-1β-induced alteration in 4 (9.3%) out of the 43 spots. The production of AMP deaminase 2 and procollagen-lysine, 2-oxoglutarate 5-dioxygenase 2 were increased by IL-1β and the increase was suppressed by SSZ and by tofacitinib. [Conclusion] SSZ and, to lesser extent, tofacitinib suppress the effects of IL-1β on the protein profiles of chondrocytes. Our data would promote understanding of effects of the drugs on chondrocytes.

P3-017

IL-6 signaling modulates expression of circadian clock genes in rheumatoid synovial cells

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Conflict of interest: None

[Objectives] Cryptochrome (*Cry*) and Period (*Per*) genes are the clock gene that cooperate to form a core feedback-loop of the circadian rhythm. We previously showed that 1) *Cry* deficient mice were significantly aggravated experimental arthritis, and 2) TNF-a inhibited the mRNA expression of *Per2* resulting from up-regulating expression of *E4BP4* and down-regulating those of *Dbp*, a transcriptional repressor and activator of *Per2* gene, respectively, in primary cultured rheumatoid synovial cells. In this study, we examined the effect of IL-6, a pro-inflammatory cytokine as well as TNF-a, on the expression of circadian clock genes. **[Methods]** Total RNA was extracted from IL-6/IL-6R (100 ng/ml) with or without anti human IL-6R monoclonal antibody (anti hIL-6 mAb) –stimulated synovial cells to analyze quantitative expression of *Per2* and *Dbp* genes by real-time PCR. **[Results]** IL-6/IL-6R stimulation inhibited expression of *Per2* and *Dbp*, which was cancelled by anti hIL-6 mAb treatment in rheumatoid synovial cells. **[Conclusion]** IL-6 signaling could modulate the expression of *Dbp* gene, thereby inhibits those of *Per2* in rheumatoid synovial cells.

P3-018

The expressions of connexin 43 in synovium of rheumatoid arthritis

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Conflict of interest: None

[Objectives] Connexin 43 (Cx43) is one of a gap junction protein. Cx43 plays an important role in inflammation and immune response and that is highly expressed in normal human synovium. We revealed that Cx43 is increased in synovium of animal models of rheumatoid arthritis (RA). But the role of Cx43 in human synovium of RA remains unclear. The aim of this study is to evaluate the expression of Cx43 in human synovium of RA. [Methods] Synovium were obtained from patients with RA and osteoarthritis (OA) at the time of operation from January 2010 to September 2013. Sixteen RA (2 male, 14 female) and 10 OA (2 male, 8 female) cases were sampled. The expressions of Cx43 in synovium were analyzed by using real-time RT-PCR and immunostaning. [Results] Cx43 gene expressions in synovium of RA were significantly increased compared with OA. Immunostaining for Cx43 showed that synoviocytes on the surface of RA synovium were strongly stained, but those of OA were not. [Conclusion] Silencing the expression of Cx43 suppressed inflammatory cytokines and reduced synovitis in animal models of RA. This study showed that expression of Cx43 is increased in human synovium of RA. These indicate that Cx43 may play an crucial role in synovitis of RA.

P3-019

miRNA expression profiling of RA fibroblasts stimulated with EP4 agonist

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Conflict of interest: None

[Objectives] miRNA expression profiling of RA fibroblasts stimulated with EP4 agonist were investigated. [Methods] The synovial fibroblasts were isolated from the synovial tissue after total replacement surgery of (RA) (n=4). Confluent cells were stimulated with either interleukin (IL)-1b (10 ng/ml) or EP4 agonist (1μM) for 24 hours in a serum-free condition GroupA: Control (EP4 agonist-, IL-1b-), GroupB: EP4 agonist (EP4 agonist+, IL1b-) GroupC: IL-1b (EP4 agonist-, IL-1b+), GroupD: EP4 agonist + IL-1b (EP4 agonist+, IL-1b+) Total RNA was d purificated, using the miRNeasy (QIAGEN). Analysis of miRNA Expressions in RA fibroblasts by Agilent miRNA Array systems. Differentially expressed miRNAs: fold change ≥ 2.0 or ≤ 0.5 compared with healthy mix. [Results] As a result of miRNA array system, the expression of miR-543 **and** miR-132-3p were significantly increased in EP4 agonist treated RA cells compared with non-treated RA cells. The expression of miR-155-5p was decreased in EP4 agonist and IL-1b treated RA cells compared with IL-1btreated RA cells. [Conclusion] There is a possibility that these miRNA are an alternative treatment of EP4 agonist has been suggested.

P3-020

Immunohistochemistry of synoviocytes in rheumatoid arthritis

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Conflict of interest: None

Inflammatory synovitis is histologically characterized by increasing synoviocytes such as macrophages. Recently, two main polarized macrophage subsets were known: M1 which have activated microbial killing, and M2 which have immunoregulatory properties. Phenotype of macrophage may have specific polarization because of disease. [Objectives] To examine phenotype of synoviocytes in rheumatoid arthritis (RA) and osteoarthritis (OA). [Methods] 12 RA, 10 OA. The tissue were stained by

using antibodies directed toward CD68 (PGM1, Dako), iNOS (Ab3523, abcam), CD206 (5C11, abnova), CD163 (10D6, Novocastra). The number of positively stained cells was counted of 10 fields. [Results] CD68+ cells were 44.1% (26.4-98.2) in RA, 44.3% (23.3-89.9) in OA. iNOS+ cells were 88.3% (76.0-93.8) in RA, 87.2% (82.6-91.1) in OA. CD163+ cells were 81.5% (61.0-98.0) in RA, 89.9% (82.0-97.0) in OA. CD206+ cells were 72.1% (37.5-93.2) in RA, 92.7% (87.3-96.1) in OA. [Conclusion] CD206, known as M2 marker, is macrophage mannose receptor, functioning of phagocyte and uptake antigen by mannose recognition at bacterial surface. In the dominant polarization of macrophage toward to M1 phenotype in active RA synovium, relative decrease of CD206+ synoviocytes in comparion with OA was a peculiar finding in-loco.

P3-021

The role of uric acid in atheroeclerosis in mice

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Conflict of interest: None

[Objectives] Recent retrospective studies imply that serum uric acid level predicts the progression of atherosclerosis as an independent risk factor. But to date it is not clear whether serum level of uric acid contributes to the progression of atherosclerosis. [Methods] We utilized the secretable uricase transgenic mouse in which the serum uric acid level is around 2/3 of the wild type. The uricase transgene was crossed to LDLR or ApoE deficient mice to generate $LDLR^{-/-}Uricase^{Tg}$ or $Apoe^{-/-}Uricase^{Tg}$ mice, respectively. These mice along with their control mice were fed with Western high fat diet for 16 weeks starting at the age of 6 week old, sacrificed and analyzed for the atherosclerotic area of aorta by Oil Red O staining. The amount of the atherosclerotic lesion was expressed relative to the whole area of the aorta. [Results] The area of atherosclerosis was 8.1±0.9% in $LDLR^{-/-}Uricase^{Tg}$ (n=24) and 7.4±1.2% in $LDLR^{-/-}$ mice (n=14), showing no difference between groups. The area of atherosclerosis was 6.0±0.8% in $Apoe^{-/-}Uricase^{Tg}$ (n=15), which was not also different from $Apoe^{-/-}$ mice (5.4±0.6% (n=7)). [Conclusion] This study using uricase transgene did not support the hypothesis that serum uric acid contributes to the progression of atherosclerosis in mice.

P3-022

Decreasd Semaphorin3A expression correlates with histoligical features of rheumatoid arthritis

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Conflict of interest: Yes

[Objectives] To clarify whether Semaphorin3A (Sema3A) is expressed in synovial tissues, and if Sema3A expression is associated with both disease actibity in rhematoid arthritis (RA) patients and histological features of RA in synovial tissues. [Methods] Humam synovial tissues samples were obtained from RA and OA (osteoarthritis) patients. Disease actibity of in RA patients was calculated using the 28-joint Disease Activity Score based on C-reactive protein (DAS28-CRP). The histological feature of RA synovial tisseus were evaluated by Rooney's inflammation scoring system. The localization of Sema3A and vascular endothelial growth factor 165 (VEGF165) positive cells was immunohistochemically determined in synovial tissues. Expression levels of mRNA for Sema3A and VEGF-A were determined using quantitative real-time polymerase chain reaction. [Results] In OA specimens, Sema3A and VEGF165 protein were expressed in the synovial lining and inflammatory cells beneth the lining. Immunohistochemistry revealed that the density of Sema3A was decreased in RA. Sema3A expression level correlated with Rooney's inflammation score. [Conclusion] Reduction of Sema3A expression in RA synovial tissues may contribute to pathogenesis of the disease.

P3-023

Gene expression analysis of peripheral blood from systemic lupus erythematosus patients by high-throughput sequencer

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Conflict of interest: None

[Objectives] Although gene expression abnormalities in peripheral blood from systemic lupus erythematosus (SLE) patients have been reported, single nucleotide level information of the transcriptome is unrevealed yet. [Methods] Peripheral blood samples from 3 SLE and 3 RA patients, and 6 healthy controls were collected. Next, total RNA was purified and then cDNA library was prepared. Using high-throughput sequencer, base sequence data were collected by pair end sequencing. [Results] Number of total read pair was around 50 million in all samples. Transcript mapped on human genome was compared with reference and then read coverages in all exon and samples were calculated. In gene expression analysis, many genes were significantly up-regulated in SLE samples compared to those from HC and RA. As a example, SDC1, highly expressed on plasma cells and plasmacytoid dendritic cells, was over transcribed in SLE. Moreover, comprehensive variant analysis could identify various isoforms characterized by SLE. [Conclusion] Gene expression analysis used by high-throughput sequencing and bioinformatics could reveal transcriptomewidly quantitative and qualitative abnormalities in single nucleotide level. This information would be useful for deep understanding of SLE pathogenesis.

P3-024

Identification of $FPR2^{+}CD4^{+}$T cell subsets in GPI-induced arthritis and patients with rheumatoid arthritis

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Conflict of interest: None

【Objectives】 The FPR2 is a G-protein coupled receptor that potently possesses pro- and anti-inflammatory role. Although FPR2 is known to be expressed on T cells, its function in arthritic condition is unclear. We investigated the involvement of FPR2 on T cells in GPI-induced arthritis (GIA) and RA. **【Methods】** 1) Fluctuated expression of FPR2 mRNA on $CD4^{+}$T cells was analyzed in GIA mice. 2) We sorted $FPR2^{+}$ or $FPR2^{-}$ $CD4^{+}$T cells from arthritic lymph nodes, and the mRNA expression of various markers on $CD4^{+}$T cell subsets was examined. 3) Naïve T cells were cultured favoring Th1 and 17 cell differentiation, and the expression of FPR2 was analyzed. 4) In human, the expression of FPR2 on $CD4^{+}$T cells from healthy subjects (HS) or patients with RA was compared. **【Results】** 1) The expression of FPR2 on $CD4^{+}$T cells was upregulated in the early phase of arthritis. 2) $FPR2^{+}$ T cells showed higher expression of T-bet and IFNg than $FPR2^{-}$T cells. 3) $FPR2^{+}$T cells were frequently detected on Th1 condition but not on Th17. 4) The expression of FPR2 on $CD4^{+}$T cells was significantly higher in RA than in HS. **【Conclusion】** We identified that $FPR2^{+}$T cells showed Th1 phenotype in mice and this molecule was highly detected on $CD4^{+}$T cells in patients with RA, suggesting $FPR2^{+}$T cells might play a crucial role in RA.

P3-025

The DNA methyltransferase inhibitor azacitidine prevents symptoms of MRL/lpr mice with the plasticity of Foxp3 positive cells

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Conflict of interest: None

[Objectives] Administration of 5AzC was reported to increase the number of regulatory T cells (Tregs) in patients with AML or MDS. Demethylation of the Treg-specific demethylated region has been elucidated to be important for 1) development of Tregs, and 2) suppressive activity of Tregs. We analyzed effects of 5AzC in MRL/lpr mice. [Methods] Four-week-old MRL/lpr mice or MRL/+ mice were treated twice a week from 4 to 20 weeks with intraperitoneal injections of 50ug of 5AzC. [Results] 1) 5AzC treatment inhibited autoimmune symptoms in MRL/lpr mice with the change of phenotypes of T cells and B cells. 2) The number of Foxp3 positive cells was increased in the MRL/lpr mice treated with 5AzC. However, in vitro, the suppressive activity and losing Fosp3 expression of these cells were same levels as those of MRL/lpr mice without treatment. [Conclusion] 1) 5AzC effectively prevents symptoms of MRL/lpr mice as previously reported. 2) In vitro, the plasticity of increased Foxp3 positive cells from MRL/lpr mice treated with 5AzC was accelerated to the same levels as Foxp3 positive cells from MRL/lpr mice without treatment. Furthermore, we will examine the phenotype of Foxp3 positive cells after 5AzC treatment, and clarify the mechanism of preventing autoimmune symptoms of MRL/lpr mice.

P3-026

A pivotal role of GM-CSF in a novel mouse model of connective tissue disease-associated interstitial lung disease

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Conflict of interest: None

[Objectives] The aim of this study was to assess the suitability of Interstitial lung disease (ILD) in zymosan-treated SKG mice as a model of Connective tissue disease (CTD)-associated ILD and to clarify its molecular mechanisms. [Methods] The phenotype of infiltrating cells in the lung of zymosan-treated SKG mice were analyzed by intracellular cytokine staining and the contribution of IL-17A, GM-CSF or IL-6 to the development of ILD was examined using their neutralization/blocking antibodies. [Results] ILD in zymosan-treated SKG mice is characterized with infiltration of Th17 cells, GM-CSF-producing $CD4^+$ T cells, neutrophils and fibrosis and resembled non-specific interstitial pneumonia in human CTD. Naive SKG T cells preferentially differentiate into GM-CSF-producing cells, which enhanced IL-6 and IL-1β production by macrophages, and thereby enhanced differentiation of IL-17A- and/or GM-CSF-producing T cells and infiltration of neutrophils. GM-CSF neutralization blocked the development of ILD, and IL-6 signal blocking partially ameliorated it, whereas IL-17A neutralization did not. [Conclusion] Zymosan-treated SKG mice can be a model of CTD-associated ILD, and GM-CSF is a useful therapeutic target.

P3-027

Infection of *Mycoplasma fermentans* faciltates the development of arthritis in gp130F759 with changes of the immune-cell composition and cytokine gene expression

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Conflict of interest: None

[Objectives] Gp130F759 is a knock-in mouse having the gp130Y759F mutant, which spontaneously develops autoimmune arthritis. We previously reported that RA-like arthritis in gp130F759 is facilitated by systemic infection with *Mycoplasma fermentans* (Mf), which has been suggested to involve in the development of rheumatoid arthritis (RA). We have examined the pathophysiological effects of Mf infection on the arthritis of gp130F759. [Methods] Gp130F759 with no symptoms of arthritis were infected with Mf *via* vein. After 1 month, we examined the histology and cytokine gene expression in the joints. The cells in the synovia were analyzed by flow cytometry. We also compare the arthritis of gp130F759 injected with live or heat-killed (HK) Mf. [Result] The joints of infected gp130F759 showed mild synovial hyperplasia and diminished *il-6* gene expression compared to the uninfected group. The hematopoietic cells, mainly neutrophils and B cells, increased in the synovia. Importantly, administration of HKMf did not facilitate the arthritis of gp130F759. [Conclusion] These data indicate that Mf infection facilitates synovial hyperplasia of gp130F759 with increased immune cells and cytokine gene expression. Furthermore, it is suggested that viable Mf plays critical roles in this arthritogenic effect.

P3-028

Pathological examination for the remodeling possibility by hyaluronic acid treatment on the experimental knee osteoarthritis model in rabbits

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Conflict of interest: Yes

[Purpose] Treatment by intra-articular injection of hyaluronic acid (HA) is performed for osteoarthritis (OA), and various types of HA are used. We histologically examined the effect of HA and the remodeling possibility for experimental OA model. **[Materials and Methods]** Saline (control), Svenyl (SVE) or Synvisc (SYN) are injected to OA rabbit model every each 5day after meniscectomy, 5 times, 5 times and 3 times, respectively. After formalin fixation and decalcification by EDTA, we performed histopathological examination by hematoxylin and eosin staining, immunostaining for type II collagen, aggrecan, ki67 and TUNEL staining. We also performed mRNA *in situ* hybridization for hyaluronan synthase (HAS). **[Results]** In comparison with control group, matrix degeneration such as type II collagen or aggrecan was inhibited by SVE, SYN, and apoptosis decreased in SVE and SYN. By comparison of SVE and SYN, type II collagen degeneration was inhibited more in SVE than in SYN. In addition, the number of positive cells of HAS mRNA was larger in SVE and SYN than in control group. There was no significant difference between SVE and SYN in HAS mRNA. **[Conclusion]** The protective effect of HA for damaged cartilage was demonstrated histopathologically.

P3-029

Muscle injury and regeneration activate innate immunity in muscle tissues to contribute to development of autoimmune myositis

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Conflict of interest: None

[Objectives] To examine muscle injury and subsequent regeneration can contribute to development of autoimmune myositis. [Methods] The quadriceps of C57BL/6 mice were injured with bupivacaine (BPVC) injection. After 3 days, macrophages in the treated muscles were examined for expression of various cytokines with RT-PCR. Cytokine production from differentiating C2C12 myotubes was evaluated with ELISA. Mice were immunized with C-protein fragments emulsified in CFA at the tail bases and right hind paws (day 0) to establish systemic anti-C-protein T cell immunity and to induce local myositis in the right limbs. BPVC was injected into the contralateral quadriceps at day 7, followed by histological evaluation at day 21. [Results] The BPVC-injected muscles had massive infiltration of macrophages that expressed several cytokines including TNFα, CCL2, and CXCL9 3 days after the injury. These cytokines were also expressed by differentiating myotubes. When anti-C-protein T cell immunity was evoked, the BPVC-treated muscles had mononuclear cell infiltration and muscle necrosis around regenerating areas at day 21. At the time point, unimmunized mice exhibited only regenerating fibers. [Conclusion] Muscle injury could activate local innate immunity and contribute to development of autoimmune myositis.

P3-030

Establishment of a sarcopenia model based on concepts in traditional herbal medicine

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Conflict of interest: None

[Objectives] Various treatment methods have been proposed for reductions in motor function in patients with rheumatoid arthritis (RA); however, no methods currently exist for reductions in muscle quality and mass. Sarcopenia is a condition in which muscle mass, strength, and physical ability are reduced with age. We searched for sarcopenia model animals and investigated the effectiveness of Gosha-jinki-gan (GJG) which are said to be effective for age-related symptoms. [Methods] The skeletal muscles in senescence-accelerated mice were investigated. These muscles were subjected to HE staining and immunostaining. Gene expression was assessed using Western blotting. GJG was administered, and assessments were made using the same technique. [Results] The mice exhibited the pathology of sarcopenia. Although these mice had abnormalities in the expression of IGF-1/Akt/GSK3B, which are involved in gluconeogenesis, FoxOs/MuRF1, which are involved in muscular atrophy, PGC-1, which are involved in mitochondrial function, and proteins involved in microinflammation, they all improved following GJG administration. [Conclusion] These findings suggest both that senescence-accelerated mice are an appropriate model for sarcopenia, and that GJG is effective for improving sarcopenia.

P3-031

Contralateral inflammation is induced by a regional sensory-sympathetic axis in a rheumatoid arthritis model

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Conflict of interest: None

[Objectives] This study is designed to elucidate mechanisms behind the contralateral inflammation commonly observed in rheumatoid arthritis (RA). [Methods] The inflammation amplifier is a hyper chemokine inducer in non-immune cells including synovial fibroblasts and contributes to autoimmune diseases including RA. We have developed an inflammation amplifier-dependent arthritis model in which cytokines are injected into the joints of F759 mice lacking negative regulation of the IL-6 signal and neurological responses are observed. [Results] Deafferentation of sensory neurons at the 5th lumbar dorsal-root ganglion (L5 DRG) reduce the development of both ipsilateral and contralateral arthritis after cytokine injections in F759 mice, suggesting bidirectional sensory communications between symmetrical joints affect RA development. Furthermore, cytokine injections into contralateral joints enhanced the development of cytokine-mediated arthritis in other joints. Mechanistic analysis showed interneurons in the thoracic cords and sympathetic neurons innervated in contralateral joints are important for contralateral inflammation. [Conclusion] Blockades of the sensory-sympathetic interaction between joints might be a therapeutic target for RA.

P3-032

Fli-1 transcription factor impacts lupus nephritis development by regulating expression of IL-6

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Conflict of interest: None

[Objectives] We have reported that the Fli-1 heterozygote (Fli-1+/-) MRL/lpr mice has significantly prolonged survival and reduced glomerulonephritis compared to Wild-type (WT) littermates. We hypothesized that Fli-1 affects IL-6 expression and regulates lupus nephritis development. [Methods] We investigated the serum IL-6 and mRNA expression in the kidneys of Fli-1+/- MRL/lpr and WT mice. T cells were isolated and compared IL-6 production. Next, we examined IL-6 expression in the kidney by immunofluorescence staining. In vitro studies, we performed Fli-1 specific siRNA transfection to murine endothelial MS1 cells and measured IL-6 production. We also performed Chromatin Immunoprecipitation assay (ChIP) to examine Fli-1 directly binds to the IL-6 promoter region. [Results] The serum IL-6 levels and relative IL-6 expression in the kidney were significantly decreased in Fli-1+/- MRL/lpr mice. Fli-1+/- MRL/lpr T cells also showed reduced IL-6 production. IL-6 staining was mainly observed in WT glomerulus but rarely seen in Fli-1+/- mice. MS1 cells transfected with Fli-1 siRNA showed significant reduced IL-6. We also found that Fli-1 directly binds to the IL-6 promoter region by ChIP assay. [Conclusion] Fli-1 directly regulates IL-6 production and affects lupus nephritis in mice.

P3-033

Development of sensitive ELISA for anti-Mi-2 antibody and its clinical significance

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Conflict of interest: None

[Objectives] Anti-Mi-2 antibody (Ab) was the first to be identified as a DM-specific marker Ab. However, the simple assay for anti-Mi-2 Ab is not commercially available except for an ELISA kit from a foreign company. We aimed at development of ELISA for anti-Mi-2 Ab and to clarify its clinical significance. [Methods] We screened anti-Mi-2 Ab in sera from 124 patients with DM (including 13 with juvenile DM, 39 with clinically amyopathic DM and 19 with cancer-associated DM) as well as from 20 healthy individuals. Biotinylated recombinant protein was produced from the full-length Mi-2b cDNA by in vitro translation and transcription and applied to streptavidin-coated plate. [Results] By using prototype sera which had been confirmed to be positive for anti-Mi-2 Ab by immunoprecipitation-western blotting with K562 extract, the optimal dose of antigen and the serum dilution fold were determined. When we set the mean+5SD of controls as the cut-off value, we found 7 anti-Mi-2 Ab-positive patients. Although the dominant presence in female was different from a previous report from Japan, other characterestics, including absence of cancer, interstitial lung disease and CADM, were similar. [Conclusion] Our newly developed ELISA for anti-Mi-2 Ab will be useful for DM clinics.

P3-034

Autoantibodies associated with inflammatory myopathy and other systemic autoimmune rheumatic diseases in sera from breast cancer patients

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Conflict of interest: Yes

[Objectives] Striking association between anti-p155/140 (transcription intermediary factor (TIF) 1g/a) antibodies and malignancy in dermatomyositis (DM) has been documented, however, their presence in cancer patients without DM is not known. In the present study, systemic autoimmune rheumatic diseases (SARD)-associated autoantibodies were examined in breast cancer patients. [Methods] Serum autoantibodies were tested by immunoprecipitation (IP) and ELISA (anti-Ro52, TIF1g) in 152 unselected breast cancer patients. [Results] By IP, anti-TIF1g/a were found in 2 and anti-PM-Scl in one case, however, no other PM/DM,

scleroderma, or SLE-specific antibodies were found. Among autoantibodies not associated with particular diagnoses, anti-Su/Argonaute 2 (Ago 2, 3%, 4/152), anti-Ro60 (4%, 6/152) and anti-Ro52 (6%, 9/152) were common. Anti-U1RNP or -Sm were not found, however, rare anti-U5RNP specific antibodies were found in 2 cases. Combining these together, 14.5% (22/152) of breast cancer patients had autoantibodies associated with SARD. None of SARD-associated autoantibodies positive patients had SARD except one case of RA with anti-Ro52. [Conclusion] Although anti-Ro60, Ro52 and Su were the most common, unique specificities such as anti-TIF1g/a and -U5RNP were found in breast cancer patients.

P3-035

Identification of autoantibody markers from SLE specific for cerebral and myocardial infarction

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Conflict of interest: None

[Objectives] The mortality rate of myocardial and cerebral infarction is high in patients with SLE. The recent studies reported that specific autoantibodies appear in patients of not only collagen diseases but also arteriosclerosis. The purpose of present study is to investigate common autoantibody markers for SLE and vascular diseases. [Methods] By using protein microarrays we examined each six sera from patients with SLE and healthy donors to identify autoantibody patterns and associated antigens. Furthermore we compared patients' sera (SLE: 84 samples, myocardial infarction: 128 samples, cerebral infarction: 128 samples) with 128 healthy donor sera by using AlphaLISA. [Results] Level of Ten autoantibodies for specific antigens in SLE samples showed higher than those of control sera. The antibody maker for SOST was more high level in sera of cerebral infarction patients than in those of healthy donors. The antibody maker for CTNN was more high level in sera of myocardial infarction patients in those of control donors. Moreover, The specific maker for CLDN was high in patients' sera of both cerebral and myocardial infarction. [Conclusion] We would predict the onset of cerebral and myocardial infarction in not only SLE patients but also healthy donors.

P3-036

Specific autoimmune response against Ribonuclease-H (Rnase-H) as a novel autoantigen in systemic lupus erythematosus

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Conflict of interest: None

[Objective] We have reported that patients with SLE often elicit autoimmune responses against proliferating cell nuclear antigen (PCNA) multiprotein complexes. We previously have reported increased autoimmune response against chromatine assembly factor-1 (CAF-1) which is one of constitutional proteins of PCNA complexes existing ubiquitously in intracellular space, in patients with SLE. Therefore, we conducted this study to clarify autoimmune response against Ribonuclease-H (Rnase-H), another constitutional protein of PCNA complexes. **[Methods]** Immunoreactivity against Rnase-H was measured by ELISA in sera with normal healthy controls (NHCs), SLE, and diseases controls (PM/DM, SSc, SjS, MCTD, and RA). The gene expression of Rnase-H was evaluated by quantitative RT-PCR in peripheral mononuclear cells (PBMCs) from patients with SLE and NHC. **[Results]** Increased autoimmune response was significantly observed in sera with SLE compared to NHCs and disease controls. Rnase-H gene expression was significantly upregulated in PBMCs of SLE patients. **[Conclusion]** We reported anti-Rnase-H antibody as a novel antibody which specifically recognized in patients with SLE and anti- Rnase-H antibody could be useful against diagnosis of SLE.

P3-037

Autoantibodies against GM-CSF in patients with connective tissue diseases

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Conflict of interest: None

[Objectives] Anti-GM-CSF antibodies cause pulmonary alveolar proteinosis (PAP). We have previously reported a SLE patients with anti-GM-CSF Ab and PAP. It remains unknown whether there exist autoantibodies against GM-CSF in connective tissue disease (CTD) patients without PAP. To answer this question, we made ELISA and measured sera from CTD patients. [Methods] ELISA was developed; GM-CSF was coated on the plate that was blocked with BSA, diluted serum with PBS was added, and after washing the Abs were detected by anti-IgG Ab. To avoid non-specific binding, OD of the antibodies was calculated as following; OD (GM-CSF coated well)-OD (GM-CSF negative well). Using this ELISA, we examined samples from 337 CTD patients (SLE; 66, DM/PM; 52, RA; 114, scleroderma; 79, vasculitis; 26). [Results] Anti-GM-CSF Abs were detected in 40.3% of CTD (frequencies of positivity: SLE; 54%, DM/PM; 41%, RA; 39%, scleroderma; 25%, vasculitis 53%). GM-CSF in liquid phase blocked serum IgG binding to ELISA in 90% of cases. PAP was not found in all cases except one SLE that has been reported previously. Immunosuppressive therapy decreased the titers of the Abs. [Conclusion] Autoantibodies against GM-CSF were frequently detected in CTD patients, suggesting the Abs might play roles in the development of CTDs.

P3-038

Anti-SS-A autoantibody as a risk factor for the development of fingertip ulcer in systemic sclerosis

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Conflict of interest: None

[Objectives] To clarify the relationship between anti-SS-A autoantibody and clinical feature in patients with systemic sclerosis (SSc). [Methods] Patients with SSc who were registered in Y-CURD, the integrated database of medical records of patients at our department and its affiliated hospitals, were divided into anti-SS-A antibody-positive and anti-SS-A antibody-negative groups. [Results] Among 187 patients with SSc registered in Y-CURD, 45 were anti-SS-A-positive and 113 were anti-SS-A-negative, while 29 were unknown. The anti-SS-A-positive group showed significantly lower age of onset (50.2 ± 11.6 vs 56.5 ± 12.6 years, $p = 0.0054$) and higher frequency of comorbid rheumatoid arthritis (16% vs 18%, $p = 0.0023$) as compared to the negative group. Anti-CCP and anti-RNP antibodies were observed more frequently in the anti-SS-A-positive group as compared to the negative group (33% vs 6.5%, $p = 0.038$, 27% vs 11%, $p = 0.043$, respectively). Furthermore, the anti-SS-A-positive group showed significantly increased frequency of fingertip ulcer (6% vs 16%, $p = 0.015$) and sicca syndrome (73% vs 26%, $p = 3.1\times10^{-7}$) as compared to the negative group. [Conclusion] Anti-SS-A antibody can be a new risk factor for the development of fingertip ulcer in

SSc.

P3-039

Anti-Mx1 antibody as a biomarker for idiopathic non-specific interstitial pneumonia

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Conflict of interest: None

[Objectives] The aim of our study was to seek for the diagnostic marker for idiopathic non-specific interstitial pneumonia (INSIP). [Methods and Results] Anti-myxovirus resistance protein-1 (Mx1) antibody was selected by comprehensively analyzing serum autoantibodies by protein array. Next, enzyme-linked immunosorbent assay (ELISA) measuring anti-Mx1 antibody was developed. Serum anti-Mx1 antibody, which was measured by our ELISA, differentiated INSIP from IPF with 100% specificity and 26% sensitivity. Finally, we measured samples from IPF diagnosed by American Thoracic Society guideline 2011 (N = 58), other idiopathic interstitial pneumonias (IIPs) (N=45), collagen vascular diseases (CVDs, N=47), autoimmune pulmonary alveolar proteinosis (N=17), bacterial pneumonia (N=15), pulmonary tuberculosis (N=23), and healthy controls (N=10). High titer of anti-Mx1 antibody was observed exclusively in INSIP and CVDs complicated with interstitial pneumonia. [Conclusion] The measurement of anti-Mx1 antibody is a specific marker for differentiating INSIP in the setting of IIPs. However, considering its low sensitivity, our ELISA needs to be improved or replaced by another assay in the future

P3-040

PD-1^{+}CD45RB^{lo}122^{lo} autoantibody-inducing CD4 T cell (*ai*CD4 T cell) is the key for the cause of SLE

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Conflict of interest: None

[Objectives] Our 'self-organized criticality theory' shows that the generation of autoantibody-inducing CD4 T cell (*ai*CD4 T cell) is indispensable for the cause of SLE. We further showed that CD45RB^{lo}122^{lo} CD4 T cell could did induce autoantibodies and *ai*CD4 T cell seemed to belong to this subset. We here show that *ai*CD4 T cell belongs to PD-1^{+}CD45RB^{lo}122^{lo} CD4 subpopulation. **[Methods]** BALB/c mice were repeatedly immunized with ovalbumin (OVA). We performed microarray analysis to investigate gene expression of CD45RB^{lo}122^{lo} CD4 T cell in mice immunized 12x with OVA. These CD4 T cells were further isolated referring to programmed cell death-1 (PD-1) and were adoptively transferred into naïve recipients. Autoantibodies were measured in the recipients 2 weeks after transfer. **[Results]** We found that gene expression of PD-1 was increased x2 in the CD45RB^{lo}122^{lo} CD4 subset. Simultaneously, surface expression of PD-1 protein was also significantly increased in this subset. Adoptive cell transfer of PD-1^{+}CD45RB^{lo}122^{lo} CD4 T cell of mice immunized 12x with OVA showed that autoantibodies were indeed significantly increased in naïve recipients. **[Conclusion]** The *ai*CD4 T cell that induces SLE belongs to PD-1^{+}CD45RB^{lo}122^{lo} CD4 T subpopulation.

P3-041

Antibodies to biologics in rheumatic diseases

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Conflict of interest: None

[Objectives] To examine serum antibodies to biologics, whole molecule or IgG F (ab')$_2$ fragment as antigen, in patients with rheumatic diseases and characterization of the antibodies. [Methods] A hundred eleven patients with rheumatic diseases, 64 RA and 47 non-RA, were enrolled. We used etanercept (ETN), adalimumab (ADA) and tocilizumab (TCZ) as antigen. ETN was used only in whole molecule, while ADA and TCZ were used both in their whole molecule and in IgG F (ab')$_2$ fragment that were obtained by pepsin digestion, followed by Sephadex G-150 gel filtration and protein A absorption procedure. Anti-biologic DMARDs antibodies were measured by ELISA and presented as absorbance. [Results] IgM class of anti-ADA and anti-TCZ were significantly high in RA, although anti-ETN was not. Positive patients of RF and/or ACPA showed significantly high IgM anti-ADA, anti-TCZ and anti-ETN. Meanwhile IgM anti-ADA F (ab')$_2$ and anti-TCZ F (ab')$_2$ were not significantly high in RA. IgG anti-TCZ F (ab')$_2$ was significantly high in RA and RF ad/or ACPA positive patients, although IgG anti-ADA F (ab')$_2$ was not. [Conclusion] There seems to be isotypic differences among antibodies to biologics.

P3-042

Uneven temperature among fingers after cold water soak is a useful parameter to evaluate peripheral circulation in patients with Raynaud's phenomenon

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Conflict of interest: None

[Objectives] To find characteristic changes of peripheral perfusion in patients with Raynaud's phenomenon (PRP). [Methods] Thirty-one PRP who had thermographic data for fingers after cold soak were included. Controls were 25 healthy individuals. After hand soak into 10℃ water for 10 seconds, skin temperatures at nail fold and at dorsum of metacarpophalangeal (MCP) joint were measured at prior and by 30 min after the soak. Mean temperature at nail fold, recovery rate (RR: temperature recovery from the soak/temperature decrease by the soak), coefficient of variation (CV: standard deviation/mean temperature of 5 fingers) and distal-dorsal difference (DDD: nail fold-MCP temperature) were calculated and compared between the groups. [Results] Nail fold temperatures were significantly lower in PRP. PRP had significantly higher CV and lower RR and DDD. CV and DDD showed a significant negative correlation. On the basis of ROC curve analyses for these parameters, CV differentiated most effectively the two groups. [Conclusions] The characteristic feature that differentiated PRP from HC was uneven temperature among fingers. Thermographic analysis might be used to assess efficacy of vasodilators.

P3-043

The treatment of the rheumatoid arthritis according to the renal function

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Conflict of interest: None

[Objectives] In recent years, With aging and the increase in diabetes case, the cases that are accompanied by renal dysfunction and the rheumatoid arthritis increase. Treatment for them is, however, difficult. [Methods] We investigated the patients who were diagnosed as rheumatoid arthritis (RA) and treated at our hospital in October 2013. We classified them by chronic kidney disease (CKD) stage that was established by Japanese society of nephrology. We researched an association between their disease activity and therapeutic method and renal function. [Results] We could investigate 89 cases. Their average serum Cr was 0.83mg/dL and eGFR was 72.7mL/min. About CKD stage, patients with G1 and G2 occupied about 75%, on the other hand, there were two patients with G5 (severe renal dysfunction). There were no significant association between disease activity and renal function. About treatment, we found negative correlation between renal function and the doses of MTX, but, positive correlation between the doses of steroid. There was no significant association between renal function and use of biological agents. [Conclusion]

There were about 25% patients who had both rheumatoid arthritis and impaired renal function. We have to pay attention to renal function, when we treat patients with RA.

P3-044

A case of High Serum Level of KL-6 without Lung disease

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Conflict of interest: None

A-72-years old woman who suffered from rheumatoid arthritis for 35 years, was pointed out serum KL-6 833U/ml in Sep, 2012, CA125 >1,000U/ml, too. There was no symptoms of lung, gastrointestinal, ovarian and uterine diseases, in medical examinations including computed tomography, gastrointestinal endoscopy, and positron emission tomography. In Nov. 2013, she felt bloating and amount of urine decrease, and she was admitted to our department for examination.

P3-045

Characteristics of bronchoscopy to diagnose pulmonary lesions on patients who have rheumatic diseases

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Conflict of interest: None

[Objectives] To examine the characteristics of bronchoscopy on patients who have rheumatic diseases. [Methods] We retrieved medical records of patients who attended our department and underwent a bronchoscopy from June 2003 to November 2011. We analysed the data about primary diagnosis of rheumatic diseases, objectives for bronchoscopy, results of bronchoscopy (bronchoalveolar lavage, pathology, culture, PCR test of *Pneumocystis jirovecii*) and clinical diagnosis after bronchoscopy. [Results] In the patients who attended our department, 113 cases of bronchoscopy was performed in this study period. Major primary diagnoses of rheumatic diseases were 57 cases of rheumatoid arthritis, 9 cases of systemic sclerosis, 6 cases of systemic lupus erythematosus, 5 cases of Sjogren's syndrome, 4 cases of sarcoidosis, 4 cases of dermatomyositis, and 3 cases of ANCA-related vasculitis. In 42 cases (37%), final diagnoses were confirmed by bronchoscopy. Major final diagnoses were 9 cases of interstitial pneumonia, 8 cases of pneumocystis pneumonia, 4 cases of adenocarcinoma, 3 cases of squamous cell carcinoma, 3 cases of atypical mycobacterial infection and 2 cases of sarcoidosis. [Conclusion] Bronchoscopy may help to diagnose pulmonary lesions on patients who have rheumatic diseases.

P3-046

Nutritional status and control of disease activity by therapy in RA patients - Based on case reports -

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Conflict of interest: None

[Objectives] We encountered a case in which chronic inflammation from rheumatoid arthritis (RA) was accompanied by severe hypoalbuminaemia. Serum albumin (ALB) is an index of nutritional status. We investigated change in ALB due to RA therapy to examine its relationship to disease activity. [Methods] A retrospective study was conducted on RA patients treated with MTX at our hospital whose ALB, CRP, and ESR were continuously measured during the 1-year period tracing back from the survey point of September 2013. [Results] The 21 patients' disease activity had subsided over the 1-year period, and ALB, as measured every 3 months, was stable at 3.9 (P=0.65). After 3 months of treatment with MTX, ALB increased from 3.8 to 4.0, and CRP decreased from 2.5 to 1.2 (both P=0.003). [Conclusions] Although the number of cases was small, it was confirmed that ALB rises when RA activity falls and stabilizes when RA activity remains subdued. As the age of RA patients increases, it will be necessary to pay attention to nutritional status index ALB when planning treatment.

P3-047

Anti-cyclic citrullinated peptide (anti-CCP) antibody positivity in individuals without arthritic symptoms and development of rheumatoid arthritis during prospective observations

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Conflict of interest: Yes

[**Objectives**] Serum anti-CCP was measured as part of annual comprehensive health screening in individuals without joint symptoms. The development of arthritis and diagnosis of rheumatoid arthritis (RA) in this population was prospectively followed. [**Methods**] Commercial anti-CCP assay (SRL, Inc.) was included as part of health screening. Subjects with a history of RA or with active joint symptoms were excluded. Anti-CCP positive persons were counselled on smoking cessation if applicable, and advised to present immediately upon arthritic symptom onset. [**Results**] Among the 574 male and 906 female individuals (n=1480; mean age 50.0yrs) with at least one screening visit, 23 (1.6%) were anti-CCP positive at first visit, with 3 out of the 23 (13%) developing RA by the 2010 ACR/EULAR Classification Criteria within five years. In additional, nine individuals (0.62%) developed anti-CCP positivity anew at a subsequent visit. [**Conclusion**] Although anti-CCP positivity is uncommon in asymptomatic individuals, onset of arthritis and development of RA seems to occur at relatively high rates. Further observation in larger cohorts may enable the cost vs. benefit analysis for potentially utlizing anti-CCP as a screening modality.

P3-048

Utility of neutrophil CD64 as an infection marker for patients with rheumatoid arthritis treated with biologics in daily clinical practice

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Conflict of interest: None

[Aim] To evaluate the utility of neutrophil CD64 as an infection marker for patients with rheumatoid arthritis (RA) treated with biologics. [Methods] We collected the samples from RA patients treated with biologics regardless of infection and measured the expression of CD64. 1621 samples were collected from 206 biologics users (TCZ in 61, ETN in 58, ADA in 30, ABT in 27, IFX in 18, and GLM in 12 patients). A infection sample was collected regardless of the treatment. [Results] In total, the sensitivity of CD64 of infection was 75.9%, specificity was 94.4%, positive predictive value was 40.7%, and negative predictive value was 98.7%, respectively. The sensitivity of each biologics was 66.7% in TCZ, 66.7% in ETN, 94.1% in ADA, 77.8% in ABT, 88.9% in IFX, and 75.0% in GLM, respectively. [Discussion] This study is daily clinical practice, including samples who already started therapy, whose CD64 were normal range because of very early stage of infection, and whose

baseline was originally raised over cutoff value. We suppose that those were the reasons why the results of this study were inferior to those of the formers. Similarly, further studies are needed for the comparison in each biologics. [Conclusion] Measurement of CD64 is a useful in RA patients treated with biologics.

P3-049

Baseline and annual MMP3 levels in sera accurately predict a subgroup of rheumatoid arthritis patients with structural remission upon MTX monotherapy

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Conflict of interest: None

[Objectives] 50.4% of rheumatoid patients was classified to structural remission upon MTX monotherapy for 3 yrs. We here searched a predictor identifying this subgroup of patients. [Methods] Outcome of rheumatoid patients treated with MTX monotherapy was evaluated with the year-progression of modified total Sharp score (ΔTSS) with structural remission (ΔTSS<0.5), clinical rapid radiographic progression (CRRP; ΔTSS>3) and rapid radiographic progression (RRP; ΔTSS>5). Subgroup with structural remission was evaluated using negative predictive value (NPV). [Results] Upon 3 yrs MTX monotherapy, structural remission was increased from 62/161 (21.7%) to 69/137 (50.4%), whereas CRRP and RRP improved from 55/161 (34.2%) to 28/137 (20.4%) and from 35/161 (21.7%) to 15/137 (10.9%), respectively. ROC analyses showed that baseline and annual MMP3 levels in sera were significantly lower in the subgroup with structural remission. Serum MMP3 cut-off levels were 103.7 ng/ml at baseline, 98.0 ng/ml at 1 yr, and 68.8 ng/ml at 2 yrs for CRRP. They were 103.7 ng/ml with NPV 60/62 (96.8%) at baseline, 184.9 ng/ml with 94/103 (91.3%) at 1 yr, and 62.3 ng/ml with 39/39 (100%) at 2 yrs for RRP. [Conclusion] Serum MMP3 levels below 103.7~68.6 ng/ml reliably identifies a subgroup with structural remission.

P3-050

Quantitative evaluation of muscle atrophy induced by steroid therapy in patients with collagen vascular diseases

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Conflict of interest: None

[Objectives] Measurement of muscle volume by CT and MRI is quantitative, but X-ray exposure and the cost are the matter. On the other hand, a bioelectrical impedance analysis (BIA) is easy to handle. We examined steroid effects on muscle mass by using these three methods in patients with collagen vascular diseases. [Methods] We retrospectively obtained the data from 8 collagen vascular disease patients to compare the estimated skeletal muscle mass measured by using a BIA device (Tanita model MC-190) with cross-sectional area (CSA) of mid-thigh muscle measured by CT and MRI before and after steroid therapy. All CT and MRI data were analyzed by using ImageJ. The area with attenuation values between -29 to 151 Hounsfield units corresponds to the density of muscle tissue. [Results] We compared the measurements before and after steroid therapy. 1) All muscle mass measured by BIA decreased from 36.4±5.4kg to 33.9±4.6kg after steroid therapy ($p<0.01$). 2) CSA of mid-thigh muscle by CT and MRI also significantly decreased after steroid therapy ($p<0.0005$). [Conclusion] Quantitative measurement of muscle mass by BIA and CSA of mid-thigh muscle by CT and MRI could be available in evaluation of steroid induced muscle atrophy in patients with collagen vascular disease.

P3-051

The role of ultrasonography (US) of the joints in diagnosing polyarthritis in patients who fail to meet the ACR/EULAR Classification Criteria

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Conflict of interest: None

[Objectives] To study the role of ultrasonography (US) of the joints in diagnosing polyarthritis in patients who fail to meet the ACR/EULAR Classification Criteria. [Subjects & methods] Subjects: Patients who suffered from polyarthritis for less than a year and had a score below 6 according to the ACR/EULAR criteria. In total, there were 47 subjects, 12 of whom were patients receiving medication to treat RA (RA) and 35 who were not diagnosed with RA (non RA). Each joint was scored for synovial hypertorophy (GS), power Doppler (PD), bone erosion, in the finger and wrist joints and other symptomatic joints. [Results] (1) In 12 RA patients, 6 had negative serology for RA. In 35 non-RA patients, 12 had positive serology for RA. (2) In each 12 RA patients, the highest grade were PD grade ≧1 or GS grade ≧2. (3) 6 RA patients with negative serology had PD grade≧ 2 or GS grade≧2. Both GS and PD scores were higher in RA with negative serology than positive serology. (4) In 12 RA patients, 6 underwent an ultrasound of symptomatic joints besides finger and wrist joints; all 6 were found to have evidence of RA in those joints. (5) Thirty to 50% of non RA were found to have PD 1 or GS 1. There were no Significant differences between RA and non RA about tendinitis and teno-synovitis.

P3-052

Screening of Non-tuberculous mycobacterial (NTM) tenosynovitis of the hand with musculoskeletal ultrasonography (MSUS)

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Conflict of interest: None

[Objectives] Screening of NTM tenosynovitis of the hand. [Methods] We examined 2 patients who had undiagnosed tenosynovitis of the wrist. [Results] Patient 1: A 70-year-old man who had the histry of Diabetes mellitus. He presented a painful swelling of right dorsal wrist. With MSUS, heterogenous thickend proliferative synovial tissue and a lot of tiny echogenic round nodules were seen within the tendon sheaths of the wrist. The tenosynovectomy of the tendon sheaths was performed for the definitive diagnosis. The acid-fast stein of the tenosinovium was positive, but we could not identify the species of mycobacteria. Patient 2: A 74-year-old man who had the history of bronchial asthma and oral administration of corticosteroid. He presented painful swelling of the right dorsal wrist. With MSUS, the similar images of patient 1 were seen. The acid-fast stein was positive, and it was identified *mycobacterium gordonae.* [Conclusion] NTM tenosynovitis is chronic inflammation of the tendon sheaths. Rheumatic diseases must be ruled out, but the differentiation is not easy. Moreover, the diagnosis requires the biopsy of the tenosynovium and need more time of the culture. We review the characteristics of MSUS imaging and discuss the screening of the NTM tenosynovitis.

P3-053

Development of Disease Activity Classification Criteria for Rheumatoid Arthritis (RA) Based on Power Doppler Ultrasonography (PDUS)

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Conflict of interest: None

Purpose: The purpose of this study was to develop disease activity classification criteria for RA based on PDUS. Methods: The study involved 72 RA patients managed at our hospital during the 2010-2011 period. 22 joints of PIP, IP, MCP and both hands were assessed in 4 grades (0-3) by PDUS; PD22 score was the sum of these grades. In 51 of all patients, PD24 score (22 joints + both knee joints) and PD26 score (22 joints + both knee joints + both elbow joints) were additionally calculated. SDAI served as an indicator of clinical evaluation and its correlation with each PD score was analyzed. Results: In PD22 score analysis, remission (R), low disease activity (LDA), medium disease activity (MDA) and high disease activity (HDA) were defined as 0, ≤3, ≤6 and >6, respectively. The sensitivity/specificity of SDAI in each disease activity classification was 64%/97% in R group, 69%/83% in LDA, 87%/75 in MDA and 75%/87% in HDA group. The coefficient of correlation (r) of SDAI with PD22, PD24 and PD26 scores was 0.76, 0.77 and 0.76, respectively, without a significant difference. Conclusion: The new disease activity classification criteria for RA based on PDUS were shown to be comparable to the classification based on clinical evaluation.

P3-054

The utility of musculoskeletal ultrasound in determining biologic agent withdrawal in rheumatoid arthritis patients: a preliminary study

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Conflict of interest: None

[Objectives] To investigate whether musculoskeletal ultrasound is useful to determine the timing of Infliximab (IFX) withdrawal in rheumatoid arthritis (RA) patients. [Methods] Eleven RA patients in sustained clinical remission with IFX 3mg/kg, who discontinued IFX were enrolled. Musculoskeletal ultrasound (US), DAS, and HAQ were examined at the end of IFX treatment and every 3 months after IFX withdrawal. [Results] The findings of power Doppler signal (PD) at the end of IFX treatment were as follows: Four cases showed PD ≧ 2 in any joint, and other seven cases showed at most PD 1 in any joints. In the former group, two cases showed PD ≧ 2 in multiple joints three months later, and one of them restarted IFX, and the other increased the dose of methotrexate (MTX). In the latter group, one case increased the dose of MTX three months later because of joint pain (without changes in US images), and another case presented PD 2 only in the knee joint three months later though did not change the treatment. All of the other cases presented no changes in US images and retained clinical remission only by DMARDs. [Conclusion] Careful follow up is necessary when we detect PD ≧ 2 in any joints; however, it may not always predict the exacerbation of RA and involve restart of IFX treatment.

P3-055

Effect of adalimumab on work productivity and assessment of ultrasonography in patients with rheumatoid arthritis

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Conflict of interest: None

[Objectives] We examine the effects of adalimumab (ADA) on work productivity and associations between the work productivity and ultrasonographic (US) assessments in patients with rheumatoid arthritis (RA). [Methods] The work productivity was assessed using the Work Productivity and Activity Impairment Questionnarie before and after ADA initiation (week 0, 12, and 24). The US examination was performed on 22 joints (metacarpophalangeals, proximal interphalangeals and wrists) before and 12 weeks after ADA initiation. The Grayscale and power Doppler (PD) was graded on a semiquantitative scale from 0 to 3. [Results] Of the 20 enrolled patients, 19 were women and the mean age was 56.3 years. The 11 patients were paid worker and 9 were home worker. After 24 weeks, 16 patients continued treatment and showed significant decreases in overall work impairment (58% at baseline versus 30% at 24 weeks, p=0.002), absenteeism (11% versus 3.8%, p=0.016), and presenteeism (31% versus 12%, p=0.003). The mean total PD score decreased from 11.3 at baseline to 4.4 at week 12 (p=0.002). Total PD score at 12 weeks was correlation with presenteeism (r=0.48, p=0.04), but not with overall work impairment. [Conclusion] Total PD score at 12 weeks was correlation with presenteeism.

P3-056

Assessment of Ultrasonography of the Metatarsophalangeal Joints in Rheumatoid Arthritis

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Conflict of interest: None

[Objectives] We investigated an association between the prevalence of ultrasonography (US) abnormalities in the forefoot and clinical findings used by ultrasound. The purpose of our study is to investigate related factors to forefoot disease activities in rheumatoid arthritis patients. [Methods] nnNinety RA patients (28 males and 62 females, mean age: 64.2±11.2 years, ranging from 35 to 87 years; mean disease duration: 8.7±8.9 years). The US and clinical and laboratory examinations of the individual subjects were performed on the same day. The patients were divided into two groups: the “forefoot synovitis group” detected the synovitis by US and the “Non-forefoot synovitis group”. Between these two groups, SJC, TJC, CRP, DAS28-CRP, CDAI, and SDAI. Power Doppler examination was performed by the same rheumatologist well experienced musculoskeletal US. [ResultsEffusion with synovial proliferation was visualized at MTP joint in 22 of 90 (24%). SJC, DAS28CRP, SDAI, SDAI was statistically significantly higher compared with non-forefoot synovitis group. And patients did not achieve remission of CDAI and SDAI were showed significantly in forefoot synovitis group. [Conclusion] we should assesse forefoot in rheumatoid arthritis patients do not achieve remission of CDAI and SDAI.

P3-057

Ultrasonographic (US) evaluation of articular manifestations in systemic lupus erythmatosus (SLE)

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Conflict of interest: None

[Objectives] Although US examination is a valuable imaging tool in RA, its significance in SLE is not yet confirmed. To investigate articular manifestations in SLE using US technique. [Methods] 50 SLE patients with episode of joint symptoms (45 women, 5 men, mean age of 47.5 years) were recruited, and bilateral wrist, MCP, PIP and IP joints and extensor and flexor tendons were assessed for grey scale and power Doppler activity. [Results] Synovitis was detected in 27 cases. Tenosynovitis was also found in 24 cases. [Conclusion] Not only the joint lesion but also the tendon lesion was regarded as the important condition of the patients in SLE.

P3-058

Utility of fluorodeoxyglucose positron emission tomography/computed tomography for early diagnosis and evaluation of disease activity of relapsing polychondritis

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Conflict of interest: None

[Objectives] We investigated the utility of FDG-PET/CT for the diagnoses of Relapsing polychondritis (RPC) and evaluation of disease activity. [Methods] 5 RPC patients undergoing FDG-PET/CT hospitalized in our hospital between 2006 and 2012 were studied. 8 RPC cases examined by PET reported in the literature were also assessed. [Results] Typical FDG accumulation was noted in tracheobronchial trees of 9 patients, costal cartilage of 5, joints of 5, larynx of 4, nasal cavity/paranasal sinuses of 3, auricles of 3, lymph nodes of 3. 1 patient showed nasal chondritis on PET scan despite absence of nasal changes on physical examination. Of 5 patients with costochondritis, 4 remained asymptomatic. Of 9 patients with airway FDG accumulation, 8 developed respiratory symptoms and all had CT abnormalities. In the other patient, airway FDG accumulation was evident despite the absence of airway symptoms and a lack of abnormalities in the respiratory function test and CT. In 5 patients with PET post-treatment, FDG accumulation had diminished. [Conclusion] FDG-PET/CT is a potentially powerful tool for the early diagnosis of RPC, especially in patients without easily biopsied organ involvement. This modality also facilitates the evaluation of extent of disease and disease activity during treatment.

P3-059

Evaluation of diagnostic value of FDG-PET in polymyalgia rheumatica

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Conflict of interest: Yes

[Objective] To assess the clinical usefulness of FDG-PET for the diagnosis of PMR. [Methods] Nine patients who were referred to our hospital because of polymyalgia, and RA was ruled out, were included in this study. [Results] Among 9 cases that we performed FDG-PET, accumulation of FDG in periarticular sites was observed in 7 patients: The accumulated sites were as follows, shoulder (7/7, 100%), sternoclavicularis (4/7, 57%), ligament between the spinous process (6/7, 85%), hip joint (6/7, 85%), and ischial tuberosity (5/7, 71%). Each 2 patients with no accumulation on periarticular sites was diagnosed as an infectious disease. Case 1 showed FDG accumulation in the body of vertebra, and was diagnosed as purulent spondylitis. Case 2 showed FDG accumulation to the left middle lung field and nasal sinus, and diagnosed as sinobronchial syndrome. [Conclusion] Seven patients with PMR all showed FDG accumulation of the shoulders, confirming high disease sensitivity. In addition, FDG was frequently accumulated in the ligament between the spinous process and ischial tuberosity, where were previously reported to show high disease specificity, and difficult to assess by ultrasonography. These findings indicate that FDG-PET is useful for the diagnosis of PMR.

P3-060

Effectiveness of FDG-PET/CT for Diagnosis of Polymyalgia-like Illness

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Conflict of interest: None

[Objectives] Polymyalgia rheumatica (PMR) is a clinical syndrome affecting the elderly and characterized by proximal muscle pain and stiffness. However, similar muscle pain from malignant tumors complicates the situation. Therefore, the differential diagnosis as Polymyalgia-like illness has been recommmended. Here, we underwent FDG-PET/CT in Polymyalgia-like illness and report on its analysis. [Methods] The subjects of this study were 12 cases of Polymyalgia-like illness (9 cases are PMR and 3 cases are of paraneoplastic syndrome). [Results] All patients met the diagnostic criteria of Bird et al. and the required criteria from 2012 ACR / EULAR. Average scoring algorithm of these criteria in the PMR group and cases of paraneoplastic syndrome showed 4.5 point and 4.3 point respectively. No apparent difference between the two was recognized. The FDG-PET/CT results, among the three places of spinous process, ischial tuberosity, greater trochanter, cases showing uptakes in two places or more amount to 8 of the 9 cases in the PMR group, but in the cases of paraneoplastic syndrome, it was no accumulation of two or more at the same site. [Conclusion] The variation of FDG-PET/CT in the patients of Polymyalgia-like illness suggested the diversity of pathogenesis of this condition.

P3-061

Effectiveness of FDG-PET/CT in the Differential Diagnosis of Chronic Inflammatory Disease

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Conflict of interest: None

[Objectives] The rheumatic diseases can be recognized as the fever of unknown origin in some cases. Therefore, with the diverse imaging examinations, comprehensive evaluation is recommended. Here, we investigated effectiveness of FDG-PET/CT in the differential diagnosis of chronic inflammatory diseases (CID). [Methods] From 2011-2013, among the patients with fever of unknown origin, we assessed 29 cases who underwent FDG-PET/CT and analyzed 23 cases given a definitive diagnosis later. [Results] In the 23 cases, 13 cases are rheumatic diseases (aortitis 2, adult onset still's disease (AOSD) 3, polymyalgia rheumatica 4, others 4). 10 cases are infection or malignancy (malignant lymphoma 3, ovarian cancer 2, rectal cancer 2, lymphadenitis 2, and infectious endocarditis 1). Analysis of the uptake site in FDG-PET/CT, in rheumatic disease, showed an accumulation in disease-specific sites (e.g. large blood vessels or joint). Increased uptakes in the spleen were non-specifically in all cases. However, only AOSD and lymphoma showed uptake in the bone marrow. Whereas only partial accumulation was recognized as lymphoma invasion, an accumulation of the entire bone marrow in AOSD was observed. [Conclusion] Distribution of FDG-PET/CT uptake is effective in elucidating mechanisms of CID.

P3-062

Association of Obesty with Rheumatoid Arthritis (RA): Will the Visceral-Subcutaneous Fat Ratio be able to affect Disease Activity in RA?

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Conflict of interest: None

[Objectives] Adipose tissue is well known to induce adipocytokines and inflammatory cytokines. In the recent reports, it has been obesity may associate with disease activity in RA and with resistance to treatments. Meanwhile, the differences in the biological characters of visceral adipose tissue (VAT) and subcutaneous adipose tissue (SAT) have been discussed. Therefore, we investigated relevance of disease activity in RA to a body mass index (BMI), VAT, SAT, and VAT/SAT ratio (V/S ratio). [Methods] A cross sectional image at navel level by Computed Tomography (CT) was used for measuring the area of VAT and SAT in 125 women with RA. The correlations between DAS and BMI, VAT, SAT, or V/S ratio were analyzed. The data of DAS were used at 3-6 months after the initial treatment if the patients were newly diagnosed at our hospitals; otherwise the data at the time of CT were used for the analysis. [Results] The positive correlation was found only with VAT ($p<0.05$) and V/S ratio ($p<0.01$). [Conclusion] The disease activety of RA did not correlate with BMI, but affected by VAT, especially V/S ratio. Investigating the differences in component cells of VAT or SAT and its patterns of secreting adipocytokines may be valuable in predicting refractory disease or developing new treatments.

P3-063

High disease activity in patients with rheumatoid arthritis is associated with reduced fat volume -TOMORROW study-

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Conflict of interest: None

[Introduction] Chronic Rheumatoid arthritis (RA) inflammation is associated with changes in body composition such as decreased body weight, skeletal muscle mass and increased body fat mass, defined as rheumatoid cachexia (RC). The present study prospectively determines the disease activity in relation to body composition in patients with RA who participated in the TOMORROW study that was started in 2010. [Method] The participants in the study were consisted 208 RA patients (mean 58 years) and 205 age- and sex-matched healthy volunteer (mean 57 years). Body composition was determined by whole body dual X-ray absorptiometry at baseline and the third year. [Result] RA patients had significantly higher percentage of body fat rate ($p<0.001$) and lower body lean mass ($p<0.01$) than controls at baseline and the third year. Change values of weight and body fat rate during 3 years were significantly higher in RA patients with high disease activity (HDA) than in those with low disease activity (LDA) ($p<0.05$). But, there is no difference in change value of body lean mass and bone volume between patients with HDA and LDA. [Conclusion] The results confirm that high disease activity decreased weight and fat mass, but did not change lean mass and bone volume during 3 years in RA patients.

P3-064

Monocarboxylate transporter (MCT)-4, associated with the decrease of synovial fluid pH, is a novel therapeutic target of rheumatoid arthritis

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Conflict of interest: None

[Objectives] Although it is well known that synovial fluid pH is decreased in rheumatoid arthritis (RA) patients, the mechanisms remain unclear. Here we investigate the correlation between synovial fluid pH and the disease activity of RA. We reveal the mechanisms regulating synovial fluid pH. [Methods] We measured the values of pH and the concentration of lactate in synovial fluid of RA patients. Next, we investigated the expression of monocarboxylate transporter (MCT)-4 in RA synovial fibroblasts (RASFs) obtained from the inflamed joints using quantitative RT-PCR and Western Blotting. Finally, we examined whether the proliferation of RASFs was inhibited by knockdown of MCT4 using small interfering RNA (siRNA). [Results] Synovial fluid pH correlated negatively with the disease activity score (DAS)-28 using CRP in RA patients, accompanied by increased level of lactate. The levels of MCT4 mRNA and protein were increased in RASFs. Knockdown of MCT4 induced apoptosis of RASFs and inhibited their proliferation. [Conclusion] Synovial fluid pH of RA patients correlated negatively with DAS28-CRP due to increased expression of MCT4 in RASFs. Silencing of MCT4 inhibit RASF proliferation, indicating that MCT4 could be a novel therapeutic target of RA.

P3-065

CD45RA−Foxp3^{high} regulatory T cells in the CD27+CD28+ central memory subset are decreased in peripheral blood from patients with rheumatoid arthritis

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Conflict of interest: None

[Objectives] CD4+ T cells can be classified as either naïve, central memory (T_{CM}), or effector memory (T_{EM}) cells. To identify the T cell subsets most important in the pathogenesis of RA, we phenotypically defined human CD4+ T cells as functionally distinct subsets, and analyzed the distribution and characteristics of each subset. [Methods] Peripheral blood CD4+ T cells were classified into different subsets based on the expression of CD45RA, CCR7, CD27, and CD28. The frequency of cytokine-producing cells, and of Foxp3+ cells was analyzed by flow cytometry. Foxp3+ cells were further classified into three subpopulations based on the expression of Foxp3 and CD45RA. [Results] We classified CD4+ T cells into six novel subsets based on the expression of CD45RA, CCR7, CD27, and CD28. The CD27+CD28+ T_{CM} subset was significantly decreased in the CD4+ T cells from RA. The proportion of TNF-α-producing cells in the CD27+CD28+ T_{EM} subset was increased in RA. The frequency of CD45RA−Foxp3^{high} activated/effector Treg cells in the CD27+CD28+ TCM subset was decreased in RA. [Conclusion] The increased proportion of TNF-α-producing cells and the decreased proportion of CD45RA−Foxp3^{high} activated/effector Treg cells in particular subsets may have critical roles in the pathogenesis of RA.

P3-066

Enhanced expression of mRNA for triggering receptor expressed on myeloid cells 1 (TREM-1) in CD34+ cells of the bone marrow in rheumatoid arthritis

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Conflict of interest: None

[Objectives] TREM-1 is a recently identified cell surface receptor, and plays an important role as amplifier of inflammatory response. Recent studies have disclosed increased TREM-1 expression in rheumatoid synovial tissue, and have suggested that TREM-1 ligation contributes to the pathogenesis of RA. The current study therefore examined the mRNA expression of TREM-1 in bone marrow (BM) CD34+ cells from RA patients. [Methods] CD34+ cells were purified from BM samples from 48 RA patients and 30 OA patients during joint operations via aspiration from iliac crest. The expression of mRNA for TREM-1 was examined by quantitative RT-PCR. [Results] The expression of mRNA for TREM-1 was significantly higher in RA BM CD34+ cells than OA BM CD34+ cells. The TREM-1 mRNA expression level was not correlated with serum CRP or with the administration of MTX or oral steroid. TREM-1 mRNA expression was significantly correlated with NF κB1, Krüppel-like factor 5 (KLF-5) and FK506-binding protein 5 (FKBP5) mRNA expression in RA BM CD34+ cells. [Conclusion] These results indicate that the enhanced expression of TREM-1 mRNA in BM CD34+ cells plays a pivotal role in the pathogenesis of RA, and might be closely associated with the enhanced mRNA expression of NF κB1, KLF-5 or FKBP5.

P3-067

Decoy receptor 3 regulates the expression of tryptophan hydroxylase TPH1 in rheumatoid synovial fibroblasts

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Conflict of interest: None

[Objectives] Tryptophan hydroxylase (TPH) is the rate-limiting enzyme involved in the synthesis of serotonin. We previously reported that decoy receptor 3 (DcR3) was overexpressed in rheumatoid synovial fibroblasts (RA-FLS). Further, by using comprehensive genetic analysis using microarrays, we newly identified TPH1 as one of the genes of which expression in RA-FLS were suppressed by DcR3. In this study, we investigated the expression of TPH1 in RA and osteoarthritis (OA)-FLS stimulated with DcR3. [Methods] After RA or OA-FLS were incubated with DcR3 for 12h, or TNFα or IL-1β for 24h, the relative expression levels of TPH1 mRNA were quantified by real-time PCR. Serotonin expressed in RA-FLS was detected by immunohistochemistry. [Results] TPH1 mRNA was expressed in both RA and OA-FLS. TPH1 mRNA expression was decreased significantly by DcR3 in RA-FLS, but not in OA-FLS. Meanwhile, TPH1 mRNA expression was significantly decreased by TNFα or IL-1β both in RA and OA-FLS. Serotonin expression in RA-FLS was confirmed. [Conclusion] We first revealed that TPH1 expression in RA-FLS was suppressed by DcR3 in a disease-specific fashion. TPH1 in RA-FLS regulated by DcR3 may affect serotonin expression to be involved in the pathogenesis of RA, such as modulating inflammatory pain or bone remodeling.

P3-068

Interleukin-12B is up-regulated by decoy receptor 3 specifically in rheumatoid synovial fibroblasts

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Conflict of interest: None

[Objectives] Decoy receptor 3 (DcR3), a secreted tumor necrosis factor receptor, inhibits FasL, LIGHT, and TL1A. We reported DcR3 binds to TL1A expressed on rheumatoid synovial fibroblasts (RA-FLS) resulting in the negative regulation of cell proliferation induced by inflammatory cytokines. We newly reported the microarray data analysis revealed DcR3 regulates gene expression in RA-FLS. The profiles indicated shared p40 subunit (IL-12B) of IL-12 and IL-23 was up-regulated by DcR3. In this study, we analysed IL-12B expression in RA-FLS stimulated with DcR3 in detail. [Methods] IL-12B mRNA expression in RA and OA-FLS were analysed by real-time PCR. IL-12B p40 protein expression in RA-FLS was analysed by western blotting. IL-12B mRNA expression in RA-FLS stimulated with DcR3 following the pre-incubation with anti-TL1A Ab was analysed by real-time PCR. [Results] Real-time PCR showed DcR3 increased IL-12B mRNA in a dose dependent manner specifically in RA-FLS. Western blotting confirmed DcR3 increased IL-12B p40. Anti-TL1A Ab inhibited the up-regulation of IL-12B expression in RA-FLS induced by DcR3. [Conclusion] IL-12 and IL-23 are linked with RA via Th1 and Th17 immune responses, respectively. DcR3 may affect the pathogenesis of RA through the regulation of IL-12B by binding to TL1A.

P3-069

Potential of a 70 kDa IL-10-like factor in synovial fluid from rheumatoid arthritis patients to augment superoxide generation by human neutrophils

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Conflict of interest: None

[Objectives] To elucidate the role of polymorphonuclear leukocytes (PMNs) in joint destruction during the inflammatory process in rheumatoid arthritis (RA) as related to superoxide generation. **[Methods]** Superoxide generation by human peripheral PMNs was measured by using a water-soluble formazan dye under PMN stimulation with fMLP and cytochalasin B. Factors in synovial fluids (SF) that may augment PMN superoxide generation were characterized via high-performance liquid chromatography and isoelectric focusing. **[Results]** The formazan dye allowed measurement of superoxide generated in the xanthine-xanthine oxidase system and by stimulated PMNs. An RA-SF protein with an apparent molecular size of 70 kDa and an isoelectric point of 8.3 was isolated, demonstrating to increase superoxide generation by PMNs. The activity was adsorbed by PMNs and was immunoadsorbed with a specific monoclonal antibody against interleukin (IL)-10. **[Conclusion]** The 70-kDa protein in RA-SF increased superoxide generation by human PMNs suggesting of its being related to IL-10. The factor may have a pathological role in RA joint destruction caused by PMNs, coinciding with rheumatoid inflammation. IL-10 therefore likely has biological activity toward PMNs during synovial inflammatory chain reactions in RA.

P3-070

Alternation of glycans on glycoproteins in rheumatoid arthritis

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Conflict of interest: None

Objectives. To understand aberrant protein glycosylation in rheumatoid arthritis (RA). ***Methods.*** Proteins from peripheral blood mononuclear cells of patients with RA and of healthy (HL) donors were separated by 2-dimentional electrophoresis. Then, proteins and their *N*-glycans were detected by SYPRO Ruby® and Concanavarin A, respectively. Mannosylation levels of each detected glycoprotein were compared between the RA and HL groups. Differently glycosylated proteins were identified by mass spectrometry. ***Results.*** 465 glycoprotein spots were detected, 11 out of which showed different mannosylation levels ($p<0.05$). Seven proteins were identified. SOD2, with low glycosylation in RA, was investigated. We found that 40% of tested patients with RA and also 40% of tested patients with systemic lupus eryhtematosus (SLE) possessed autoantibodies to SOD2. In RA, the autoantibodies to SOD2 were directed to neo-epitope (s) that were exposed by the lack of *N*-glycans, but not in SLE. Functionally, deglycosylation reduced the antioxidant activity of SOD2. ***Conclusion.*** We identified proteins with altered glycosylation in RA. SOD2 in RA possessed neo-epitope (s) generated by the lack of *N*-glycans. Our data would promote understanding of immunological and functional disorders of glycoproteins in RA.

P3-071

Expression of STEAP4 in patients with RA

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Conflict of interest: None

[Background] STEAP4 deficient mice spontaneously develop polyarthritis, suggesting its regulatory role in arthritis. [Objectives] To clarify the expression, localization and pathophysiological function of STEAP4 on PBMC in patients with rheumatoid arthritis (RA). [Methods] 1) STEAP4 mRNA expression in PBMC from 68 patients with RA, 24 healthy subjects (HS) and 20 patients with Sjögren's syndrome (SS) were examined. 2) The dominant expressing cell population of STEAP4 was analyzed using FACS and the expression in monocyte subsets (CD16+/-) were compared. 3) The fluctuation of TNFα, IL-6 and STEAP4 mRNA expression of $CD14^+$cells after stimulation with TNFα were examined. 4) STEAP4 mRNA expression before and 3 months after administration of tocilizumab (TCZ) and abatacept (ABT) were compared. [Results] 1) STEAP4 expression in PBMC from RA was higher than HS and SS. 2) STEAP4 was expressed in $CD14^+$cells, especially in $HLA\text{-}DR^+CD14^+CD16^-$cell population. 3) Up-regulation of TNFα and IL-6 expression in $CD14^+$ cells by TNFα was followed by up-regulation of STEAP4. 4) STEAP4 mRNA expression in PBMC and also in

$CD14^+$cells was decreased after TCZ treatment, but not after ABT treatment. [Conclusion] The expression of STEAP4 is elevated in $CD14^+$cells in patients with RA, and induced by TNFα and IL-6.

P3-072

Mechanism of eosinophil increasement before the onset of a murine model of rheumatoid arthritis

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Conflict of interest: None

[Background] We previously reported that before the onset of arthritis in the gp130F759, in which gp130 with Y759F mutation is knocked-in, the synovial cells increased 3 times compared with wild type (WT), particularly eosinophils increased 7.8 times. It is suggested that eosinophils in the synovium before onset of arthritis have an arthritogenic role. [Objective] Eosinophils increase not only in the synovium but also in the inguinal lymph node (LN) in gp130F759, suggesting that increase of eosinophils in the synovium is related to the systemic pathological changes. To know the correlation between the synovial eosinophils and spreading of inflammation throughout the whole body, we check the difference of gene expression between the synovium and inguinal LN. [Methods] We used real-time PCR for analyzing gene expression of mediators affecting eosinophils in the synovium and inguinal LN. [Results] Expression of *IL-33* was increased in the synovia of gp130F759 compared with wild type. On the other hand, expression of *IL-33* and *CCL11* were increased in the inguinal LN. It is suggested that increase of eosinophils in the synovia is a part of dynamic change of eosinphil in gp130F759. We are currently studyng the role of eosinophils in another murine arthritis model (antigen-induced arthritis).

P3-073

Analysis of involvement of osteoclast-like cells in cartilage degradation in rheumatoid arthritis

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Conflict of interest: None

[Objectives] The aim of this study is to reveal the involvement of osteoclast-like cells in cartilage destruction. [Methods] Expression of a disintegrin and metalloproteinase with thrombospondin-like motifs 4 (ADAMTS-4) and ADAMTS-5 in osteoclast-like cells in joint of RA patients were analyzed by immunohistochemistry. RAW264.7 cell was differentiated to osteoclast by RANKL and stimulated with TNF-α, TNFSF14, IL-1α, or TGF-β. ADAMTS-4 and ADAMTS-5 mRNA expression in differentiated cells was analyzed by RT-PCR. [Results] Immunohistochemistry showed that osteoclast-like cells in RA joint expressed ADAMTS-4 and ADAMTS-5. In osteoclast-like cells from RAW264.7 cells, ADAMTS-4 mRNA was upregulated by TNF-α, and ADAMTS-5 mRNA was upregulated by IL-1α and TGF-β. [Conclusion] Property of osteoclast-like cells differentiated in the presence of cytokine, which detected in joint synovial fluid of RA patients, differs from that of normal chondrocyte. It suggested that osteoclast-like cells play a role in cartilage destruction and involve in joint destruction.

P3-074

Transient EB virus reactivation and multiple lymph node swellings caused by methotrexate and adalimumab in a patient with rheumatoid arthritis

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Conflict of interest: None

A 36-year-old woman was admitted to our department because of high fever and diarrhea. She was diagnosed as rheumatoid arthritis ten years ago, and has been treated by methotrexate (MTX) and infliximab, but infliximab was discontinued due to secondary invalidity. Adalimumab (ADA) 40 mg every other week was administered from November 2010, and led to clinical remission. From late August 2013, she presented with high fever for two weeks. On admission, her body temperature was 38.6℃. Physical examination revealed multiple lymph node swellings. Laboratory tests showed elevation of CRP (7.6 mg/dl), procalcitonin (2.68 ng/ml), and soluble IL-2 receptor (5480 U/ml). Polymerase chain reaction (PCR) of EB virus (EBV) from peripheral blood was positive (3052.5 copy /mgDNA). Enhanced CT scan showed bilateral axillary, neck, and inguinal lymph node swellings, and FDG-PET also revealed uptakes in these lymph nodes. Discontinuation of MTX and ADA and administration of antibiotics gradually improved clinical signs, and PCR of EBV became negative. Axillary lymph node biopsy showed reactive hyperplasia, and repeated CT scan showed regression of lymph node swellings. This case demonstrated that EBV reactivation and reactive lymph node hyperplasia can regress by discontinuation of MTX and ADA.

P3-075

Initial manifestation of rheumatoid arthritis mimicking RS3PE syndrome: A case report

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Conflict of interest: None

A 72-year-old Japanese man was hospitalized suffering from bilateral edema in the extremities for several weeks, followed by acute symmetrical polyarthralgia. The pain lowered his ADL extraordinarily. In the same time he developed fever with high level of inflammatory reaction, C reactive protein (CRP) ranging 5-10mg/dl. Blood serology tests revealed high MMP3 up to 206 mg/dl, bilateral and symmetrical multiple synovitis and pitting edema developed in the elderly, and the autoimmune antibodies were negative such as rheumatoid factor (RF) and anti-CCP antibody. The diagnosis of RS3PE syndrome was made from these findings. We started the treatment with prednisolone (PSL) 15mg/day. Although edema disappeared rapidly following the treatment, the arthralgis remained. Because we found that RF had converted positive 2days after the treatment, we initiated methotrexate (MTX) as early RA. In ACR/EULAR 2010 criteria, they emphasizes the importance of differentiating RA from other diseases in diagnosing, which includes RS3PE syndrome in the case of the elderly like this case. We'd like to suggest the risk of easy diagnosis with manifestation and test results at a certain time.

P3-076

The change of serum rheumatoid factor during administration of tumor necrosis factor inhibitors correlates to treatment responsiveness in patients with rheumatoid arthritis

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Conflict of interest: None

The change of serum rheumatoid factor during administration of tumor necrosis factor inhibitors correlates to treatment responsiveness in patients with rheumatoid arthritis. [Objectives] To clarify whether change in serum level of rheumatoid factor (RF) during administration of tumor necrosis factor inhibitors (TNFIs) correlates to treatment responsiveness in patients with rheumatoid arthritis (RA). [Methods] Biologics-naïve TNFIs-treated RA patients with high titer of serum RF (>100IU/ml) were enrolled in this study, in whom serum RF and DAS28 was examined before and during treatment every three months. [Results] Serum level of RF was significantly decreased in the first 3-month after administration of TNFIs, and thereafter, was mildly changed. RF in 3-month after start of TNFIs treatment was decreased in 6-month in 56.4% of RA patients, and was not changed in 20.0% and was increased in 23.6%. 35.8 % of RA patient with increase of RF titer during 3-6 months after start of TNFIs treatment showed No Response of EULAR response criteria, com-

pared to 3.3% of those with dearease and 9.1% of unchanged RF. [Conclusion] Change of serum RF during administration of TNFIs correlates to treatment responsiveness in RA patients, and may serve as a predictive factor of treatment responsiveness.

P3-077

Does treatment based on T2T improve efficacy?

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Conflict of interest: None

[Objectives] To evaluate the effectiveness of T2T based treatment over conventional treatment for RA patients in clinical practice. [Patients and methods] 99 patients who received biologics after October 2010 were enrolled as T2T group and 135 patients received before September 2010 were enrolled as non-T2T group. These groups were compared on baseline disease activity, improvement rate after the treatment, clinical remission rate by DAS28 (ESR), CDAI, SDAI and Boolean, adverse event rate, and non-withdrawal rate. [Results] At the baseline, disease activity and the use of MTX were significantly lower in T2T group than non-T2T group. Improvement on disease activity after the treatment was significantly higher in T2T group. The clinical remission rates were higher in T2T group, by SDAI and Boolean (with significance), and by DAS28 (ESR) and CDAI (without significance). The rate of overall adverse events was significantly lower in T2T group, but there was no significant difference between the groups on pneumonia. There was no significant difference on non-withdrawal rate. [Conclusions] Although T2T based treatment is still a new idea, this study showed some advantages over conventional treatment.

P3-078

DAS remission but not DAS disease activity contributes to radiographic progression upon 3-yrs continuous methotrexate (MTX) monotherapy

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Conflict of interest: None

[Objectives] To evaluate contribution of the annual evaluation of DAS remission/ DAS disease activity to radiographic progression upon MTX monotherapy. [Methods] Outcome of rheumatoid patients treated with MTX monotherapy (mean: age 57.4 yrs, disease duration 4.4 yrs) was evaluated with DAS28, mHAQ), and the year-progression of modified total Sharp score (ΔTSS) prospectively for 3 yrs. [Results] MTX monotherapy was started for poor-prognosis RA (n=161) with mean DAS28-ESR (4) 5.5 and ΔTSS 7.9. After 1 yr of MTX monotherapy, ΔTSS was 1.55±1.97 in DAS remission patients (n=44), 2.00±2.47 (n=27) in DAS low active patients, 4.10±3.96* in DAS moderately active patients (n=74), and 6.69±6.75* in DAS high active patients (n=16). They were 1.26±1.65 (n=63), 4.94±5.59* (n=22), 2.80±2.67* (n=53), and 8.32±7.48* (n=8), respectively after 2 yrs. They were 1.55±1.93 (n=68), 2.86±3.42 (n=22), 3.38±3.52* (n=39), and 2.59±2.22 (n=5). The results indicate that annual DAS disease activity did not always reflect radiographic progression, whereas radiographic progression of the patients with DAS remission was minor. [Conclusion] A half of poor-prognosis RA patients can be introduced to structural remission upon MTX monotherapy, where DAS remission but not DAS disease activity contributes to radiographic progression.

P3-079

Influence of patients' global assessment on the determination of disease activity and remission in RA

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Conflict of interest: Yes

Influence of patients' global assessment (PtGA) on the determination of disease activity and remission in RA was studied. 104 patients were divided according to PtGA by 100mm VAS, and clinical background, tender and swollen joint counts, and such lab data as CRP, ESR and MMP-3 were compared. SDAI, four types of DAS28 (CRP or ESR; with or without PaA), and clinical remission by Boolean criteria were evaluated. The median value of PtGA was 17.5. In high PtGA group (>17.5), functional status was poorer and comorbidities were more, but other background showed no differences. Prescription of NSAID and steroid was significantly more often in high PtGA group but no difference in MTX and biologics. Tender and swollen joint counts and physician's global assessment were significantly more in high PtGA group, but lab data exhibited no differences. All indices of disease activity were higher in high PtGA group. DAS28, either including CRP or ESR, was higher in low PtGA group whereas lower in high PtGA group, when PtGA was excluded from the formula. No patient in high PtGA group met Boolean remission, but about 20% of them would have achieved it only if PtGA had fulfilled the requisite. PtGA greatly influences the determination of disease activity and remission in RA.

P3-080

Discrepancy between DAS remission and structural remission under MTX monotherapy: MMP3 as a predictor identifying a subgroup of rheumatoid arthritis patients with structural remission

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Conflict of interest: None

[Objectives] Contribution of DAS remission to structural remission and the relationship between clinical and structural remission were studied in 161 rheumatoid patients treated with MTX monotherapy. [Methods] Outcome was evaluated with DAS28, mHAQ, and the year-progression of modified total Sharp score (ΔTSS) prospectively classifying the patients into subgroups with structural remission (ΔTSS<0.5), clinical rapid radiographic progression (CRRP; ΔTSS>3) and rapid radiographic progression (RRP; ΔTSS>5). [Results] MTX monotherapy was started for active RA. After 1 yr, DAS remission and low, moderate and high activities were achieved in 44, 27, 74 and 16 patients, respectively. After 3 yrs of MTX monotherapy, they were achieved in 68, 22, 39 and 5 patients, respectively. Among the first year 44 patients with DAS remission, 24 (54.5%) patients were with structural remission, whereas 9/44 (20.5%) were with CRRP, and 4/44 (9.1%) were with RRP. Serum MMP3 levels of those with structural remission were 140±135 and this was significantly lower than those of CRRP (263±180) and RRP (353±169) (p=0.04). [Conclusion] Only half of the patients with DAS remission was with structural remission under MTX monotherapy. Serum MMP3 levels tended to be higher in the patients with radiographic progression.

P3-081

Clinical remission and prevention of joint destruction of biologics

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Conflict of interest: None

[Objectives] Rates of clinical remission and prevention of joint destruction of biologics were compared among 7 biologics. [Methods] Rates of clinical remission and prevention of joint destruction of biologics were investigated based on all kinds of literatures all over the world. The best rate of each biologic was picked up and each data was compared among 7 biologics. [Results] Actual rate of complete remission by means of DAS28-ESR was 18.7 to 59%. Actual rate of discontinuance of biologic after the remission was 41.2 to 73%. Prevention rate by means of

Total Sharp Score was 56.8 to 87%. Method and period of investigation were different and direct comparison was not possible. However, actual rate of remission, actual rate of discontinuance, and rate of joint destruction prevention were thought to be not significantly different. [Conclusion] No prominent difference was found in clinical use of 7 biologics for RA.

P3-082

Glucocorticoid should not be prescribed without a loss-in-dosage schedule to patients with rheumatoid arthritis

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Conflict of interest: None

[Objectives] If the glucocorticoid (GC) is prescribed for patients with RA in early stage of treatment, the dosage should be reduced after the control of disease activity. However, there is no report how the dosage of GC is decreased, and so we performed this survey. [Methods] Among 388 patients with RA in our hospital, 142 patients with clear starting date and initial dosage of GC were included. Patients were divided into GC secession (n= 63, 58.5 ± 13.0 years old) and GC non-secession group (n= 79, 62.1 ± 11.7), and several factors were compared. [Results] There was no difference in initial dose of GC (5.7 ± 3.9 / 5.1 ± 2.5 g / day), mean MTX dose (8.5 ± 4.8 / 7.7 ± 4.7 mg/week), maximum MTX dose (16 / 20 mg/ week), DAS28-CRP at the time of reducing GC (2.08 ± 1.17 / 1.92 ± 1.29) and the rate of biologic use (22.2 / 24.0%) in GC secession and non-secession group, respectively. Moreover, there was no difference in DAS28 at the time of the last observation among groups. In GC secession group, it took 46.5 ± 44.1 months to stop GC. [Conclusion] In our retrospective research, we could not identify the feature of GC non-secession group. It means that reducing GC is not performed intentionally. It is necessary to plan the dose reduction beforehand at the prescription of GC for RA patients.

P3-083

Consideration of a shared goal with patients with rheumatoid arthritis (RA) for implementation of Treat to Target (T2T) strategy

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Conflict of interest: None

Background and objectives: On the T2T statement, the primary target for RA treatment is a clinical remission. However, since the word "remission" is possibly not pervasive throughout all patients, the remission may not be optimal to be a shared goal. In this study, we investigated the gap between patients' comprehension and the concept of T2T. **Method**: The questionnaire survey was conducted on 598 patients in our clinic and the results were analyzed. **Results and Discussion**: Patients comprised mean age: 61.7 years, mean disease duration: 8.7 years, mean DAS28-ESR: 2.5. The proportion of patients who answered yes was 50.6% (have heard of the word, REMISSION), 43.9% (know the meaning of REMISSION) and 57.6% (know own disease activity). However, even in patients who achieved remission, mean VAS for level of their own remission was 49.0 and that for level of disappearance of signs and symptoms was 62.1. What bothers patients was the amount of time (40.1%) and frequency (20.9%) of routine visit to clinic rather than the frequency (10.9%) and pain (9.3%) of injection/intravenous, implying the demand to incorporate RA treatment into daily routine. The results suggest the necessity of reconsidering the treatment goal through eyes of patients and that of exploring forms of therapy needed.

P3-084

Clinical characteristics of the super old rheumatoid arthritis patient

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Conflict of interest: None

[Objectives] As society becomes aged, rheumatoid arthritis (RA) patient also progresses aging. Especially, so called "super old", that means more than 75 years old patient is predicted to increase in next decades. However, there is no statistical report that describes characteristics of super old RA patient. We have investigated clinical characteristics of them. [Methods] 350 patients who have started treatment and continued for more than 3 years have been used in this study. Patients were divided into four groups according to age class. That is less than 55 years old (Y), 55 to 64 years old (O), 65 to 74 years old (VO), and no less than 75 years old (SO). Mean value of DAS28, CDAI, SDAI, TJC, SJC, PGA, EGA, CRP, MMP3, mHAQ, Pain Score, concomitant methotrexate dosage (MTX), and GCS dosage were measured for each treatment year, and average values were compared for each group statistically. [Results] SO have demonstrated significant greater in mHAQ, and smaller in MTX for every year ($p<0.01$). The other parameters demonstrated no significant differences. [Conclusion] Super old patient tends to effect comparable results even with less MTX dose than younger patient. ADL of super old patient is limited from the beginning of therapy, and is not expected ADL recover as in younger patient.

P3-085

Prognostic factors and changes of lymphocyte/neutrophilratio in RA patients receiving biologics

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Conflict of interest: None

[purpose] To determine possible prognostic factors and factors reflecting the efficacy of biologics, markers including lymphocyte/neutrophilratio (L/N) were examined in RA patients receiving biologics. [Materials and Methods] Medical records of 378RApatients receiving biologics (IFX143, ETN127, ADA30, TOC42, ABT31, GLM5) were examined. Prior to biologics and 6 months after the initiation, DAS28-ESR (DAS) and its changes (dDAS), SDAI, white blood cell count, lymphocyte / neutrophil ratio (L / N), platelet number and serum MMP-3 levels were evaluated. Results after 6 months were assessed according to EULAR response criteria (good response: G, moderate response: M and no response: N). [Results] There was a significant changes in IFX and ABT. In IFX, DAS in G, M and N were 5.3, 5.7, 4.2, respectively and those in G and M were higher at the initiation. L/N were 0.24, 0.25, 0.28, respectively and the values was correlated with DAS ($r= -0.35$: $p<0.05$). Moreover dDAS and changes of L/N have some correlation. At 6 months, DAS and L/N showed a weak correlation ($r=-0.27$: $p<0.05$). In ABT, DAS in G, M and N were 4.5, 3.6, 3.9, respectively. L/N were 0.21, 0.23, 0.18, respectively and the values was correlated with DAS ($r= -0.38$: $p<0.05$). At 6 months, DAS and L/N showed a significant correlation ($r=-0.51$: $p<0.01$). [CONCLUSION] L/N showed significant changes under the treatment of biologics and may have possible value to determine the efficacy.

P3-086

Serum adiponectin-C1q complex (APN-C1q) level is elevated in RA patients compared to non-RA controls and correlates with disease severity evaluated by the extent of joint destruction

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Conflict of interest: None

[Objectives] Serum APN and complement C1q levels are reported to correlate with disease severity of RA. In addition, APN and C1q forms complex (APN-C1q) in human serum and correlates with metabolic syndrome risk. [Methods] 146 RA patients (124 female 22male / 65.7 years old / BMI 21.1kg/m^2 / CRP 1.0 mg/dl / MMP-3 126.4ng/ml / prednisolone (PSL) 1.3mg/day / biologics 13.3%) and 87 non-RA controls (82 female 5 male / 68.8 years old / BMI 21.9kg/m^2) were enrolled in this cross-sectional study. The severity of RA was evaluated according to the number of destructed joints (101 mild RA and 45 severe RA). [Results] Serum levels of ①APN (ug/ml) ②C1q (ug/ml) ③APN-C1q (units/ml) were non-RA controls (①13.5 ②67.0 ③85.9) mild RA (①13.2 ②67.1 ③97.9) severe RA (①18.9 ②66.5 ③111.4). Serum APN-C1q levels showed significant difference between non-RA v.s. RA ($P<0.001$), and between non-RA v.s. mild RA v.s. severe RA ($P<0.01$). Meanwhile, APN and C1q levels didn't show difference between non-RA v.s. mild RA. In RA group, Serum APN-C1q levels showed no correlation with MMP-3 ($P=0.75$), RF ($P=0.13$), ACPA ($P=0.34$), PSL dosage ($P=0.76$), and biologics treatment ($P=0.34$). [Conclusion] Monitoring serum APN-C1q levels may be a novel predictor of disease severity evaluated by the extent of joint destruction.

P3-087

The change of serum levels of 17 biomarkers after tocilizumab and infliximab treatment for bio-naive rheumatoid arthritis patients

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Conflict of interest: Yes

[Aims] Recently we have reported the association of profoundly suppressed IL-6 by methotrexate or infliximab (IFX) with clinical remission at 1 year. Here, we explored relations between serum levels of biomarkers and clinical parameters after the inhibition of IL-6 signaling as well as TNF-α targeted treatment. **[Methods]** Consecutive RA patients who started tocilizumab (TCZ, n=70) or IFX (n=57) as first-bio were included in this study with the written informed consent. We evaluated up to 1 year DAS28-ESR, CDAI, and total Sharp score as well as serum levels of 17 biomarkers measured by ultra-sensitive electrochemiluminescence binding assay (except MMP-3). **[Results]** Baseline IL-6 level was correlated with DAS28-ESR and CDAI at baseline. The following biomarkers after each treatment had significantly changed from baseline: TCZ, IL-6, sIL-6R, VEGF, sICAM-1, osteocalcin, osteonectin, MMP-3; IFX, IFN-γ, IL-6, sIL-6R, IL-10, IL-12p70, TNF-α, VEGF, sICAM-1, MMP-3. The serum levels of IL-6 and VEGF after either TCZ or IFX treatment were significantly correlated with DAS28-ESR and CDAI score after the treatment. **[Conclusion]** The suppression of IL-6 and VEGF by both TCZ and IFX resulted in better clinical response and may play important role in rapid quiescence of underlying disease pathways.

P3-088

Stringent therapies in early-stage RA patients improve clinical and radiographic outcome; Result from Nagasaki University Early Arthritis Cohort

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Conflict of interest: None

[Objectives] We have tried to examine whether the change of therapeutic strategy affect the clinical and radiographic outcome of early-stage RA patients. [Methods] Early-stage RA patients were recruited from Nagasaki University Early Arthritis Cohort in which the subjects received Gd-enhanced MRI of both wrist and finger joints and osteitis was scored by RAMRIS. Plain radiographic outcome of both wrist and finger joints were scored by Genant-modified Sharp score. Rapid radiographic progression (RRP) in this study was identified as a score > 3/year. Stringent therapies group was considered as the patients entried after 2008. [Results] Ninety-five patients were included. Median age and disease duration at entry were 54 y.o and 3 months, respectively. Median RAMRIS osteitis score and Genant-modified Sharp score at entry were 1 and 0, respectively. The rate of SDAI remmision and Median RAMRIS osteitis score at 1 year were 0 and 46%, respectively. Multivariate logistic regression analyses have identified; SDAI remmision at 1 year is associated with stringent therapies and RRP. RRP is associated with stringent therapies and RAMRIS osteitis score at entry. [Conclusion] Present data suggest that stringent therapies in early-stage RA patients improve clinical, and radiographic outcome.

P3-089

Methotrexate-associated lymphoproliferative disorders (MTX-LPDs) in patients with rheumatoid arthritis (RA): a report of 2 cases

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Conflict of interest: None

(Introduction) We experienced 2 cases suspected of MTX-LPDs in patients with RA. (Case 1) A 70-year-old man with the disease duration of 4 years. MTX therapy was started 3 years ago. He consulted a gastrointestinal doctor complaining of high fever and abdominal symptoms. Intra-abdominal lymph node swelling was pointed out by CT. Incisional biopsy of the inguinal lymph node was performed and it revealed DLBCL and EBV positive. MTX therapy was ceased and he was in complete remission after 8 courses of chemotherapy with R-CHOP. (Case 2) A 84-year-old woman with the disease duration of 17 years. MTX therapy was started 5 years ago. She consulted a otolaryngologist with a firm right neck mass. CT scan showed 8 cm mass in diameter in the right neck. Incisional biopsy of the mass was performed and it revealed DLBCL and EBV minus. MTX therapy was ceased and after chemotherapy with THP-COP was performed the mass regressed to about 2 cm in diameter. (Discussion) The frequency and etiology of MTX-LPDs have not been well known. Although about 50% of patients with MTX-LPDs are EBV positive, there is no pathological character of MTX-LPDs. However, if suspected of MTX-LPDs, MTX therapy is needed to intercept immediately because MTX-LPDs are reduced by cessation of the therapy.

P3-090

A case of ruptured popliteal cyst associated with rheumatoid arthritis; differential diagnosis of soft tissue tumor of lower leg and tibial compartment syndrome

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Conflict of interest: None

[Objectives] Popliteal cysts occur commonly in both normal and arthritic knees. A case of rupture of popliteal cyst which produced symptoms related to the anteromedial lower leg are reported. [Case presentation] A 59-year-old woman, with rheumatoid arthritis, presented with sub-acute onset of swelling of her right lower leg without pain. Radiological investigations suggested that she had a ruptured Baker's cyst in the calf with development of complexes cysts in her lower leg. Her symptoms was not contained progressive distal neurological deficit and/or increasing pain, we decided any surgical/medical intervention was performed. [Conclusion] Popliteal cysts, especially if ruptured, mimic the clinical picture of deep vein leg thrombosis or compartment syndrome, but our case not represented those picture.

P3-091

A case of rheumatoid arthritis related methotrexate-associated lymphoproliferative disorders (MTX-LPD) presenting a reactive lymphadenitis histologically and lacked Epstein-Barr virus (EBV) infection

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Conflict of interest: None

EBV positive MTX-LPD manifested with non-Hodgkin lymphoma has often been reported. We describe here a case of RA patient of MTX-LPD with reactive lymphadenitis lacking EBV infection. A 61 year-old female visited our medical center in summer 2011, because of right wrist joint and right-III-PIP joint swelling, and bilateral shoulder and knee joints pain. Serologic examination showed RF181IU/ml, anti-CCP antibody 2060U/ml, CRP6.38mg/dl and ESR108mm/hr. Diagnosis of RA was obtained and started a treatment with bucillamin. Disease activity was not well controlled, then MTX was added in March 2012. The activity decreased, however, right inguinal lymphadenopathy appeard in May 2013. Soluble IL-2 receptor was 2560U/ml. Abdominal/pelvic CT and Ga scintigraphy showed multiple lymphadenopathy in right external iliac and inguinal area. A right inguinal lymphnode biopsy-specimen showed a reactive lymphadenitis without a monotonous cell proliferation histologically. Considering possibility of MTX-LPD we stopped MTX treatment. After stopping MTX medication for one month, the lymphnode enlargement diminished. EBV infection was not demonstrated. Our case showed that MTX-LPD is a clinically and histologically heterogeneous entity, and EBV infection is not always required for its pathogenesis.

P3-092

Rheumatoid Arthritis presenting with carpal tunnel syndrome

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Conflict of interest: None

[Objectives] We have experienced three cases of RA presenting with CTS. [Results] Case 1: 62 year old, female. She developed numbness in her right fingers, and diagnosed as CTS, which was treated with surgical release of median nerve. Later on, she developed polyarthritis and left CTS. Bone erosion was detected by radiography and she was diagnosed as RA. Her arthralgia as well as CTS was ameliorated with Methotrexate (MTX). Case 2: 72 year old, female. She was diagnosed as right CTS 2 years before developing left CTS and referred to our hospital for surgery. Tenosynovitis was detected around flexor tendons, and she was diagnosed as RA. Her symptom was ameliorated with MTX. Case 3: 68 year old, female. She has been diagnosed as bilateral CTS, and had steroid injection into carpal tunnel several times, before being referred to us for surgery. Tenosynovitis was detected with MRI, and she was diagnosed as RA. MTX ameliorated her symptoms. [Conclusion] RA presenting with CTS is rare. Majority of idiopathic CTS shows good response to steroid injection into carpal tunnel, therefore, refractory cases to steroid should be carefully examined for the joint swelling and presence of tenosynovitis, which are signs of RA. Symptoms were effectively ameliorated with MTX in all three cases.

P3-093

The importance of foot care in rheumatoid arthritis patients– Using the VAS scale –

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Conflict of interest: None

[Background] Concern for foot care has heightened in recent years, but it is mostly in diabetes and dialysis patients rather than in RA patients. However, about 85 to 95% of RA patients have lesions in the forefoot, and calluses often cause pain when walking. RA patients receiving callus-centered foot care at our clinic were able to walk pain free afterwards. [Objectives] Usefulness of foot care in RA patients was studied. [Methods] Pain from calluses when walking was compared by VAS scale before and after foot care for 50 RA patients. [Results] Mean pre-treatment VAS of 62.0 decreased substantially to 18.9 afterwards ($P < 0.001$). Thirteen patients were totally pain free after treatment. [Conclusions] RA patients are susceptible to infection because of immunosuppressant and biologics use, and preventing infection from entering through the sole of the feet is important. When nurses provide care that enables patients to walk on their own feet, it leads to better mental health care and overall physical health care for patients. Foot care is important for RA patients from the standpoint of preventing infection, declines in ADL, and difficulty walking.

P3-094

What's the problem of dementia with patients of rheumatoid arthritis?

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Conflict of interest: None

[Objectives] Number of aged patients with RA is increasing. Some of them give up staying at home, even though their RA activity is in good control. Some who live by themselves can't take their medicine, and fail to keep good control, others who live with their family appeal their pain all day, and the family become exhausted. How can we solve these trobles, and help them stay at home? [case report] 86y.o woman diagnosed RA at her 81y.o. Though her disease activity was good after she introduced adalimumab, she appealed pain to her daughter-in-law all day. She even cried like panic attack. Donepezil, yokukansan, and quetiapine abated her pain and gave them calm life. 82y.o. woman diagnosed RA at her 60y.o. Her disease activity was higher at her 81y.o, however after introduced MTX and PSL, she could keep in good control. But once she caught cold, she couldn't cook her own meal and stopped both eating and taking medicine. Then she had to stay in hospital, untill she recovered from her sickness. Same accident happened again. She can stay by herself after she started taking rivastigmine, and asking a helper to help her with taking MTX, and to pack other medicines in calendar. [Conclusion] Some troublesome cases with RA can be improved by care of cognitive dysfunction. Intervention may help them stay at home.

P3-095

Diagnosis of central nervous system complications of rheumatoid arthritis by cerebrospinal fluid anti-CCP antibody

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Conflict of interest: None

[Background and Objective] The complications of the central nervous system in rheumatoid arthritis (RA) are rare and reported as pachy/leptomeningitis, meningoencephalitis, vasculitis. For diagnosis thickening image of pia and dura mater and multiple vascular lesions in MRI are useful to detect. Brain biopsy (such as rheumatoid nodules) is essential to confirm diagnosis, but is invasive. We report a case of measurement of CSF anti-CCP antibody. [Case] A 57-year-old woman diagnosed as RA 7 years ago and had been treated with low-dose prednisolone and MTX showed a sudden manic symptom. The serum anti-CCP antibody marked high of 44.3 IU/mL (average<4.5). MRI and CSF exams indicated inflammation of the pia mater. No rheumatoid nodules but infiltration of plasma cells and lymphocytes in the pia mater was found by brain biopsy. CSF anti-CCP antibody increased to 7.6 IU/mL. She was diagnosed with rheumatoid meningitis, and treated with intravenous methylprednisolone (1000 mg/day for 3 days) followed by oral prednisolone (50mg/day). Her symptoms improved and both the serum and CSF anti-CCP antibody decreased (serum 22.1, CSF<0.6). [Conclusion] We found this meaningful to measure CSF anti-CCP antibodies as an indicator of diagnosis and therapeutic efficacy of CNS complications of RA.

P3-096

A Felty's syndrome patient complicating with hemophagocytic syndrome

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Conflict of interest: None

A 65 years old male with longstanding active RA admitted in our hospital complicating with severe anemia. He had been administrated several DMARDs but the adherence was poor. Examination of complete blood cell count showed pancytopenia with neutrocytopenia and marked splenomegaly was detected by CT, which demonstrated Felty's syndrome. Spiking fever continued despite antibiotics therapy, and bone marrow analysis showed hemophagocytosis without myelodesplasity or abnormal chromosome, which we thought of complication of hemophagocytic syndrome with Felty's syndrome. DMARDs discontinuation and prednisolone administration ameliorated symptoms of hemophagocytic syndrome and Felty's syndrome, however, it recurred one month later and acquired resistance to therapy. Neutrocytopenia deteriorated and he deceased due to pneumonia. DMARDs discontinuation was thought to cause recurrence of Felty's syndrome with hemphagocytic syndrome. It is suggested that Felty's syndrome may become an underlying condition of autoimmune hemophagocytic syndrome.

P3-097

Subcutaneous xanthogranulomatosis at juxta-articular sites with bone cystic changes in a patient resembling and misdiagnosed as rheumatoid arthritis: a case report

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Conflict of interest: None

【**Objectives**】We report a case of subcutaneous xanthogranulomatosis at juxta-articular sites with bone cystic changes, resembling RA.【Case report】A 58-year-old male patient, who had had multiple subcutaneous nodules at juxta-articular sites from 47 and had been diagnosed and treated as RA in a community-based clinic, consulted to our hospital for a surgery of disrupted finger extensor tendons. The serum levels of RF and ACPA were elevated with CRP and MMP-3 within normal limits. In Xp there were no apparent joint space narrowing and erosion, but multiple bone cystic changes like 'geode' in RA were evident. The nodules at extensor tendons were excised, and tendon transfer was performed. Pathological examination revealed features of xanthogranuloma consisting of foam cells, giant cells, histiocytes and lymphocytes. All the multiple nodules were excised sequentially. At the sites of bone cystic changes, the nodules invaded bone, for which curettage and artificial bone grafting was performed. All specimens were pathologically diagnosed as xanthogranuloma, and synovitis was not recognized. To date, no recurrence has been observed.【Clinical importance】Although very rare, we should consider the possibility of xanthogranulomatosis in the diagnosis of RA, especially in atypical cases.

P3-098

Clinical efficacy of the iguratimod monotherapy for rheumatoid arthritis patients

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Conflict of interest: None

[Objectives] Iguratimod (IGU) is newly synthetic DMARDs and under clinical use to the rheumatoid arthritis (RA) patient from 2012 in Japan. We examined the efficacy of the IGU monotherapies for RA patients in our department. [Methods] Eleven (5 men, 6 women) patients who underwent IGU monotherapies from September, 2012 to April, 2013, were included in this study. The clinical therapeutic effect at week 24 after the initiation of IGU were analyzed (LOCF). The age of this cohort was 71.5±8.0 years old, and the disease duration 13.1±14.0 years. [Result] Before IGU treatment; CRP 1.9±1.8 mg/dl, ESR 61.6±28.7 mm/h, TJC 13.2±10.7, SJC 14.5±8.7, Pt VAS 50.9±21.5, Dr VAS 58.6±25.5, MMP-3 219.0±168.6 ng/ml, DAS28-ESR (4) 6.3±1.6, DAS28-CRP (4) 5.4±1.8, SDAI 40.5±23.5, CDAI 38.6±22.8. PSL combination rate; 45.5% and the amount of PSL; 6.2±1.7 mg/day. At week 24; CRP 1.6±2.9 mg/dl, ESR 51.5±25.9 mm/h, TJC 2.2±5.9, SJC 6.4±7.2, Pt VAS 29.2±27.6, Dr VAS 28.3±23.4, MMP-3 281.8±407.5 ng/ml, DAS28-ESR (4) 4.1±1.4, DAS28-CRP (4) 3.1±1.4, SDAI 16.0±15.4, CDAI 14.4±15.6. All parameters except for CRP, ESR and MMP-3 were significantly reduced at week 24. [Conclusion] The IGU monotherapy might clinically be one of the useful methods to RA patients.

P3-099

Changes of the medication of the rheumatoid arthritis in our out-patient clinic

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Conflict of interest: None

[Objectives] Investigate the changes of the medication and patient's background in 2005, after biological DMARDs (Bio) was approved, and in 2012, after increase of dosage up to 16 mg/week of methotrexate (MTX) was accepted. [Methods] Comparison about the differences of medication and background of the patients who suffer from rheumatism, between in 2005 and in 2012 was carried out. [Results] BBio was used for 3.2% of patients in 2005, and was used for 17.2% of patients in 2012, and frequency in use of Bio was increased sharply. MTX was prescribed for 36.6% of patients in 2005 an average of 5.6 mg, and was prescribed for 66.2% of patients in 2012 an average of 7.8mg. In 29.7% of patients exceeding 10mg/week of MTX was prescribed in 2012. However, with 17.6% of cases, the prescription dosage of MTX in 2012 was decreasing as compared with that of in 2005 because of complications. As for other disease modifying anti rheumatic drugs (DMARDs), dosage and frequency of prescription decreased. The average of CRP decreased from 1.3 mg/dl in 2005, to 0.67 in 2012. [Conclusion] The dosage and frequency of prescription of MTX, and the use of Bio were increased for tight control for Rheumatoid arthritis. But some patients couldn't receive benefits of these therapy, because of complications.

P3-100

Efficacy and safety of tacrolimus for rheumatoid arthritis patients associated with interstitial pneumonia

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Conflict of interest: None

[Objectives] To evaluate the efficacy and safety of tacrolimus (TAC) for rheumatoid arthritis (RA) patients associated with interstitial pneumonia (IP). [Methods] We examined 13 RA patients associated with IP who had treated with TAC at Osaka Rosai Hospital. Patient characteristics, DAS28-ESR, KL6, chest computed tomography (CT), and adverse events were examined. [Results] Two male and 11 female patients were included. The average age was 65.9 years and average disease duration was 9.3 years. Maximum TAC dose was 1 mg in 1, 1.5 mg in 3, 2 mg in 4, and 3 mg in 5 patients. The average administration period of TAC was 32 months (3-89). Concomitant drug were methotrexate in 2, prednisolone in 4, and biologic agents in 3 patients. DAS28-ESR improved significantly from 5.04 (0 month), to 4.30 (3 months), and to 3.27 (last follow-up) ($p<0.001$). KL6 tended to decrease from 758 (0 month), to 621 (3 months), and to 608 (last follow-up) ($p=0.33$). Nine patients could be followed by chest CT, there was no case of exacerbation of IP, and 2 cases demonstrated reduction in the size of IP lesion after TAC treatment. As for the adverse events, lung cancer was occurred in one patient. [Conclusion] TAC treatment for RA associated with IP is useful.

P3-101

Effect of vitamin E on methotrexate hepatotoxicity

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Conflict of interest: None

[Objectives] The details of a hepatotoxic mechanism of MTX are not understood, but there is a report that the MTX hepatotoxicity is the clinical condition that is almost lipid hepatitis. Efficacy of vitamin E is confirmed for nonalcoholic steatohepatitis in RCT. Therefore we examined the effect of vitamin E on MTX hepatotoxicity. [Methods] Subject: Seven patients with rheumatoid arthritis in under the folic acid combination were abnormal values reference value upper limit double or more continued it twice without liver dysfunction being detected before MTX administration. Method: We gave 300 mg/day of tocopherol for six months. Primary outcome: ALT level six months later Second outcome: CT value, AST, γ-GTP, T-bil, DAS28, patients pain VAS, fatigue VAS, TG, T-cholesterol, HDL and LDL [Results] The mean patient background is 61 years old and all women. The mean MTX doses, the folic acid doses, and the MTX dosing period were 9.9 mg/week, 7.9 mg/week and 5.9 years. The ALT level was improved from 69IU/L to 36.9IU/L ($p < 0.05$). The AST level was improved from 50.1IU/L to 33.3IU/L. The CT level was improved in 49.3HU from 45HU. DAS28 was improved from 3.7 to 3.28. [Conclusion] Vitamin E was effective for MTX hepatotoxicity in the RA patients. Liver function test abnormalities were improved.

P3-102

The effects of oral steroid and conventional synthetic disease-modifying antirheumatic drugs in patients with idiopathic multiple flexor tenosynovitis

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Conflict of interest: None

[Objective] Sometimes flexor tenosynovitis may appear as an initial symptom of RA. Patients with idiopathic multiple tenosynovitis of the hand may be in a status of Pre-Rheumatoid arthritis (RA). This study examined the effect of low-dose steroid (ldS) and conventional synthetic disease-modifying antirheumatic drugs (csDMARDs) in these patients. [Methods] Among 11 outpatients who had multiple tenosynovitis in both hands at the initial visit and did not fulfill the 2010 ACR-EULAR classification criteria for RA, 10 patients started to receive ldS, and 1 started csDMARDs. Seven patients deteriorated in the course of tapering ldS and were given csDMARDs. [Results] Two patients had monoarthritis at initial visit, 3 had Rheumatoid factor and/or anti-cyclic citrullinated peptide antibodies, 2 had a mild increase of CRP without arthritis. Of the 10 patients who were given methyl-prednisolone 6mg/day, 9 patients showed obvious improvement in the symptoms of tenosynovitis. Of the 7 patients who were given csDMARDs in the course of tapering ldS, 5 were withdrawn from steroid. One patient who started with csDMARDs achieved sustained remission. [Conclusion] These results indicate that the effect of oral steroid and csDMARDs lasts for a long time, and these drugs may prevent progression to RA.

P3-103

Clinical experience of iguratimod (IGU) at the author's institution (2nd report)

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Conflict of interest: None

[Objective] We previously reported the efficacy and safety of iguratimod (IGU) in rheumatoid arthritis (RA) patients at our institution. The second report is hereby presented. [Methods] 23 RA patients (17 females, mean age 66.3±12.0 years, Stage III or IV all 17) receiving IGU from September 2012 onwards were studied. Treatment of at least 24 weeks was achieved for 15 who were subjects of the efficacy analysis. Subjects were grouped into IGU monotherapy (n=3), DMARDs combined use (n=5), Bio agents combined use (n=7). [Results] 16 cases of adverse events were seen in 14 of 23 subjects. Namely gastrointestinal disorders 9 cases, liver dysfunction 2, worsened acute interstitial pancreatitis 1, cerebral infarction 1, rash 1, head ache 1, and fatigue 1 case. Mean changes in DAS28-CRP at 24 weeks compared to baseline in the IGU monotherapy group was from 4.23±0.35 to 3.15±0.92, in the DMARDs combination treatment group from 5.16±1.03 to 3.79±1.37, and the biological agent combination group from 4.06±1.22 to 2.85±0.41. [Conclusion] IGU was effective not only in monotherapy and combination with DMARDs, but also in subjects responding poorly to Bio agents. Adverse events were mostly mild and IGU could be continued, or the symptoms improved upon discontinuation or dose decrease.

P3-104

Treatment of elderly-onset reumatoid arthritis in our department

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Conflict of interest: None

[Objectives] To examine the efficacy of treatment of Elderly-onset reumatoid arthritis (EORA). [Methods] 27 cases (male:9 female:18) of EORA were treated in our depatment. Patients at baseline had a mean age of 74. [Results] RF positive: 52% ACPA positive: 43% disease activity at baseline: high disease activity (HDA) 9, moderate disease activity (MDA) 13, low disease activity (LDA) 5. MTX was used for 22cases, steroid for 7cases, and biologic agents for 7cases. disease activity at final stage: HDA 0, MDA 5, LDA 13, Remission 9. Five patients need no drugs. Total knee arthroplasty were performed for four patients with severe destructive osteoarthritis of the knee, resulted in good function. Synovectomy were performed for another four patients. Four patients had side effect of DMARDs; pneumonia 2cases, mulk suppression 2cases. Careful examination is useful for decrease of drug complication. [Conclusions] Caution should be exercised in prescribing DMARDs to elderly patients because the associated risk of adverse effects and toxicity elevated in the elderly. However, excessive caution may prevent elderly patients from being implemented the ideal therapy. EORA should be treated with appropriate DMARDs instead of corticosteroids in order to maintain the physical function maximal.

P3-105

Benefit of tacrolimus in elderly patients with rheumatoid arthritis

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Conflict of interest: Yes

[Objectives and Methods] Tacrolimus (TAC) is expected to cause few potentially fatal adverse reactions and is thus considered to be easily usable in elderly patients or those with complications. In this study, we evaluated 86 patients started on TAC between July 2009 and May 2012 for disease activity score (DAS), CRP, continuation rate, and adverse events by age, disease period, and use or nonuse of concomitant drugs. [Results] The mean TAC dose was 1.21 mg. In the groups younger than 65 years and 65 years or older, the rates of combining MTX were 52% and 31%, DAS28CRP were 3.37 vs. 2.80, decreasing from 3.78 vs. 4.35 ($p = 0.04$), and the continuation rates at one year were 71.8% and 85.0%, respectively, showing significantly decreased activity and a higher continuation rate in the 65 years or older group. Meanwhile, DAS28CRP was 2.37 vs. 3.08 decreasing from 4.57 vs. 4.12 ($p = 0.04$), respectively, in the less than one year versus the one year or more group, showing significantly decreased activity in the early stage patients. Blood trough levels tended to be higher in the older group. [Conclusion] Low-dose TAC is useful in elderly patients with rheumatoid arthritis, particularly in the early stage.

P3-106

Case report: Complications of methotrexate or biologics in the therapy of male patients with rheumatoid arthritis

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Conflict of interest: None

Objectives To investigate complications requiring admission in patients with rheumatoid arthritis (RA) who were treated with methotrexate (MTX) or biologics at my clinic. Among 166 patients with RA, seven (4.2%) suffered complications requiring admission. Case 1: A 64-year-old male whose smoking index was 880, with a 4-month disease duration, stage I, class II, and DAS28-CRP 6. After cessation of smoking, he was prescribed 8 mg/week of MTX, which was increased to 12 mg/week due to arthritis of his wrist joint. Two weeks later he complained of general malaise and fever, a chest X-ray showed reticular shadow and he was diagnosed of interstitial pneumonia (IP). Case 2: A 67-year-old male past smoker whose smoking index was 800, with a 7-year disease duration, stage I, class II, and 4.9 of DAS28-CRP. He was treated with MTX and other DMARDs, but suffered IP. Case 3: A 66-year-old male past smoker whose smoking index was 1600, stage III, class II. He was treated with MTX and TCZ, but developed suppurative arthritis of the right knee joint. Case 4: A 74-year-old male current smoker whose smoking index was 1600. He was treated with etanercept and suffered extensive phlegmon of right buttock. The occurrence of complications seems to be high among male patients who are past or current smokers.

P3-107

MTX-associated lymphoproliferative disorder (MTX-LPD) with CNS involvement

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Conflict of interest: None

A 64-year-old female was diagnosed with Rheumatoid Arthritis (RA) on 2000. She had been administered to Methotrexate (MTX) since 2005. She was added anti-TNF agent, Etanercept on 2006, and switched to Adalimumab on 2009 for RA activity control. Her RA disease activity was well controlled with these biologics. One day in September 2013, she was suddenly carried in convulsion and admitted to hospital emergently. She was pointed out multiple tumors in brain and cervical lymph node enlargement by Computed tomography (CT) scan. Cervical lymph node biopsy showed only nonspecific fidings. We supposed to the possibility of MTX-associated lymphoproliferative disorder (MTX-LPD) and stopped MTX treatment. We observed multiple brain tumors reduction after two weeks MTX cessation and confirmed their vanishment after four weeks by radiological examinations. Though we were not able to gain histological specimen, we highly suspected this case is MTX-LPD on brain due to its clinical course. Recently, MTX usage increase as an anchor-drug on RA treatment, it comes to be discussed about the relation between MTX and MTX-LPD. Few reports have been issued according to MTX-LPD with brain involvement. We reported rare case of MTX-LPD with CNS involvement.

P3-108

As for 3 patients of Rheumatoid Arthritis administrated DMARDs without remission or low disease activity, joint destruction has not advanced

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Conflict of interest: None

[Objectives] The rheumatoid arthritis patients by whom remission or low disease activity is not attained by DMRADs need biologics. In spite of not attaining remission or low disease activity, there are some patients to whom joint destruction does not advance. [Methods] Although remission or a low disease activity could not be attained wity DMARDs, three cases in which joint destruction did not advance were examined. [Results] Case 1, An 87-year-old woman was medicated with mizoribine, as for CRP about 2 mg/dL and DAS28-CRP became moderate disease activity, and joint destruction did not advance. Case 2, A 65-year-old woman was medicated with combinntion therapy with MTX and tacrolimus hydrate, as for CRP about 2 mg/dL and DAS28-CRP became moderate disease activity, and joint destruction did not advance. Case 3, A 58-year-old woman was medicated with combinntion therapy with MTX and tacrolimus hydrate, as for DAS28-CRP became high disease activity. Three patients' HAQ-DI was less than one, respectively. [Conclusion] As for three patients by whom remission or a low disease activity is not attained with DMARDs, joint destruction did not advance. That HAQ-DI is not a high price may become a standard to which joint destruction does not advance.

P3-109

The clinical feature of treatment of RA patient over 80 years old

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Conflict of interest: None

[Objectives] To examine the clinical feature of treatment of RA patient over 80 years old in our clinic. [Methods] 33 patients with RA over 80 years old were analysed. [Results] Among 33 patients, 24 (72%) were female. The mean average was 89.9 years old. 18 patients had concomitant heart disease, 14 had HT, 12 had HL, 10 had bone fracture, 8 had respiratory disease, 8 had eye disease, 7 had gastrointestinal disease, 7 had DM, 5 had malignancy, 4 had CKD. The mean average concomitant disease number were 3.5. DMARD+PSL group had 18 patients, DMARD group had 11, PSL group had 3,and no medication group had 1. DMARD treated 29 patients (87.8%) and PSL treated 21 patients (63.2%). MTX treated 9 patients (the mean average dose 4.3mg/w), SASP treated 9 (543mg), TAC treated 7 (0.5mg), MZR treated 7 (62.4mg), BUC treated 2 (150mg), and REF treated 1 (10mg) in DMARD. The mean average of PSL were 3mg, and PSL group were higher dose than DMARD+PSL group. 12 of 24 patients (50%) showed Remission or low disease activity by DAS28ESR analysis. These 12 patients included 5 patients in DMARD group and 6 patients in DMARD+PSL group. [Conclusion] The dose of DMARD and PSL were low in RA patient over 80 years old. DMARD+PSL and DMARD group had good result by DAS28ESR analysis, because the mean average concomitant disease number were low.

P3-110

Patient awareness survey on shortened infusion time of infliximab

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Conflict of interest: None

[Background] We have treated more than 200 patients with infliximab in our clinic since the product was approved, but the infusion time of infliximab was longer than other biologics, which imposed burdens on the patients. In April 2012, the label extension for infliximab to shorten infusion time was approved, which allows a shorter infusion time who have tolerated three initial infusions at weeks 0, 2, and 6 without exceeding an average of 5 mg/kg per hour. [Objective] To test risks and benefits associated with shortening infusion time of infliximab. [Method] In April 2013 through July 2013, we have conducted a questionnaire with 76 patients who were on infliximab treatment with shortened infusion time and given infliximab during the period. [Result] 64 patients (84%) answered the infusion time was "long" or "slightly long" before shortening infusion time, but only 12 patients (16%) answered the same after shortening infusion time. In addition, 71 patients (93%) answered the shortened infusion time was "satisfied" or "moderately satisfied". No infusion reactions occurred in 76 patients during the survey period. [Conclusion] Shortening the length of infusion proved to improve patient satisfaction and be performed safely.

P3-111

Evaluation of golimumab (GLM) therapy for rheumatoid arthritis (RA)

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Conflict of interest: None

[Objectives] We examined the effect of GLM administration to RA. [Methods] 17 cases of GLM has been administered in our department and related facilites. We have examined patients their background, effectiveness, adverse events. [Results] Male: female = 1:16. Mean age 51.6 years (35-70 years). Disease duration 3 months 8 years (4 months-33 years). MTX average 7.5mg (0-16mg), 82% combined rate. stage I: II: III: IV = 3: 5: 3: 6, class 1: 2: 3: 4 = 7: 10: 0: 0. Naive (N) 8 cases, switches (S) 9cases. Before the introduction average DAS 28CRP 4.5 (HDA: 9, MDA: 8). 24 week course at the time was 2.5 (MDA: 7, LDA: 8). 7 cases of DAS remission. Two cases of invalid stop (S2 cases). EULAR improvement criteria good response N: S = 3: 1, moderate response N: S = 5: 6. Average improvement rate of MMP-3 N: S = 63: 44.9%. 100mg administration cases 5, 3 cases of intolerated case of MTX. 2 casses because of the increased insufficient effect, 2 cases of witch is discontinous. Adverse events was only observed one case of Herpes Zoster. [Conclusion] GML was also useful in the switch case not only naive patients.

P3-112

A case of rheumatoid arthritis developed into dermatomyositis under the treatment with etanercept

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Conflict of interest: None

There are many reports with development of autoimmune diseases under the treatment of biologics. Here we report a case of rheumatoid arthritis developed into dermatomyositis (DM) under the treatment with etanercept (ETN). A forty-five years-old woman affected rheumatoid arthritis (RA) in 2008. Methotrexate (MTX) was started in 2008 followed by etanercept (ETN) in 2009. Under the treatment with 8 mg/week MTX and 50 mg/week ETN, arthritis, erythema on the face, Gottron's sign, and erythema keratodes on elbows and knees appeared in March 2013. There was an elevation of aldolase without an elevation CK. Anti-ARS antibodies are now under investigation. Skin biopsy revealed spongiform deformity of basal zone, edema of collagen and deposition of mucin in dermis, massive lymphocyte infiltration onto vessels, which are compatible with DM. Accordingly, we diagnosed as DM and PSL 0.3 mg/kg was started resulting in good response. In conclusion, we reported this case because the development of DM under the treatment with ETN is rare but exists.

P3-113

Long term treatment results of Golimumab against rheumatoid arthritis

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Conflict of interest: None

[Objectives] Golimumab (GLM) is a fully human anti-TNF-alpha monoclonal antibody, high persistency rate, because of low anti-GLM antibody appearance and hypodermic injection site reaction. We conducted a retrospective study for safety and efficiency confirmation with five GLM cases treated in more than 52 weeks. [Methods] The retrospective study enrolled 5 patients of Rheumatoid Arthritis (1 men, 4 women; mean age 60.8, 13.3 years) treated with GLM. GLM was given in a dose of 50 mg: 4, 100mg: 1. Combination MTX rate: 100% (average does: 6.7mg). First experience of biologics (naive group): 3, switch over from other biologics: 2. Clinical results are evaluated by DAS28 (CRP). [Results] 4 cases were high disease activity (80%), and one case was middle disease activity. Clinical remission rate is 80%, and persistency rate is 100%. In two cases, which had been switched from other biologics, one case was remission, another was high disease activity. All cases of three Bio- naives experienced remission. [Conclusion] GLM shows efficiency and high persistency rate. Moreover, GLM is only biologics, which can increase dosage, and this is contributing to remission maintenance for a long term.

P3-114

Clinical results and efficacy of Adalimmab for Rheumatoid Arthritis: 48weeks

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Conflict of interest: None

[Objectives] Adalimmab (ADA) is a human anti-TNF-alpha monoclonal antibody, high persistency rate. We conducted a retrospective study for safety and efficiency confirmation with ADA cases treated in more than 48 weeks. [Methods] The retrospective study enrolled 27 patients of Rheumatoid Arthritis (6 men, 20women; mean age 55.7, 12.4 years) treated with ADA. ADA was given Combination MTX rate: 100% (average does: 7.3mg) PSL rate 73.1% (4.84mg). Naive group 20 cases, switch 7cases over. Clinical results are evaluated by DAS28 (CRP). [Results] 4 cases were high disease activity (80%), and one case was middle disease activity. Clinical remission rate is 80%, and persistency rate is 100%. In two cases, which had been switched from other biologics, one case was remission, another was high disease activity. All cases of three Bio- naives experienced remission. [Conclusion] ADA shows efficiency and high persistency rate. Moreover, ADA is only biologics, which can increase dosage, and this is contributing to remission maintenance for a long term.

P3-115

Analysis of ten years continuous administration cases of infliximab

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Conflict of interest: None

[Objectives] Ten years passed after infliximab (IFX) came to be used for RA. We examined the cases that continuously administered IFX for ten years. [Methods] IFX dosage started in our department in 2003 and intended for 6 RA patients who continuously administered it now. We observed DAS28, the amounts of MTX, PSL and IFX, and use of other combination therapy. [Results] The case that performed IFX introduction for RA in 2003 was 17 cases, and 6 cases that continued were now. The average age at the time of the IFX start was 51 years old (41-62 years old). The average of disease duration: 9 years and DAS28-ESR: 5.46. Decrease of MTX was possible in 5 cases, and decrease of PSL or cancellation was possible in 5 cases. Extension of the interdose interval of IFX was possible in 4 cases. We used tacrolimus combination therapy for 5 cases that an effect attenuated, and increased IFX in quantity in 2 cases. DAS28-ESR of the endpoint was an average of 2.48 (2.0-2.95). [Conclusion] Because the case that a contraction of a disease duration of RA was long as for this case was most, might be forced to continuation of IFX. It is thought that the cases that early remission and Bio free are enabled increase in the case that used relatively early so that it is recommended now.

P3-116

The case in which GLM showed great effectiveness on a patient under high disease activity with progression of structural damage

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Conflict of interest: None

(Objectives) Medical treatment for RA has been changed due to rise of biologic agents. Here we report that GLM showed great improvement in his RA symptom after failure of first biologic agent. (Case) 49 years old male for rheumatoid arthritis with 5 years duration. Medical treatment by DMARDs started at the 1st year after symptom arose. However, the increase of swollen joint count observed, and also MMP-3, CRP, and DAS28 increased at four years later. DAS28 was still 4.07 after five years treatment, and progression of structural damage and growth of synovitis by US were also observed. Therefore, 480mg of TCZ was introduced. Although score of MMP-3, DAS28 decreased, CRP was not responded well. After 8 months follow up with additional MTX dose up, his symptom had not improved enough. Since the effectiveness of TCZ was insufficient, this case was switched to GLM 100mg. Finally, CRP decreased to negative score and also disappearance of the synovial inflammation observed by US. (Clinical meanings) The medical treatment of MTX+TCZ did not improve the patient's condition good enough, as a result, GLM100mg+MTX obtained good response after switching. This case tells importance for us to check not only result of clinical examination but also joint evaluation and use of US.

P3-117

Experience of MTX dose reduction on switch from anti-TNF biologic agents to Golimumab

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Conflict of interest: None

[Objectives] In general, when anti-TNF biologic agents were treated with MTX in patients with rheumatoid arthritis (RA), higher efficacies and lesser incidences of injection site reactions were induced than without MTX. Also, allergic signs such as rash with anti-drug antibody were appeared in patients failed efficacy frequently. In such cases, almost patients were improved allergic signs and regained previous efficacy by MTX increase. Because Golimumab (GLM) manufactured by transgenic mice is low immunogenicity, MTX may be decreased in patients with switch from other anti-TNF drugs to GLM. We investigated effects of MTX decrease on patients with switch from other anti-TNF drugs to GLM. [Methods] In 9 patients (8 females, mean age: 59.6, mean disease duration: 17.2 years) who were appeared some allergic signs that were assumed efficacy failure after treatment of Etanercept or Adalimumab, we evaluated MTX decrease (3-12mg/week, mean 7mg/week) on efficacy and allergic reactions in patients with switch to GLM. [Results] all 9 patients with switch to GLM were improved allergic signs and disease activity, and not necessary to increase MTX through 24 weeks. [Conclusion] These results suggested that it is possible to decrease MTX in RA patients with switch from other anti-TNF drugs to GLM.

P3-118

Clinical experience with certolizumab pegol: observations in biologic-naïve and –switch patients

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Conflict of interest: None

Objective: Certolizumab pegol (CZP) is the 5th anti-TNFα agent to be approved for use in Japan. The unique PEGylated structure, low molecular weight, as well as the use of a loading dose may allow for an early manifestation of response. Hereby, we report results of clinical use in both biologic-naïve and –switch cases. Methods: 14 patients were treated with CZP (12 female; 8 with concomitant MTX; 9 biologic-switches) with mean age and disease duration 54.7 and 11.7 years, respectively. The DAS28-CRP, DAS28-ESR, SDAI, CDAI, and HAQ-DI were obtained. Results: LOCF was used to report the 12 week observations. The mean decrease of the composite measures (DAS28-CRP, DAS28-ESR, SDAI, CDAI, and HAQ-DI) after 4 weeks were comparable for the biologic-switch (-0.76, -0.80, -7.59, -6.75, 0.05) and -naive groups (-1.08, -1.30, -6.98, -6.70, -0.13). After 12 weeks, the same values were -1.17, -1.19, -10.99, -9.93, 0.01 for the switch group, and -2.17, -2.21, -11.72, -11.37, -0.71 for the naive group; the biologic-naïve cases had a higher remission rate. Conclusion: Although CZP was effective in both biologic-naïve and –switch cases soon after treatment, -naïve patients had a higher remission rate at week 12.

P3-119

Rheumatoid Arthritis (RA) Patients have been Getting Bio-Free Term After used Biological Agent (adalimmab : ADA)

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Conflict of interest: None

[Objectives] Using DMARDs such as Methotrexate (MTX) and biological agents in RA is important, and can be control disease activity. Some authors report RA patients can get Bio-free term. So we will report RA patients have been getting bio-free term after using ADA. [Case1] 45 y-o female. She had morning stiffness and edema of bilateral hand fingers since 42 y-o. She had unknown fever, fatigue, bilateral wrist joints and MP joints swollen and pain, and left shoulder pain at 43 y-o. RF, anti-CCP antigen, ESR were high. She was diagnosed RA. After using MTX (8mg/W) joints pain were getting better, but joints swollen were continued. After 4 months starting MTX, ADA was used, because MTX wasn't be able to increase for her nausea. After 3 months joints pain and swollen had been getting better. She got remission disease activity, bio-free term after 22 months. After 6 months ADA off, she keeps remission. [Case 2] 39 y-o female. She was diagnosed RA at 26 y-o and started by MTX (4mg/W) at 35 y-o. Although MTX was increased to 12mg, ADA was started at 37 y-o. because her hand finger joints and elbow had pain and swollen. She had kept low disease activity for 24 months, so ADA was been off because her hope for getting a child. After 6 months ADA off, she keeps low disease activity.

P3-120

A case of systemic lupus erythematosus developed in rheumatoid arthritis patient who was treated with infliximab

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Conflict of interest: None

[Case] 80-year-old, female [current history] 10 years ago, she was diagnosed with rheumatoid arthritis (RA), and had been treated with 3mg/kg/8w of infliximab, and 6mg/w of methotrexate (MTX) from August 2007. After skin rash and hair loss appeared on May 2013, she had body weight loss low-grade fever with antinuclear antibody positive and pancytopenia on June, she was admitted to our hospital. Because we considered the side effect of MTX, we discontinued MTX and administered the leucovorin. but they didn`t work. Infection and malignancy including malignant lymphoma were excluded. She was diagnosed with SLE with skin rash, pancytopenia, antinuclear antibody positive, anti-dsDNA antibody-positive. After administration of 15mg/day of prednisolone (PSL), her general condition and pancytopenia improved immediately. Her disease activity of RA and SLE are well controled with low dose of PSL. [Conclusion] It has been reported that antinuclear antibody often increase in RA patient treated with anti-TNFα inhibitors. but the onset of SLE is rare. We report the association with SLE and anti-TNFα inhibitors.

P3-121

Efficasy of certlizmab pegol in Rheumatoid Arthritis

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Conflict of interest: None

[Objectives] The aim of this study is to evaluate the efficacy of certlizmab pegol (CERT) in patients with rheumatoid arthritis (RA). A total 8 (one male and 7 females) RA patients started CERT in April 2013, there was an average age of 70.4 years old (range 51-78), an average disease duration of 10.1 years (range1-24). [Methods] Disease activity was monitored for 24 weeks and was evaluated using DAS28 for ESR (DAS-28ESR) [Results] At baseline of this study, an average of DAS28ESR was 5.32 (+-0.34). An average of DAS28ESR at 12 weeks was 3.17 (+-0.46), which was significantly improved compared with baseline ($P<0.01$). At 24 weeks, an average of DAS28ESR was 3.17 (+-0.46) which was also significantly improved compared with baseline ($P<0.01$). There was no statistically significant difference between DAS28 at 12 weeks and at 24 weeks. The coefficient of correlation of DAS28ESR between 12 weeks and 24 weeks was 0.86 (pearson p-value<0.01). 3 patients who had achieved a DAS28ESR<2.6 at 12 weeks had maintained Remission at 24 weeks. One patient with low disease activity in 12 weeks had achieved Remission at 24 weeks. But the other 4 patients with moderate disease activity in 12 weeks was not improved anymore at 24 weeks.

P3-122

A case of discontinuation of Golimumab (GLM) monotherapy in a patient withRheumatoid arthritis who were in clinical remission

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Conflict of interest: None

A 42-year-old female was referred to our hospital in Oct, 2008 because of polyarthralgia and morning stiffness. She was diagnosed as RA, and was treated with MTX: 6mg/week. After 3 months of treatment with MTX, she still had bilateral swelling of PIP joints (from forefinger to fifth finger) Her past history was only pollinosis. She was 158cm tall and 58kg in weight. Lab tests revealed the following: RF23IU/ml, Anti-CCP≧100U/ ml CRP0.55g/dl; and disease activity score: DAS-28 (ESR) 4.8. in Feb 2009. MTX monotherapy was ineffective, and discontinued. The administration of 50mg/month of GLM was initiated. Arthritis improved markedly. Since the patient had maintained in remission, GLM was discontinued in May, 2011. Eight weeks. later, DAS-28 (ESR) was 2.1 after cancellation of GLM. No exacerbations of arthritis had been evident after the discontinuation of GLM without any other drug for 2 years 6months. And the clinical effect of remission was confirmed by using ultrasound echo. Even if it was GLM monotherapy, it is suggested that there is likelihood to bring about drug-free in the case that we were able to introduce GLM for early onset stage of RA patients with moderate disease activity. And, I also report the differences of late onset RA with GLM monotherapy, and combination therapy with MTX.

P3-123

The effect of combination therapy with Methotrexate and Adalimumab for early rheumatoid arthritis

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Conflict of interest: None

[Objectives] We reported two patients with rheumatoid arthritis (RA), who received combination therapy with Methotrexate (MTX) and Adalimumab (ADA). [Case 1] 50-year-old female, developed multiple arthralgia in September 2012. In December, she visited our hospital first. At that time, DAS28-ESR was 5.99. Furthermore, RF test was positive, and bone erosions were shown in some joints. This result was adverse prognostic factor. Therefore we started combination therapy with MTX and ADA, MTX was administered 6mg per every week, ADA was administered 40mg per every two weeks. As a result, she got remission after three months later. [Case 2] 58-year-old male, developed multiple arthralgia in December 2012. In April 2013, he visited our hospital first. At that time, DAS28-ESR was 6.31. He was diagnosed high activity RA. Furthermore, both RF test and ACPA test were strong positive. Therefore we started combination therapy with MTX and ADA, having the same dose as case1. Nevertheless, he couldn't get remission, so we added MTX sequentially. As a result, he got remission after six months later. [Conclusion] Combination therapy with MTX and ADA is effective for early RA. It is necessary to examine the initial dose of MTX.

P3-124

Adalimumab remains stable switching from certolizumab pegol in rheumatoid arthritis with stable activity by treated certolizumab pegol

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Conflict of interest: None

[Background] Certolizumab pegol (CZP) is one of TNF blockers, very efficacy for rheumatoid arthritis (RA). and very similar to adalimumab. [Objectives] We studied clinical efficacy of adalimumab switching from certolizumab pegol in RA patients with stable activity by treated CZP. [Methods] 9 RA patients with stable activity by treated CZP are switching to adalimumab. Clinical efficacy were collected at baseline and 16 weeks. We compared DAS28 at baseline with 16 weeks. [Results] Disease activity of all cases were stable at 16 weeks ($P=0.77$). [Conclusion] Adalimumab remains stable switching from certolizumab pegol in rheumatoid arthritis by treated CZP. There are so many problems, inventory management, cost, et,,,. If CZP makes good control in RA patients, we might switch adalimumab from CZP.

P3-125

Tuberculous peritonitis during infliximab therapy for rheumatoid arthritis

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Conflict of interest: None

[Objectives] We experiensed tuberculous peritonitis during infliximab (IFX) therapy. [Methods and Results] A 80-year-old woman with rheumatoid arthritis receiving infliximab therapy for five years, developed abdominal pain and nausea. Although she and her family had not been exposed to tuberculosis. CT images revealed the ascites. Laboratory data showed WBC (6400/ ml), ESR (67mm/1 hour), CRP (17.4). QuantiFERON was positive. Ascites analysis showed an adenosine deaminase activity value (101.5dl/l), cell counts (1000/ml), hyaluronic acid (176000ng/dl) and protein (4.4g/dl). PCR for Mycobacterium tuberculosis was negative. Open biopsy was performed and a diagnosis of tuberculous peritonitis was finally established. After initiating antituberculosis regimen with four drugs, her clinical condition ameliorated and ascites promptly regressed. [Conclusion] Although tuberculous peritonitis during IFX therapy is rare, this report emphasized the importance of initial suspicion of tuberculosis in these patients with tumor necrosis factor inhibitors such as IFX.

P3-126

Infliximab-induced discoid lupus erythematosus in a patient with rheumatoid arthritis

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Conflict of interest: None

Case report: A 43 year-old woman with rheumatoid arthritis (RA) was admitted for acute onset of arthralgia with malar and discoid rash, and thrombocytopenia. She had 6-year history of RA. Past history was unremarkable and she had no family history for rheumatic diseases. Infliximab (IFX) was initiated at a dose of 4 mg/kg on 0, 2 and 6 weeks and then every 8 weeks after therapeutic failure with methotrexate, tacrolimus, and salazosulfapyridine. She responded well to IFX, however, she no-

ticed erythematous rash and exacerbation of arthritis after 4th session of IFX. On admission, she had thrombocytopenia, hypocomplementemia and positive for ANA titer of 1: 160 (nucleolar, speckled) and for single-stranded DNA antibody. IFX was discontinued and skin biopsy was performed, which demonstrated superficial intradermal granuloma. She was diagnosed as IFX-induced discoid lupus erythematosus. Glucocorticoid was started with satisfactory improvement of skin and joint lesions. **Summary:** IFX-induced discoid lupus has been rarely reported previously and we report this case with literature review of IFX-induced collagen-vascular disorders.

P3-127

Experience in use of golimumab for rheumatoid arthritis

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Conflict of interest: None

Objective: To assess the efficacy and safety of golimumab for RA patients treated in our department. **Method:** The efficacy of GLM at week 52 of treatment was investigated in 12 RA patients (1 man and 11 women). **Results:** At initiation of GLM administration for these patients, mean age was 48.0±13.7 years and mean duration of disease was 13.8±7.99 years. Initial dose was 50 mg in 10 cases, and was increased to 100 mg by the time of evaluation in 5 cases. In 9 cases with concurrent administration of methotrexate, mean GLM dosage was initially 10.0±3.32 mg/week, increasing to 11.4±4.61 mg/week at the time of evaluation. DAS28-CRP was 3.56±1.39 initially and 2.42±1.17 at the time of evaluation, and response ratings according to EULAR criteria were good response in 4 cases, moderate response in 3 cases, and no response in 5 cases. The DAS remission rate was 41.7%. For the GLM 50-mg (5 cases) and GLM 100-mg (7 cases) groups, DAS28-CRP were 2.12±0.90 and 2.64±1.35, respectively. Overall persistence rate was 75%. No serious adverse events occurred at any time. **Discussion and conclusion:** The results indicate that GLM is highly safe and offers similar efficacy to other biologics. Tight control can be achieved by differentiating between 50- and 100-mg doses of GLM in accordance with disease activity.

P3-128

Efficacies and continuation rate of Golimumab for Patients with Rheumatoid Arthritis in our Clinic

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Conflict of interest: None

Objectives: We investigated the efficacies and continuation rate on patients with rheumatoid arthritis (RA) treated with Golimumab (GLM) as a first biologics, and compared with other anti-TNF drugs in our clinic. **Methods:** In 29 RA patients who were started with GLM in our clinic, we evaluated TJC28, SJC28, patient's global assessment (PtVAS), CRP, ESR, DAS28ESR and SADI on 9 patients (6 female, mean age: 60.5±14.0, mean disease duration: 7.15±7.47 years) who were treated with GLM as a first biologics and followed during more than 1year. Also, the efficacies of GLM were compared with 27 patients who were treated with infliximab (IFX: 21) or adalimumab (ADA: 6) during more than 1 year. **Result:** Although all 9 patients were treated with GLM 50mg as initial dose, only one patient was increased to 100mg. The continuation rates of GLM, IFX and ADA were 100, 85 and 67% at 52 weeks individually. In 9 patients treated with GLM, 5 patients and 4 patients achieved clinical remission based on DAS28ESR or SDAI at 52 weeks. There were no serious adverse events by GLM. GLM improved all contents of evaluations as well as IFX or ADA through 52 weeks. **Conclusions:** These results suggested that the efficacies on RA patients who were treated with GLM during 1 year were obviously maintained without failure.

P3-129

Efficacy of certolizumab pegol: A case study in a patient with rheumatoid arthritis on maintenance hemodialysis

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Conflict of interest: None

Objective We report a case of RA patient undergoing maintenance hemodialysis (HD) was successfully treated by certolizumab pegol (CZP). **Patient** The patient was 63-year-old woman who had polyarticular pain since early 2012. She was diagnosed with RA and 5mg predonine was administrated. As disease condition was not well controlled, she was referred to us from a neighbor hospital in January 2013. Her hematological baselines were as follows; CRP 5.7, RF 33, DAS28 5.92, and maintenance HD has been conducted three times per year for 6 years as she had renal failure. As prednisolone did not improve her high disease activity, Etanercept (ETN) was administrated. Her pain was not resolved and DAS28 was still 4.2 by 15 week ETN treatment. ETN was switched to CZP and pain was improved after 12 weeks. Her disease activities were changed as follows; CRP 0.3; RF 20; DAS28 2.58. **Discussion** Although biologicals, except infliximab concomitant with MTX, can be used for such patients, tocilizumab showed benefit as anti-TNFs have been shown insufficient effect. Our data suggested that CZP would have prospective benefit for HD patients who were inadequate MTX use since CZP has shown the equivalent therapeutic effect with and without MTX.

P3-130

Case Study with Certolizumab pegol for Rheumatoid Arthritis Patients at Shimizu Welfare Hospital

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Conflict of interest: None

Objective To examine the efficacy of Certolizumab pegol (CZP) in rheumatoid arthritis (RA) patients during our clinical practices **Methods** 15 RA patients whom CZP treatment was completed over 12 weeks were subjected to analysis for their baseline and efficacy. **Results** 15 patients comprised 4 men and 9 women. Mean age was 66.8 years. 10 patients had over 2 year disease duration, and 6 patients were beyond stage III. 12 patients (80.0%) were bio-switch patients. The mean value of DAS28 (CRP) was 4.5 at baseline and changed 3.6 at Week 4 and 2.7 at Week 12 after CZP administration. The mean value of the SDAI was changed from 25.1 to 17.3 and 9.3 respectively and 11 patients were introduced in low disease activity and 1 patient reached remission. 8 patients were not administrated MTX and their averaged age was 70.3 which was relatively higher. 12 week treatment showed similar degree of improvement in DAS28 (CRP) from 4.9 to 3.0 (with MTX) and 4.2 to 2.5 (without MTX). The same trend was seen in SDAI; 28.1 to 10.7 and 22.4 to 8.1 respectively. **Conclusions** CZP treatment showed rapid onset of improvement even in the majority of bio-switch RA patients or in patients without concomitant use of MTX

P3-131

Usefulness of Etanercept in Elderly Patients

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Conflict of interest: Yes

[Objectives] We retrospectively examined the usefulness of etanercept (ETN) in elderly patients. [Methods] ETN efficacy was evaluated in 55 evaluable RA patients who received ETN for more than 6 months after February 2010, by grouping the patients by age (≥65 years vs. <65 years) or concomitant use of methotrexate (MTX) or tacrolimus (TAC) in patients aged ≥65 years. [Results] The mean ETN doses in the ≥65 years and <65 years groups were 22.4 mg/w and 32.6 mg/w, respectively. In the ≥65 years group, baseline (BL) DAS28, 12-month DAS28, BL HAQ-DI, and 12-month HAQDI scores were 4.33, 2.76, 1.24, and 0.71, respectively. The corresponding scores in the <65 years group were 3.50, 2.25,

0.65, and 0.49. Both DAS28 and HAQDI scores improved in these patients. In the groups that concomitantly received MTX or TAC, the BL DAS28, 12-month DAS28, BL HAQDI, and 12-month HAQDI scores were respectively 3.95, 2.69, 1.25, and 0.82, and 4.70, 2.84, 1.59, and 0.69. Both DAS28 and HAQDI scores improved in these groups. [Conclusion] An adequate ETN dose is required for high efficacy, but lower doses may also be beneficial for the elderly. For those who cannot receive MTX, TAC should be administered concomitantly with ETN to achieve efficacy.

P3-132

3cases of pneumocystis pneumonia complicated with rheumatoid arthritis treating with anti-TNF-α-drugs

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Conflict of interest: None

[Case1] 68 years old female with DM was treated with IFX 6 years after the onset of RA. 6 months after start IFX cough, fever up appeared. Low level of oxygen saturation and GGO on film were observed. Oxygenation, ST Drug, antibiotics and steroid was administered. High level of β-D glucan and DNA PCR positive in sputum confirm the diagnosis. Symptoms and film findings were improved 3 days after treatment. [Case2] 51 years old male with 3 years history of RA was treated with IFX because of HDA. Dyspnea and gait disturbance was observed more after 14 days. Without the findings of film nor CT, we diagnosed PCP. Oxygenation, antibiotics, steroid, Benambax were started. After improving the symptoms, GGO was observed on the chest CT 2 days after treatment. β-DG was 142pg/ml. After 7 days GGO was disappeared on the chest x ray film. [Case3] 60 years old male with the history of schizophrenia and aspiration pneumonia. 8 months after onset of RA, ETN was started because of high disease activity. Symptoms of RA was improved in a month but slight fever up and low level of SPO2 were observed after 2 months. GGO was observed in right lung on film. We diagnosed PCP and started oxygenation and ST drug. β-DG was 81.5pg/ml. 5 days after treatment symptoms were improved.

P3-133

Assessment by use of IL-6 in anti-TNF drug treatment

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Conflict of interest: None

(Objective) In assessment of the effect in anti-TNF drug treatment, sometimes remission cannot be attained because of high VAS value. We studied if it was possible in such a case to determine whether or not a clinical remission was reached without VAS value by a method differing from the conventional standard. (Methods) In 38 RA patients (8 males, 30 females) under treatment with anti-TNF drugs, who presented 1 or less swollen and/or tender joints, CRP, MMP3 and IL-6 were measured. If these test values remained within normal range for 24 weeks, the patient was defined to have reached the state of clinical remission. (Results) A good correlationship existed between CRP and IL-6, MMP3 and IL-6, and with IL-6 as medium, between CRP and MMP3. When CRP and MMP3 that are listed on National Insurance tests were used as indices, remission was generally attained, with CRP $\leq$0.3 mg/dL and MMP3 $\leq$ 130 ng/mL in males, and CRP $\leq$0.2 mg/dL and MMP3 $\leq$ 50 ng/mL in females. (Discussion) In assessment of the anti-TNF drug effect, it was possible to evaluate remission only with CRP and MMP3 without using VAS value or IL-6 that is not included in National Insurance test list.

P3-134

Assessment of patients undergone with shortened Infliximab administration

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Conflict of interest: None

[Objectives] In 2012, time shortened administration of Infliximab was approved. [Methods] We surveyed 17 patients who were performed shortened Infliximab administrarion according to our protocol. [Results] Of the 17 patients who had undergone time shortened Infliximab administration since May 2012, two patients were unable to undergo time shortened administration due to infusion reaction. One patient did not wish time reduced administration. 14 patients were able to undergo time shortened administration. [Conclusion] The time shortened administration of Infliximab can be performed without serious adverse effects.

P3-135

A case of rheumatoid arthritis complicated with membranous nephropathy after use of etanercept: a cace report

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Conflict of interest: None

Etanercept (ETN) has been taken for the treatment of rheumatoid arthritis (RA) widely in Japan and shows high efficacy. But there are only 3 reports of membranous nephropathy caused by ETN. We had experienced that ETN-induced membranous nephropathy (MN) was developed and it was restored renal function by switching from ETN to certolizumab-Pegol (CZP) There is no report of changes to CPZ for the MN caused by ETN. In this case, ETN showed a certain effect against rheumatoid synovitis then TNF inhibition was effective pathway. We expected that CZP improve the adverse effects of ETN. [a case] 69-year-old woman. She diagnosed with RA 2 years ago. She had a poor prognostic factor (ACPA; 147 U/mL, RF; 33 IU/L), and we started the methotrexate with 4mg and stepped up to 8mg. 3 months later, we combinated ETN 25mg/week and increased ETN to 50mg/week as soon as possible, then desease activity has achieved to the low disease. 9 months after a further, because of getting worse of the urine protein, we underwent a renal biopsy in consultation with nephrologist. As the result, we have a diagnosis of MN and ETN was considered as a causing drug. For the reason, we stopped ETN and switched to CPZ, and then we have observed the recovery in urine protein and occult blood.

P3-136

Analysis of GLM efficacy under combination with high dose of MTX

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Conflict of interest: None

【Objective】Differences between clinical remission rates according to different doses of concomitant methotrexate in patients treated with golimumab were investigated.【Methods】Of the 57 patients who started to receive golimumab in our hospital, 38 who had been observed for 52 weeks from the start of golimumab administration were examined. The remission rates based on DAS28 (CRP) at the end of the 52nd week were analyzed with respect to the past history of treatment with or without biologics and different doses of concomitant methotrexate at the time of initiating golimumab administration.【Results】The remission rates based on DAS28 (CRP) at the end of the 52nd week in the bio-naïve and bio-switch patients were 50.0% and 21.1%, respectively. The mean dose of methotrexate at the time of starting golimumab treatment was 8.0 mg/

week, and the remission rate of the 16 patients (42.1%) administered 10 mg/week or more of methotrexate was 56.3% (9 in 16 patients). Higher methotrexate doses tended to show higher clinical remission rates ($p<0.05$) and gave more stable efficacy for a longer period.【Discussion】The remission rate by golimumab treatment appears to be improved by concomitantly using a sufficient dose of methotrexate.

P3-137

Efficacy of TNF inhibitor in our Department study,

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Conflict of interest: None

[Objectives] TNF inhibitors used in this study: IFX, ADA of report each investigated its effectiveness [Methods] How to TNF inhibitor drugs each evaluated regarding its effectiveness in disease activity index (CDAI, DAS28-ESR). Case IFX20 case ADA14 case in the investigation period were either 102 weeks. Divided into two groups of disease activity and age differences, compared the difference in effectiveness. Also, IFX also bulking effect decision made. [Results and conclusion: Increase approved earlier data with IFX (102 weeks until) many, bulking effect on the whole could not be verified. In data weighting when increased three times by bulking effect in check (DAS28-ESR 3.8-2.9) high disease activity until 10 weeks early in the big improvement confirmed. We found differences in the analysis of the use of age and MTX. Regardless of the patients, 102 weeks at the time of appeals to low disease activity in most cases. Using IFX increase, bringing it to low disease activity at an early stage in future issues. Was comparatively mild cases in the ADA. Where baseline average value DAS28-ESR 3.8 cutoff value, analysis, baseline > also reduce disease activity in 3.8. difference between two groups. We found differences in the analysis of the use of age and MTX.

P3-138

Efficacy of abatacept (ABT) against elevation of anti-dsDNA antibody in patients with rheumatoid arthritis under anti-TNF treatment: a report of two cases

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Conflict of interest: None

Case 1: A 45-year-old woman developed RA and infliximab (IFX) was started 7 years later, which resulted in remission; however, the disease relapsed after 6 years. Although she had no clinical features suggesting lupus, the titer of anti-DNA antibody (Farr assay) was over 100 IU/mL; that was not detected at her first visit. After she was switched to ABT, arthritis subsided along with decreasing anti-DNA antibody titer. ***Case 2:*** A 35-year-old woman had been suffered from SLE since she was 12 years old. She developed RA 4 years ago. IFX was started the next year, but she was switched to adalimumab (ADA) because of IFX failure and she was referred to our hospital. Gradually, skin rash appeared after ADA injection and she was switch to golimumab (GLM) after 9 months; however, erythema worsened along with increasing anti-DNA antibody titer to 97 IU/mL and exacerbating arthritis slightly. GLM was stopped and she was switched to ABT. Then her erythema and arthritis subsided along with decreasing anti-DNA antibody titer. ***Discussion:*** Abnormal activity of adaptive immune response such as increase of anti-DNA titer might be induced by TNF blockers and ABT may contribute to normalize conditions of the disease by suppressing adaptive immune system.

P3-139

Transition of disease activity and persistency in abatacept (ABT) therapy

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Conflict of interest: None

[Objectives] To describe early and long term efficacy of ABT for RA patients in daily clinical practice. [Methods] Change of disease activity and drug survival were examined in 33 RA patients treated by ABT. Changes of DAS28 (ESR), CDAI and SDAI were evaluated by LOCF method. Drug survival rate was calculated by Kaplan-Meier estimates. [Results] DAS28 (ESR)/CDAI/SDAI were 5.14/25.8/26.8 at baseline. After 1,2,4,8,12,24 months, DAS28 (ESR)/CDAI/SDAI were 4.31/15.3/16.0, 4.34/15.5/16.2, 4.20/14.6/15.3, 4.25/15.6/16.2, 4.13/15.1/15.8, 4.15/15.3/15.9, 4.17/15.1/4.17, good response/SDAI50/70/85 achievement rate were 12/33/3/0%, 3/42/6/0%, 9/45/12/0%, 9/40/15/6%, 15/42/21/6%, 15/36/18/12%, 12/36/18/9%, DAS28/CDAI/SDAI remission rate were 6/0/0%, 3/0/0%, 6/0/0%, 12/0/0%, 12/6/9%, 18/6/9%, 15/6/9%, cumulative persistency rate were 91%, 85%, 79%, 42%, 34%, 27%, 27% respectively. SDAI50 achievement rate continued increasing until 4 months, and slightly decreased afterwards. DAS28/CDAI/SDAI remission rate increased after 8 months. Most of discontinuation occurred within 12 months. [Conclusion] In ABT therapy, significant clinical effect was shown within 4 months, effect attenuation was seen after that. Remission as the target to treat was achieved after 8 months, and was maintained afterwards.

P3-140

Short-term results of Abatacept for Rheumatoid Arthritis

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Conflict of interest: None

[Objectives] Abatacept can be used now as the 1st biologics for Rheumatoid Arthritis. The treatment results of abatacept are compared with the etanercept. [Methods] The short-term results of 13 examples which prescribed etanercept for six months or more, and 11 examples which prescribed abatacept for six months or more were compared. [Results] The etanercept persistence rate by six months after a medication start was 83%, and abatacept was 81%. DAS28-CRP of the etanercept group before a medication start was an average of 4.6, and for three months after a medication start was an average of 3.3. DAS28-CRP of the abatacept group before a medication start was an average of 4.1 and for three months after a medication start was an average of 2.7. SDAI of the etanercept group before a medication start was an average of 26.7, and for three months after a medication start was an average of 16.1. SDAI of the abatacept group before a medication start was an average of 24.6 and for three months after a medication start was an average of 13.8. [Conclusion] Effect with etanercept and abatacept sufficient by after-start three months was acquired. The persistence rate by six months of etanercept and abatcept was also equivalent.

P3-141

The efficacy of Abatacept for the elderly patients in rheumatoid arthritis

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Conflict of interest: None

[Objectives] The purpose of this study was to investigate the efficacy and safety of abatacept (ABT) for the elderly Rheumatoid arthritis (RA) patients. [Methods] Twelve RA patients over 65 years old (4 males and 8 females; mean age, 73.4 years) who were treated with ABT for at least 24 weeks were included in this study. MTX (mean dose 6.4 mg/week) was used in combination by 10 patients. There were 11 Bio naïve patients and 1 switch patient. CRP, MMP-3, RF and DAS28-CRP were measured at baseline, 4, 12, and 24 weeks, and the efficacy and complications were investigated. [Results] Mean baseline values for CRP, MMP-3, RF and DAS28-CRP were 2.7, 243.7, 138.5 and 3.4, and at 24 weeks these values improved to 0.3, 136.3, 62.3 and 2.2, respectively. Although the treatment was stopped in one patient because of cellulitis, ABT was resumed after it healed, and the continuation rate was 100%. At 24 weeks, 6 of the 12 patients had achieved a remission based on the DAS28-CRP values. [Conclusion] The incidence rate of the infection in our study (8.3%) was slightly higher than Japanese post marketing surveillance (5.9%). However, the continuation rate at 24 weeks was 100% and a remission oc-

curred in half of the cases, ABT could be a safe and effective treatment choice for the elderly RA patients.

P3-142

Abatacept with mizoribine in treatment of patients with malignant rheumatoid arthritis

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Conflict of interest: None

We report malignant rheumatoid arthritis patients treated with mizoribine and abatacept. We retrospectively analyzed patients registered as suffering from MRA scan in our university hospital. Two patients were identified. Abatacept was applied to the first patients after failure of mizoribine. The second patients received ABT, because of inefficacious PSL and MZR treatment. ABT was tolerated by both the patients, and no clinically significant side effects occured. ABT may be a promising treament option for MRA patients.

P3-143

Case report of rheumatoid arthritis and interstitial pneumonia with improvement after administration of abatacept

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Conflict of interest: None

[Objectives] We report a case of rheumatoid arthritis (RA) and associated interstitial pneumonia (IP) that improved after the administration of abatacept (ABT). [Case] A 88-year-old woman developed RA 13 years ago. She was initially treated with infliximab and etanercept plus MTX 11 years ago, but discontinued both infriximab and etanercept because of the onset of IP. Three years ago adalimumab without MTX was administered, but this too was discontinued because of IP. Use of ABT without MTX reduced activity of RA and CT imaging at 40 and 238 days showed remarkable improvement of the RA lung. [Conclusion] ABT without MTX was effective for RA and also RA lung.

P3-144

Result of abatacept treatment for rheumatoid arthritis in our Hospital

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Conflict of interest: None

[Objectives] We examined the usefulness of abatacept (ABT) treatment on RA patients. [Methods] We have observed the 13 cases of RA patients who were treated by ABT for 12 months. One case was male, the other were female. Average age was 55.5 years, and the disease duration was 97 months. Patients who have already used some biological agents (Bio) were 11 cases. Mean SDAI (Simplified Disease Activity Index) score was 32.6 when starting ABT in 13 cases, 7 cases were high disease activity (26<SDAI), the other were moderate disease activity (11<SDAI≦26). [Results] There were 9 cases who have continued ABT treatment at 12 months after ABT administration. The all reason why ABT discontinuation was ineffectiveness in the 4 cases. Average SDAI score improved 17.4, 7.5 at 6 months and 12 months respectively. In SDAI improvement criteria, patients who have obtained a major response up to 12 months after ABT administration were 4 persons, furthermore they all have been low disease activity or complete remission. In the 4 cases, 3 cases were high disease activity, and 2 cases were patients with multi-Bio effect insufficiency and long-term morbidity before ABT administration. [Conclusion] ABT may be useful for RA patients with high disease activity and multi-Bio effect insufficiency.

P3-145

The correlation between the effectiveness of abatacept treatment within the first 3 months and the achievement rate of low disease activity at 12 months

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Conflict of interest: None

[Objectives] To investigate whether the effectiveness of one-year treatment with abatacept (ABT) can be predicted by DAS28-CRP values within the first 3 months. [Methods] Among 101 RA patients enrolled in FIT-RA multicenter registry and treated with ABT, 56 patients followed up for more than 12 months were evaluated and DAS28-CRP values were observed. ⊿Improvement (⊿0-1M, ⊿0-3M, and ⊿1-3M) were defined as the decrease of DAS28-CRP values between the 2 of 3 time points (0, 1, or 3M). We assessed the correlation between the proportion of low disease activity (LDA) at 6 or 12M and ⊿improvement. [Results] The proportion of LDA was 56% at 6M and 53% at 12M for ⊿0-1M>0.25 group (n=41), and 20 and 46% for ⊿0-1M<0.25 group (n=15), respectively. The rate was 55 and 65% at 6 and 12M for ⊿1-3M>0.25 (n=29) group, and 37 and 37% for ⊿1-3M<0.25 (n=27) group, respectively. For ⊿0-3M>0.25 (n=43) group, the rate was 53% at 6M and 55% at12M, and 23 and 38% for ⊿0-3M<0.25 group (n=13), respectively. The correlation was observed between ⊿0-1M>0.25 and LDA at 6M, and between ⊿1-3M>0.25 and LDA at 12M. [Conclusion] The effectiveness of ABT therapy at 6M and 12M can be predicted by ⊿Improvement within the first 3 months. The proportion of LDA at 12M was correlated with ⊿1-3M>0.25, but not with ⊿1-3M or ⊿1-3M.

P3-146

Efficacy of Abatacept in rheumatoid arthritis patients in our hospital-Assessment with and without MTX in combination-

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Conflict of interest: None

[Objectives] A tendency for the efficacy of Abatacept (ABT) to be little affected by Methotrexate (MTX) was suggested by PMS data. We conducted a study to determine whether similar results were obtained. [Methods] The subjects were the 51 RA patients who had been treated with ABT for 24 weeks among the RA patients in whom treatment with ABT was started in October 2010, and we used their DAS-28CRP values to evaluate changes in their disease activity according to whether MTX was used in combination. [Results] MTX was used in combination in 31 cases and not in 20 cases, and mean ages were 62.7 years/67.9 years, mean duration of illness 12.2 years/9.9 years, and mean 0 → 24 week DAS28-CRP values 4.01→ 3.07/3.94 → 3.10. Remission (DAS28-CRP < 2.3) rates at 24 weeks were 22.6%/30.0%. and the difference was not significant. Among the bio-naïve patients, 6 received MTX in combination and 4 did not, and the remission rates at 24 weeks were 16.7%/50.0%. [Conclusion] It was difficult to evaluate the bio-naïve patients because of their small number, but the 24-week remission rate tended to be higher without MTX. ABT tended to be little affected by MTX at our hospital as well, and it appeared capable of serving as biologic of first choice in patients difficult to treat with MTX.

P3-147

The effect on changing to abatacept from the other biologics in patients with rheumatoid arthritis (RA) complicated with systemic lupus erythematosus (SLE) (2nd report)

Shintaro Yano, Hiroshi Ideura, Masahiko Shinohara
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Conflict of interest: None

[Objectives] Abatacept is known as an agent inhibits the costimulation of T cells. This prompted us to examine the effect of abatacept on

RA patients complicated with SLE. [Methods] Abatacept (500mg/4w) was administered to 4 RA patients (male: 1, female: 3, age: 23-69years old) complicated with SLE who have had an inadequate response to the other biologics (infliximab: 1, etanercept: 1, adalimumab: 1, tocilizumab: 1) And we examined the change in clinical symptoms and values of immune-serological tests such as CH50, anti-DNA antibody, CRP, MMP-3, and so on. [Results] CH50 was normalized in 2 patients. Decline of serum anti-DNA antibodies was observed in 3 patients. As indicators of the activity of RA, normalization of serum CRP was observed in 1 patient. Improvement of MMP-3 was observed in 2 patients, No worse case was found for these 4 kinds of tests during the abatacept treatment. Improvement of joint symptoms was observed in 2 patients and no deteriorations was found in the other 2 patients. No side effects were observed in these patients undergoing abatacept treatment. [Conclusion] Abatacept seemed to be a useful agent for RA patients complicated with SLE.

P3-148

Is the number of the leukocytes, neutrophilsand lymphocytes changed by Abatacept treatment?

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Conflict of interest: None

[Objective] “Abatacept acts as a co-stimulation modulator, selectively, thereby inhibiting T cell activation”. However, it is difficult to measure T cell activation at clinics and hospitals. I hypotheses that Abatacept acts to normalize to the number of lymphocytes in patients with RA. [Methods] From companies all cases findings, these data is statistics, and processed several patients with RA, means wide age group and varying histories of treatment. Here, I select six women who are forties or fifties, and had not been treated with biological agents, and are confirmed RA change in an X-ray. I observed a change of the number of white blood-cell count, number of neutrophils and lymphocytes, CRP levels before and after the Abatacept treatment. [Results] The number of lymphocytes kept normal range by the Abatacept treatment. [Conclusion] About an effect of the Abatacept therapy, it is difficult prediction and for it to be determined by curative effect from a change of the number of the lymphocytes.

P3-149

A case of RA, controlled to drug free remission, managed with abatacept monotherapy and TKA operation

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Conflict of interest: None

[Objectives] Abatacept (ABT.) monotherapy and additional TKA was very effective for a RA patient, who was very sensitive for every drugs, resulted epigastralgia or skin rush, so cannot continue antiRA therapy. [Methods] The patient is 62 years old female. She got RA 4 years ago. She cannot continue drugs by the reverse effects. So she was introduced my clinic for further medication. She suffered from high disease activity state, RF56IU/ml), CRP (5.76mg/dl), ESR (84mm/hr), MMP-3 score (800ng/ml), at the first time of clinic. DAS28ESR score was 6.38. She was difficult for oral DMARDs, introduced the ABT.. [Results] At 16weeks after ABT., labo. datas were not changed but she got the negative RF score, 12IU/ml, under normal range. DAS28ESR score at 40weeks was 3.64, so she got good response. At the time of 56 weeks, pain was localized at left knee, so TKA was done. The operation finding was severely proliferated synovitis. But at 21 postoperative day, drastic relief of MMP-3 58.3ng/ml was found. After TKA, remission state has been continued, and ABT. therapy was over at May 2013 because of her decision. [Conclusion] A RA patient controlled to drug free remission with ABT. monotherapy and TKA operation. She is now managed every3 month observation at out clinic.

P3-150

Retention rates of biologics for rheumatoid arthritis 2003-2012: Analysis of abortion due to ineffectiveness

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Conflict of interest: None

[Objectives] To analyze the features of 6 biologics (Bio) for RA through their retention rates. **[Methods]** All RA cases treated with Bio at our department from 2003 to 2012 were restrospectively examined. Retention rates (where cessations not due to ineffectiveness (including secondary failure) were counted as continuing) were analyzed by Kaplan-Meier curves and log-rank test. **[Results]** 491 (IFX 152, ETN 201, TCZ 29, ADA 72, ABT 24, GLM 13) terms to 378 patients were performed. Mean age was 56 at first dose. Median retention was 50 weeks. At last dose, Bio was continued in 58%, aborted due to ineffectiveness in 17%. IFX and ETN were aborted earlier after TCZ and ADA were released. As the first Bio, ETN and IFX were continued longer than ADA. In cases with TNF inhibitor (TNFi) failure, retention of ABT was longer than that of ADA. ETN and ADA to high CRP (>20mg/L) cases and all TNFi to high ESR (>50mm/1hr) cases were aborted earlier than those to cases with lower value respectively. IFX and ETN were continued longer than ADA in cases with positive RF, positive ACPA or MTX use (and also TCZ than ADA in those without MTX). **[Conclusion]** Bio tended to be aborted due to ineffectiveness more easily with more alternative Bio. Bio may be selected according to patient characteristics.

P3-151

Which biologic agent should be selected as a second choice for patients with rheumatoid arthritis treated with a TNF inhibitor?: data from the Y-CURD study

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Conflict of interest: None

[Objectives] Although biologics (BIO) have greatly improved clinical outcomes of RA patients, the efficacy is not sufficient in some patients. Inappropriate selection of 2nd BIO results in further delay of remission induction. Here we compared the efficacy of 2nd BIO for RA patients who failed to respond to a TNF inhibitor (TNFi) as the 1st BIO. [Methods] We retrospectively examined clinical outcomes in 86 RA patients who have been treated with a TNFi followed by another TNFi (TT group, n=57) or TCZ (T6 group, n=29) in Y-CURD registry. [Results] There was no significant difference in baseline parameters between the groups. Although DAS28 was significantly decreased during 3 months after switching BIO in the both groups, the reduction was significantly larger in T6 than TT from 3 months (2.72 ± 1.14 vs 1.43 ± 1.55, $p = 0.0005$) to 12 months. Furthermore, SJC and PGA were significantly lower in T6 than TT at 12 months. [Conclusion] In RA patients who were not satisfied with 1st TNFi, TCZ was more effective than another TNFi as the 2nd BIO. In such cases, TCZ might be appropriate as not only 2nd BIO but 1st choice. It is emergent to determine clinical features of patients who re-

spond to TCZ better than TNFi.

P3-152

Retention rates of biologics for rheumatoid arthritis 2003-2012: Analysis of abortion rate due to adverse events

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Conflict of interest: None

[Objectives] To analyze retention rates of 6 biologics for rheumatoid arthritis (RA) through their abortion due to adverse events (AE). **[Methods]** Data were collected from medical records of all RA cases treated with biologics at our department from 2003 to 2012. Kaplan-Meier curves and log-rank test were used. **[Results]** 491 terms to 378 patients were extracted. At first dose, mean age was 56 years old, Median retention 50 weeks. Biologics were aborted due to AE in 106 terms (22%). AE-free retention of all 6 drugs was 40's or younger>50's≧60's≧70's or older (statistically significant). AE-free retention of each drug was as follows: tocilizumab≧ABT= golimumab≧etanercept≧infliximab≧adalimumab (without statistical significance). Principal adverse events were infection (44%), hypersensitivity to the biologics (14%), noninfectious lung diseases (NLD) (9%), autoimmune diseases (AID) (9%), malignant neoplasms (8%) (each category including cases with suspected diagnosis). NLD, AID, hypersensitivity, eruptions and cytopenia were reason for abortion only of TNF inhibitors. **[Conclusion]** Biologics for older cases were more subject to be aborted due to AE. Probability of abortion due to AE may be different among biologics. TNF inhibitors were aborted due to more various AE than the others.

P3-153

A study on the clinical effects of the change of biologics in non-TNF blocker group

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Conflict of interest: None

Although the changes of biologics from TNF-blocker to other TNF-blockers, or from TNF-blocker to non-TNF blocker are common, there are small numbers of reports on the effects of the change within non-TNF blockers. We aimed to study the effects of intra-non-TNF blocker change for RA patients who did not reach clinical remission evaluated by SDAI (less than 3.3) by one non-TNF blocker for at least 3 months. Subjects were 10 RA patients, with the mean age of 63 years, and the mean disease duration was 8.1 years. The median SDAI value at the drug change was 15.4. Abatacept (ABT) was changed to tocilizumab (TCZ) in 3 patients, and TCZ was changed to ABT in 7 patients. After the change of the non-TNF blockers, SDAI values significantly decreased, specifically in cases from ABT to TCZ, it decreased from 14.2 to 11.7, and in cases from TCZ to ABT, it decreased from 15.8 to 8.5, respectively. In conclusion, change of non-TNF blocker is thought to be useful in patients with inadequate response to one non-TNF blocker.

P3-154

Investigation of joint destruction inhibitory effects on Tocilizumab dose interval extension cases

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Conflict of interest: None

[Objectives] To investigate bone destruction inhibitory effects among patients with rheumatoid arthritis treated with TCZ and subjected to administration interval prolongation. [Methods] Twelve cases which had been treated with TCZ for more than one year and assessed by X-ray after TCZ dose interval extension for one year were retrospectively evaluated. [Results] The average of DAS-28 CRP scores were as follows. The score before treatment with TCZ was 4.4. That of the point of interval prolongation was 2.1. And that after dose interval extension for one year was 2.3. Rates of disease activity were as follows; high 20%, moderate 80% (before administration), low 20%, remission 80% (the point of interval extension start), and low 40%, remission 60% (one year after dose interval extension). Modified Total Sharp Scores of one year after dose interval extension were ⊿ erosion-0.39, ⊿ JSN-2.63, and ⊿ mTSS-1.69, respectively. Rate of structural remission achievement (⊿ mTSS <0.5) was 75%. [Conclusion] By TCZ dose interval extension, it was possible for some patients to maintain clinical remission and to achieve structural remission.

P3-155

Examination of the patients awareness with the dosage interval of the biologics by the subcutaneous injection

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Conflict of interest: None

[Objectives] This report describes patients awareness with the interval of the biologics by the subcutaneous injection. Interval of the subcutaneous injection may affect the choice of biologics for the patients. [Methods] In 30 patients with RA that was under treatment in our clinic, questionnaire survey was conducted. We investigated which of the interval was desirable for twice a week, once a week, every two weeks and every four weeks. [Results] If the patients visited a hospital for treatment, they chose the interval every four weeks (men: 90.9%, women: 73.6%). If they did self-administration, the men chose once a week and every two weeks (54.6%). If there was not pain by the injection, the men chose the dosage interval every two weeks. The patients without experience of the treatment with biologics chose the short dosage interval. If the worker visited a hospital for treatment, these chose the dosage interval every four weeks. But by the self-administration, half of patients chose every four weeks. The difference of the device, the use of the syringe, 69% of patients chose every four weeks administration. However, the pen-shaped use was 44.9%. [Conclusion] The interval of the subcutaneous injection was not affect the choice of the biologics from the standponts of patients.

P3-156

Potency comparison of MTX and Biopharmaceuticals (BIO) on Work Productivity and Activity Impairment (WPAI) in RA patients

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Conflict of interest: None

Objective: To assess the time-dependent effects of MTX and various BIO in RA patients on the clinical responses, WPAI and mental health. Methods: Patients treated with MTX (MTX group: n=21) and BIO (BIO group: n=42 (ADA n=12, ETN n=10, IFX n=5, GLM n=8, TCZ n=4, ABT n=3) were both divided into PW and HW, and their clinical, functional, EQ-5D and WPAI-RA scores were evaluated until 48 weeks after the treatment. Results: Mean DAS28-ESR of BIO group at week 0, 12, 24, 48 were 5.2, 3.6, 3.1, 2.8 (PW) and 5.6, 4.0, 3.6, 3.3 (HW) respectively, while those of MTX group were 5.4, 4.7, 4.4, 4.3 (PW) and 5.2, 4.2, 3.8, 4.0 (HW), respectively, and the clinical responses and other efficacy by MTX were not as good as those in BIO group. Improvement of WP-VAS in BIO group showed 16.9% (PW) and 28.0% (HW), while WP-VAS in MTX group were 6.4% (PW) and 5.0% (HW) at 12 weeks, and the earlier onset effects by BIO group were also observed in the other measurement items. Changes of WPAI-RA score of BIO group strongly correlated with improvements in HAQ and EQ-5D, indicating that PW were working under poor health condition with stress before the treatment. Conclusion: BIO promptly improved disease activity and function

in RA patient s, that further facilitate to improve their mental health of PW.

P3-157

Characteristics of clinical effectiveness of biologic agent for elderly rheumatoid arthritis patient

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Conflict of interest: None

[Objectives] As society becomes aged, rheumatoid arthritis (RA) patient is also increasing. It is not rare case to throw biologic agent (BIO) to those patients. We have investigated the characteristic of clinical effect for elderly RA patient. [Methods] 131 patients have been intervened BIO in our institute from July, 2005 to September 2013, in who 28 were male and 103 were female. Patients were divided into four groups according to age class. That is less than 55 years old (Y), 55 to 64 years old (O), 65 to 74 years old (VO), and no less than 75 years old (SO). Mean value of DAS28-CRP, MMP-3, mHAQ, at the beginning of BIO was thrown (BL), timed average value (AV), and the last time (EP) were measured for each group, and average values were compared for each group statistically. [Results] DAS28-CRP demonstrated no significant difference between groups. However, for MMP-3 SO demonstrated significant higher value than VO in AV and EP ($p<0.05$), and for mHAQ SO and VO demonstrated significant higher than O and Y in BL and AV, in EP SO demonstrated significant higher mHAQ than the other groups ($p<0.01$). [Conclusion] Super old patient tends to stay high mHAQ level even BIO is thrown. ADL of super old patient is tend to be in limited status. We need to consider this point if BIO is used.

P3-158

Study of serious adverse events of patients who used biological agents in our hospital

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Conflict of interest: None

[Objectives] We investigated about adverse events occurred in 80 patients among the 310 patients used IFX, ETN, TOC, and ABT, [Methods] We examined about adverse events occurred in patiens who used IFX (85cases), ETN (111), TOC (83), and ABT (31).We analyzed statistically between two groups with adverse events or no events, about. underlying disease, age, lymphocyte count, dose of steroid and MTX, when we started to used biologics. Based on the above results. we considered about 2 fatal cases caused by biologics. [Results] Rates of adverse events were ABT16%, IFX21%, ETN31%, TOC28%, and infection were the highest number, infusion reactions were second. These cases had underlying diseases, which consisted of respiratory disorder, diabetes, and amyloidosis. The higher age, and dose of steroid, the more adverse events were seen, and statistical significance was observed in some biologics. No statistically significant were obtained in lymphocyte count, but groups with adverse events were lower lymphocyte count. Statistically significant was not observed in the dose of MTX. 2patients who died by adverse events of biologics had underlying disorder and used high dose steroid. [Conclusion] We must consider about age, underlyning disorder, dose of steroid, lymphocyte count before use biolosics.

P3-159

A case of Felty's syndrome treated with rituximab and tacrolimus

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Conflict of interest: None

[Introduction] Felty's syndrome (FS) is associated with neutropenia and splenomegaly in rheumatoid arthritis. Treatment of neutropenia is mainly comprised of methotrexate (MTX) and granulocyte colony stimulating factor (G-CSF). Recently, there has been a growing interest in rituximab (RTX) in the treatment of FS. Tacrolimus (TAC) is also a promising reagent in the treatment for this disease, although its efficacy is uncertain. We report here the case of FS in whom treatment with RTX added to TAC led to a sustained neutrophil response. [Case report] The patient was a 66-year-old woman with severe neutropenis (368/μL) due to FS. She was initially treated with MTX 8mg/w, TAC 3mg/d and predonisolone (PSL) 40mg/d. However, the response to this combination therapy was not observed in 3 weeks, thus leading to require sequential administration of G-CSF. Treatment was then started with RTX at 0.5g once weekly for 4 weeks in the patient. MTX was discontinued. Treatment with RTX resulted in the improvement of neutrophil counts. Two months later, she remains clinically well taking TAC 3mg/d and PSL 5mg/d. [Conclusion] To our knowledge, no reports of FS treated with RTX and TAC have been published to date. This combination therapy might be a useful therapeutic option in the treatment of FS.

P3-160

Clinical improvement in hip joints of patients with rheumatoid arthritis after administration of biologic agents

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Conflict of interest: None

[Objectives] Recent clinical trials of biologic agents have reported that radiographic evidence of healing was seen in patients with rheumatoid arthritis (RA) who were in clinical remission. However, those results were limited to small joints (hand and foot), while the effects on large weight-bearing joints (hip and knee) have not been clarified. [Methods] We investigated the all patients who were treated with biologic agents retrospective. If they complained about hip and were taken X-ray, we check the X-ray. [Results] We found 3 cases of RA with observed clinical improvement at least 5 years or more as well as radiographic evidence of remodeling of a previously damaged hip joint. They have no pain of their hip at final follow up. [Conclusion] Some other investigater reported that all hip and knee joints examined with pre-existing damage rated as Larsen grade III/IV showed apparent progression, even in patients with a good response to biologic agents. We consider that a total hip arthroplasty may not be needed when osteophyte formation is found in who receive biologic agent administration.

P3-161

Total Knee Arthroplasty for rheumatoid arthritis patients using new Attune TKA system

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Conflict of interest: None

[Objectives] We will show that new Attune knee system, DePuy is good for rheumatoid patients as well as for osteoarthritis patients. [Methods] We performed total knee arthroplasty using PS type of Attune knee system for 22 patients, eleven OA patients and ten RA. We examined range of motion (ROM), JOA score, JKOM, Knee Score (KS) and Functional Score (FS) of the Knee Sociaty, and FTA before surgery and at three months after surgery. We compared these factors between OA and RA groups. [Results] Mean preperative VAS is 76 mm in OA group and 70 mm in RA group. JOA score is 54 in OA and 50 inOA, JKOM is 50 in OA and 62.3 in RA, KS is 46 in OA and 42 in RA, FS is 50 in OA and 36 in RA, and FTA is 182.5 degree in OA and 178 degree in RA before TKA, respectively. [Conclusion] Attune is the new knee system improved from PFC sigma, DePuy. Its design is expected to reduce the anxiety in stepping the stairs and the patellar clunk syndrome. We can use narrow size of femoral components and select insert thickness by one milimeter.

P3-162

Navigated total knee arthroplasty using the pre-cut technique of the posterior femoral condyles for rheumatoid arthritis

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Conflict of interest: None

The clinical results of 31 navigated total knee arthroplasties (TKAs) using the pre-cut technique of the posterior femoral condyles were investigated in 26 patients with rheumatoid arthritis (RA). There were 5 men and 21 women with a mean age of 68 years. In the coronal plane, 14 knees had preoperative varus deformity, 8 were neutral, and 9 had valgus deformity. The distal femur and proximal tibia were osteotomized perpendicular to the mechanical axis of the femur and tibia in the coronal plane, respectively. Next, the femoral posterior condyle was pre-cut one size larger than the measured size. After selective soft-tissue release, the gap distance was measured using the offset knee balancer/tensor at extension and 90° flexion. The size of the femoral component was decided on the basis of the gap difference and the final osteotomy was performed. The posterior-stabilized prostheses were used in all knees. The mean follow-up was 3.1 years. The mean JOA score improved from 50 preoperatively to 83 at the final review. The mechanical axis of the leg was within ±3° in 93% of the knees at the final follow-up. We obtained satisfactory results of TKA for RA by performing precise osteotomy using the navigation system and adequate gap balancing using the pre-cut technique.

P3-163

Short -term results of MIS-TKA by sub-vustus approach; from a viewpoint of the recovery of quadriceps

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Conflict of interest: None

[Objectives] We reviewed postoperative short-term results of MIS-TKA with sub-vustus approach from the viewpoint of invasion to vastus medialis. [Methods] We did pre-op. and post-operative CT examination for vustus medialis muscle cross-section area and compared a change of vustus medialis muscle volume. We investigated pre-op. and post-operative quadriceps strngth. [Results] 25 Knees of 18 OA patients were evaluated. The mean preoperative JOA score was 53 versus 90 at the latest follow-up. The mean preoperative ROM (extension/flexion) was -8 degrees/118 degrees versus 0 degrees/127 degrees at the latest follow-up. As for vustus medialis cross-section area, muscle volume ratio 122% increased after operation. As for quadriceps strength, ratio 126% increased after operation. [Conclusion] We consider that MIS-TKA with sub-vustus approach is beneficial and the recovery of quadriceps, especially vustus medialis isn't disturb by this approach.

P3-164

Time Course Analysis of Outcomes after TKA in Hemodialysis Patients

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Conflict of interest: None

[Objectives] We retrospectively evaluated the time course after total knee arthroplasty (TKA) to clarify its usefulness in hemodialysis (HD) patients. [Methods] We examined 8 HD patients (10 knees) who underwent TKA (5 cemented, 4 cementless, 1 hybrid) with Scorpio PS system. They were followed up for a minimum of 2 years. The average age at surgery was 70.3 years. The average duration of HD before surgery was 6.3 years. Cinical outcomes were evaluated preoperatively, at 1 year postoperatively and at the final follow-up of 4.4 years on average postoperatively by the JOA score and the Lysholm score. [Results] Four patients died during the follow up period. No revision was required. The average JOA and Lysholm scores were significantly improved from 48 and 48 preoperatively to 63 and 70 at 1 year postoperatively, respectively. Although these scores declined to 57 and 65 at the final follow-up, respectively, the significant improvement in the scores was maintained at the final follow-up. [Conclusion] TKA significantly improved knee functions at 1 year postoperatively. Although this improvement seems to gradually decline over time, improved knee functions continue over 2 years postoperatively. Despite HD-related problems, TKA can improve at least short-term postoperative outcomes.

P3-165

Multiple Joint Arthroplasties of the Lower Extremity in Rheumatoid Arthritis

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Conflict of interest: None

[Objectives] Functional reconstruction by THA or TKA is a means useful to ADL and QOL improve. However, operation adaptation and time are very important. Multiple joint arthroplasties of the leg performed to RA patients were investigated. [Methods] Between 1998 and 2013, total hip arthroplasties (THA) and total knee arthroplasties (TKA) were carried out in 203 patients with rheumatoid arthritis (RA). Multiple joint arthroplasties (three or more joints) were performed on 29 THAs and 35 TKAs in 18 patients with RA. [Results] All of patients had various complications before operation. General complications were found in 11 patients (17%), but they did not influence the patient's life span. There were a few local complications. [Conclusion] Surgical therapy plays an important part in management of RA once joint destruction has occurred, and therefore arthroplasty must be considered as soon as possible.

P3-166

Immunohistochemical analysis on TLR2 and NLRP3 signaling system in foreign body granuloma of periprosthetic osteolysis of hip joints

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Conflict of interest: None

[Objectives] Toll-like receptors (TLRs) and nucleotide-binding oligomerization domain (NOD)-like receptors (NLRs) as innate immune sensors could be associated with the pathogenesis of arthritic synovium. Especially, both of TLR2 and NLRP3 could work together and enhance the inflammation of arthritis. This study was objected to analyze expression of TLR2, NLRP3 and inflammatory cytokines in aseptic loose periprosthetic tissues of total hip arthroplasty. [Methods] Each ten cases of aseptic loose periprosthetic tissues and osteoarthritic synovium were analyzed by immunohistochemical staining of TLR2, NLRP3, TNF-α, IL-1β, CD68 and 5B5. [Results] Macrophages were dominantly in foreign body granulomas in aseptic loose periprosthetic tissues and they showed strong immunoreactivity of TLR2, NLRP3, TNF-α and IL-1β. Otherwise, those immunoreactivies were weak in fibroblast compared to macrophages. Macrophages and fibroblasts in lining and sublining layer of osteoarthritic synovium also showed moderate immunoreactivities of the molecules. [Conclusion] It was indicated that TLR2 and NLRP3 cascades could be associated with the pathogenesis of foreign body reactions resulting osteolysis by recognition of damage-associated molecular patterns.

P3-167

Long-term results of cementless total knee arthroplasty in patients with rheumatoid arthritis

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Conflict of interest: None

[Objectives] In order to evaluate the long-term results of cementless total knee arthroplasty (TKA) in patients with rheumatoid arthritis (RA), we investigated the outcome of patients who had undergone TKA more than a decade earlier. [Subjects and Methods] The subjects were 46knees in 36 patients (5 males and 31 females). Their mean age was 51.0 years at the time of surgery. Biological agents (bio) were used in 21 knees. The mean follow-up period was 16 years. A diverse range of prostheses were used, with hydroxyapatite (HA)-coated prostheses being employed for 25 knees. Parameters investigated included the clinical outcome, plain X-ray findings, and complications. [Results] Improvement of ROM and the JOA score was observed. The angle of the component was good overall. Common complications were loosening in 3 knees, ligament failure in 2 knees, and hydrarthrosis in 5 knees (bio were used in 3). Revision TKA was performed in 6 knees (3 knees only received an insert). [Conculusion] The long -term results have demonstrated favorable. The cause of hydrarthrosis was considered to be polyethylene wear debris. in younger patients with relatively high ADL or high disease activity. In order to obtain further improvement of the long-term results, early use of bio may be warranted in RA patients.

P3-168

Arthroplasty for better quality of life in remission stage of rheumatoid arthritis -report of 2 cases-

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Conflict of interest: None

[Objectives] Rheumatoid deformities often disturb their activities of daily living (ADL) and lower the quality of life (QOL). However, in case of younger age or lack of pain, rheumatoid patients and doctors tend to avoid surgery. We had 2 cases they chose arthroplasties for better QOL and were considerably satisfied with the outcome. [Methods and Results] The first case, a 47-year-old female with rheumatoid arthritis (RA) suffered from extension contracture of her left knee from 27 years old. She had no pain, however, the contracture disturbed her ADL such as stepping the stairs and sitting in narrow space. She chose total knee arthroplasty (TKA) and got range of motion. She has become able to put on socks and sit deeply now. The second case, a 47-year-old female diagnosed with juvenile idiopathic arthritis at 7 suffered from bilateral protrusio acetabuli and genu valgum. These deformities had made her unable to stride over a toilet or step the stairs. She had little pain and joint destruction only progressed slowly. However she decided to have bilateral total hip arthroplasties and TKA, subsequently. After operation, she has become able to do the actions. [Conclusion] If rheumatoid patients have significant deformities and they lower the QOL, arthroplasty can bring them better QOL.

P3-169

Successful arthroscopic synovectomy for refractory knee synovitis in a sarcoidosis patient

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Conflict of interest: None

[Objectives] Synovitis coexists with sarcoidosis occasionally, although many of them are cured with conservative tharapy. We report a relatively rare case of a sarcoidosis patient who suffered from refractory knee synovitis and needed arthroscopic synovectomy. We analyzed the case immunologically and histopathologically. [A Case Report] A forty-year-old woman with sarcoidosis complained of pain, swelling and limitation of flexion in her left knee. A repeated treatment of puncture, aspiration and steroid injection had almost no effect, therefore we selected surgical therapy. On admission, C-reactive protein was 0.88mg/dL and MMP-3 was 136ng/mL. CD4/8 ratio of T lymphocytes was 2.5. Rheumatoid factor and anti-CCP antibody were negative and bacteriological and tuberculosis examination showed no evidence of infection. MRI showed ring enhancement on T1-weighted image after the administration of Gd-DTPA. Arthroscopic synovectomy was performed and the symptom was relieved. CD4/8 ratio in each of joint fluid and synovium was 6.5 and 2.8. Histopathological examination showed non-caseating epithelioid cell granulomas. [Conclusion] Arthroscopic synovectomy can be an useful treatment for refractory synovitis in a sarcoidosis patient when steroid injection and medication are ineffective.

P3-170

A case report: ankle arthrodesis with preserved auto-bone grafting for loosening of total ankle arthroplasty in rheumatoid patient

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Conflict of interest: None

[Objectives] Ankle arthrodesis is mostly selected as the salvage surgery for loosening of total ankle arthrolasty (TAA) with massive bone defects and/or necrosis. We reported an ankle arthrodesis with preserved auto-bone grafting for loosening of TAA in rheumatoid patient. [Case-report] A 84 year-old man was affected by RA duration thirty-six years. He had gradually noticed the pain of his left ankle at five years after his left TAA because of loosening of it. However he had to operate the left total hip arthroplasty (THA) because of the joint destruction of that before the salvage surgery of his ankle. His resected femoral head at his left THA was preserved in our local bone banking. Arthrodesis of left ankle joint using a retrograde intramedullary nail with preserved auto-bone grafting of femoral head was performed at three months after his left THA. He was able to walk full weight bearing thirteen weeks after the salvage surgery. [Conclusion] The reconstructive procedure using the preserved auto-bone grafting was considered as one of the option to treat patients with disable rheumatoid multiple joint destructions including the ankle with massive bone defect.

P3-171

A case diagnosed as rheumatoid arthritis after the high tibial osteotomy

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Conflict of interest: None

[Aim] We report a case which was diagnosed **as** RA after the high tibial osteotomy (HTO). [Case] A 60 year-old woman suffered from pain of the both knees, since removing much snow before half a year. She received a diagnosis of OA at a nearby hospital and was done the injection of hyaluronic acid or taken NSAIDs. But the pain had not improved. At the first visit to our hospital, the both knees showed varus deformity. The range of joint motion of the both knees was -5°/120°, X-rays indicated grade 2 OA in K-L classification. JOA score was 65 points. At first, closed wedge HTO was performed in the right knee. Synovitis was detected in arthroscopic findings and biopsy was done. The pathology showed the proliferation of synovium and blood vessels, which was consistent with RA. At three weeks after the operation, both the wrists had pain and morning stiffness appeared, and then the rehabilitation was delayed. MTX was begun and her condition had improved gradually. Thereafter, closed wedge HTO was also performed in the left knee. Her symptoms have improved and can walk at the present time. [Consideration] In elderly onset type RA, there are cases of sudden onset or negative RF. Although her RA control has been stable now, prudent postoperative progress observation is required.

P3-172

Posterior dislocation after total knee arthroplasty in rheumatoid arthritis: reort of 2 cases

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Conflict of interest: None

【Introduction】Posterior dislocation (PD) after total knee arthroplasty (TKA) is a rare complication. We report of two cases of PD of the tibia after primary semi-constrained TKA in a patients with rheumatoid arthritis (RA).【Case 1】A 51-year-old female. She had a diagnosis of malignant RA at the age of 21 years old. A resection arthroplasty was performed due to post TKA infection on her right knee at 39 years old. Semi-constrained TKA was performed for severe left knee pain. Pre-operative range of motion (ROM) was -45/145. 6 days after TKA, we found PD. We applied a knee brace and restricted knee flexion. A recurrence of PD was not observed. At the time of the last follow up, ROM of her left knee was 0/100.【Case 2】A 29-year-old female. She had a diagnosis of RA at the age of 16 years old. Pre-operative ROM was -50/120 on the left, -30/120 on the right knee. Left TKA was performed at 28 years old. 6 days after TKA, her knee was dislocated. It was needed to apply a brace and restrict knee flexion. Right TKA was performed at 29 years old. 5 days after TKA, we found posterior dislocation of the tibia. We applied a knee brace and restricted knee flexion. A recurrence of dislocation was not observed. At the time of the last follow up, ROM of her both knee was 0/100.

P3-173

Relationship between D-dimer and the activity of rheumatoid arthritis before total knee arthroplasty

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Conflict of interest: None

<Objective> Various index are used as the disease activity of rheumatoid arthritis (RA). It has been reported that D-dimer is used as an deep verous thrombosis (DVT), but the value is still higher RA. Therefore, we are investeigated the relationship between D-dimer and the disease activity of RA. <Methids> The subjects were 32 knees 32cases that were diagnosed with RA in our hospital. 8cases of male, 24 cases of female, 69.0 years average age (43-83 years), all patients preoperative DVT was not recognized. Joint deformity were stage 3 or 4. No treatment groups of RA were 11 cases, and treatment groups of RA were 21 cases. We investigted each of D-dimer, CRP, and medications. <Resuts> The average value of D-dimer RA untreated group was 6.23ug/dl, CRP was 3.59mg/dl. treatment of RA group was 2.93ug/ml, 1.30mg/dl. Number of untreated RA group was significantly higher than treatment group. <Conclusion> Reported that D-dimer value increases with RA, but if there is no DVT, reports mentioned differences according to treatment history is a little. I considered D-dimer is involved in fibrinolytic system, but there are reports that the number is rising in synovitis of RA.

P3-174

Avascular necrosis of the femaral head in patients with systemic lupus erythematosus

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Conflict of interest: None

【Objectives】Avascular necrosis of the femoral head (AVN-FH) is one of most serious complications in the treatment of systemic lupus erythematosus (SLE). The aim of this study is to clarify clinical features of AVN-FH in patients with SLE.【Methods】Among 378 lupus patients enrolled in this study, AVN-FH was diagnosed in 24 patients. We retrospectively analyzed clinical features and past medical histories of these patients.【Results】2 male and 22 female patients were included. Average age of SLE onset was 27.9 years. Anti-dsDNA antibody, anti-SS-A antibody, and anti-cardiolipin antibody was positive in 18, 15, and 8 patients, respectively. 11 patients had renal lesions and 6 patients had nervous system complications. Average dose of initial prednisolone (PSL) was 49.4 mg/day, and steroid pulse therapy before AVN-FH onset was conducted in 12 patients. 17 patients had concomitant immunosuppressive drugs at AVN-FH onset. Average age of AVN-FH onset was 34.5 years. Average dose of PSL at AVN-FH onset was 9.6 mg/day. 17 patients had bilateral AVN-FH, and operative therapy was performed in 18 patients after average duration of 15.6 months.【Conclusion】The prevalence of AVN-FH in lupus patients was 6.3%. We report clinical features and risk factors of AVN-FH with some references.

P3-175

Two cases of severe Juvenile-onset SLE treated with multidrug therapy

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Conflict of interest: None

Refractory SLE, which used to be a mortal disease, is now steeped in adverse effects of immunosuppressive drugs including steroids. We presented two cases of Juvenile-onset SLE treated with multi-immunosuppressive agents, which enabled to terminate steroid therapy within 1 year. Case 1 is a 15-year-old girl, who developed neuropsychiatric SLE 3 month after diagnosis of SLE. Intravenous mPSL pulse therapy with plasma apheresis followed by short-term IVCY rapidly introduced her into remission clinically and radiologically. MMF, initiated at two month after the onset of neuropsychiatric SLE when IVCY therapy was terminated, has been successfully treated with keeping remission for 3 years, resulting in withdrawal of steroids within the first year of disease. Case 2 is a 11-year-old girl, who was diagnosed as severe lupus nephritis microscopically defined as class IV-G. mPSL pulse therapy followed by short-term IVCY and the subsequent MMF introduced her into remission, Oral steroid was discontinued within a year with keeping remission. These cases remind us of the importance of remission-induction therapy, not only in disease control but reduction of adverse effects mainly due to steroid treatment. The planned multidrug therapy might be beneficial even in the refractory cases.

P3-176

A case of SLE associated with anti-phospholipid syndrome with the initial symptom of pachymeningitis and superior sagittal sinus thrombosis

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Conflict of interest: None

A 33 years-old woman visited the outpatient clinic of the general medicine because of headache, general malaise and fever since Oct. 2012. She was diagnosed as iron deficiency anemia and was administrated with iron, but no improvement. On Dec. 2012, she was admitted to the department of hematology because of fever, progressive anemia (Hb 4.3 g/dl, MCV 105). Bone marrow survey revealed normal and anemia was attributed to hemolysis. The ACR criteria of SLE was satisfied because of the following symptoms and signs; oral ulcer, photosensitivity, arthritis, leucopenia, hemolytic anemia, positive lupus anticoagulant (LAC), and false positive of serological test for syphilis. Brain MRI showed pachymeningitis and superior sagittal sinus thrombosis. Thrombosis and positive LAC led to the diagnosis of anti-phospholipid syndrome (APS). Therapy was started with the combination of PSL (1 mg/day), azathioprine and anticoagulant, which was effective, but on Oct. 2013 CNS symptoms developed and azathioprine was replaced with IVCY. After the modification of therapy, her clinical course is good. This is the first case of these combinations in SLE as far as we searched for.

P3-177

A case of Lupus colitis and cystitis refractory to audinal treatment revealed the efficacy of IVCY

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Conflict of interest: None

[Case] 44-year-old woman [Past history] none The patient came our hospital with high fever (39 ℃), butterfly erythema on her face, vomiting and frequent diarrhea. Contrast enhanced abdominal CT revealed severe edematous wall thickening of gastrointestinal tract and bilateral hydronephrosis. She was diagnosed as SLE with following findings; high titers of antinuclear antibodies (×2560: speckled), positive anti-DNA antibody, hypocomplementemia and proteinuria. It was also suggested that CT findings as mentioned above were associated with lupus colitis and cystitis. As moderate-dose steroid therapy (PSL 40 mg/day) showed little effect, mPSL- pulse therapy was undergone. However, the efficacy of steroid treatment was poor, IVCY (750 mg/m2) was administered. After treatment of IVCY, the patient had good course with less frequent urination, increased voided volume per urination and less bowel-wall thickening on ultrasonography. We experienced a case of steroid-resistant lupus colitis and cystitis. We report and discuss about alternative therapies against refractory lupus colitis and cystitis.

P3-178

A case of overlap syndrome of systemic lupus erythematosus (SLE) and systemic sclerosis (SSc) with lupus myocarditis associated with severe heart failure

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Conflict of interest: None

The patient was a 38-year-old female. In 2004, she was suspected to be mixed connective tissue disease for Raynaud's phenomenon, positive for anti-RNP antibody, and thrombocytopenia. She was followed-up without any treatments because she denied them. In July 2013, she was pointed out retinal vasculitis. Around the same time, she presented a malaise that progressed rapidly and carried to a nearby general hospital in an ambulance. Severe acute heart failure, multiple cerebral infarctions, exudative pleural effusion, and massive proteinuria were revealed. Catecholamine and intraaortic balloon pumping were needed. She was transferred to our hospital, and diagnosed with SLE and SSc. The echocardiogram showed diffuse ventricular wall thickening, severe diffuse hypokinesis, and decreased left ventricular ejection fraction (EF), which was 20%. The cardiac enzymes were elevated, so lupus myocarditis was suspected. Oral PSL (40mg/day) was started, and tacrolimus and mizoribine were added. The result of the myocardial biopsy indicated lupus myocarditis. Although the findings of the echocardiogram were normalized and the EF was improved to 70%, the proteinuria and cardiac enzymes were not improved. Intravenous cyclophosphamide was started.

P3-179

A case of systemic lupus erythematosus (SLE) complicated with thrombotic microangiopathy (TMA)

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Conflict of interest: None

A 37-year-old female was diagnosed as SLE in 1996. She developed transverse myelitis in 2002 and treated with prednisolone (PSL) in another hospital. Anesthekinesia distal to Th6 level remains. She was referred to our hospital in June 2009. She was treated with 10 to 15 mg PSL daily. She was suffered with skin ulcers on her left sole and buttock. The skin ulcers were worsened by bacterial infection and admitted to the department of dermatology. Antibiotics administration was successful to treat the skin ulcers, but fever and pancytopenia were observed. Bilateral infiltrates in the lung, schistocytosis, and multiple organ damage were observed and transferred to our department. PSL was increased to 30 mg daily and then 1 g/day methyl-PSL (mPSL) pulse therapy was introduced with poor response. Plasma exchange (PE) was introduced and then, second mPSL pulse therapy and intravenous cyclophosphamide (IVCY) therapy were administrated. Her condition was gradually improved. PSL was tapered and azathioprine was used for maintenance therapy. TMA and ALP are rare but frequently lethal complication of SLE. Early intensive treatment including PE is supposed to be possible to improve outcome of patients with such complications. We will present this case with exploration of literature.

P3-181

Effectiveness of prednisolone (PSL) and tacrolimus (Tac) combination therapy in Autoimmune-associated hemophagocytic syndrome (AAHS) with systemic lupus erythematosus (SLE)

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Conflict of interest: None

Case1: A 64-year-old woman was diagnosed with AAHS after a duration of SLE of 17 years. Her laboratory data showed a platelet count of 58000/μl, a ferritin level of 1620ng/ml. She was administered Tac with PSL (70mg/day), after which the laboratory data showed a platelet count of 139000/μl. Case2: A 65-year-old woman was diagnosed with AAHS after a duration of SLE of 7 years. Her laboratory data showed a platelet count of 52000/μl, a ferritin level of 11ng/ml. She was administered Tac with PSL (7mg/day), after which the laboratory data showed a platelet count of 81000/μl. Case3: A 75-year-old man was diagnosed with AAHS and SLE simultaneously. His laboratory data showed a platelet count of 30000/μl, a ferritin level of 2183ng/ml. He was administered Tac with PSL (60mg/day), steroid pulse and intravenous immunoglobulin, after which the laboratory data showed a platelet count of 139000/μl. Case4: A 55-year-old man was diagnosed with AAHS after a duration of SLE of 6 months. His laboratory data showed a platelet count of 52000/μl, a ferritin level of 1171.5ng/ml. He was administered Tac with PSL (60mg/day) and steroid pulse, after which the laboratory data showed a platelet count of 107000/μl. Combination therapy with PSL and Tac is an effective treatment for AAHS with SLE.

P3-182

Neuropsychiatric systemic lupus erythematosus (NP-SLE) with various infection during intensive immunosuppressive therapy

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Conflict of interest: None

[Objectives] We experienced neuropsychiatric systemic lupus erythematosus (NP-SLE) with various infection during intensive immunosuppressive therapy. [Methods] A 55-year-old man was admitted because of fatigue and altered mental status. He was diagnosed NP-SLE serologically and high-dose glucocorticoids, plasma exchange, IV-CY, high-dose IVIg were administered., but his symptoms were persistent. After two weeks, elevated serum C-reactive protein and bilateral pulmonary infiltlation with cavity was detected and proved to be Nocardia pneumonia by bronchoscopy. He started ST and AMK. After initiation of rituximab, NP-SLE was resulted in marked clinical improvement. On the eight weeks,

nonbloody, waterly diarrhea occurred, cytomegalovirus enteritis was detected by serological antigenemia and GCV was started. Followed chest Xp and CT showed aggravation of pulmonary cavity lesion and pleural effusion. Repeated bronchoscopy revealed invasive pulmonary aspergillosis and VCZ was administered. [Results] SLE itself has the possibility of cellular immune deficiency. Lacking of organ specific symptoms, it's often very difficult to distinguish complicated infectious disease from exacerbation of disease activity. We should evaluate patient's immunological state and possible pathogens properly.

P3-183

A case of SLE and APS required laparoscopic biopsy to diagnose an intra-abdominal mass lesion

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Conflict of interest: None

The patient was 44-year-old woman with systemic lupus erythematosus (SLE) and antiphospholipid syndrome (APS). During the admission for evaluation of pulmonary hypertension (PH), she complained acute left abdominal pain. CT scan showed a mass lesion located dorsal to the descending colon, multiple irregular lesions in the omentum and lymphadenopathy, without characteristic images of lupus enteritis. Fecal occult blood was positive related to menstrual cycle, so we suspected the possibility of heterotopic endometriosis, but colonoscopy revealed no abnormality even on her menstrual phase. In the course, abdominal pain and low grade fever were continued, and laboratory tests showed normal levels of tumor markers, thrombocytopenia, low complement and elevated inflammatory responses. Microbial tests were all negative and administration of antibiotics showed no effect. We decided to perform laparoscopic biopsy and then ovarian and peritoneal cancers were finally identified. When the patient presents with new symptoms in the course of SLE, the differential diagnosis is sometimes difficult because SLE develops a variety of symptoms systemically. The surgical intervention should be required promptly if needed.

P3-184

A laparoscopic finding of intestinal bleeding in a patient with SLE associated APS during immunosuppressive and anti-coagulation therapy

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Conflict of interest: None

A 45-year-old woman was admitted due to visual impairment and leg weakness with numbness. She had been diagnosed with discoid lupus erythematosus 11 years ago. Examination revealed the transverse myelopathy at the level of T10 and severe retinitis of both eyes. Serological examination showed hypo-complementemia, anti-DNA antibody, Anticardiolipin-β2GPI antibody and lupus anticoagulant were positive. Steroid-pulse, followed by 50mg of predonisolone (PSL), and Cyclophosphamide-pulse therapy were done for neuropsychiatric-SLE and APS. She had been getting better until PSL was tapered to 25mg on 70 days. Recurrent melena occurred, but the origin had not been clarified by the esophago-gastro-duodenoscopy, colonoscopy, and 99mTc scintigraphy. Contrast enhanced CT showed thickened wall of the small intestine. During double-balloon scopy rupture of the sigmoid colon occurred. urgent laparoscopic sugery was performed. Diffuse petechia was observed on the serosal surface of small intestine and mesentery. Both laparoscopic and CT findings suggested capillary to small vessel injury of whole layers. This report is the first laparoscopic finding of intestinal bleeding in a patient with SLE associated APS.

P3-185

Low dose multiple immunosuppressants therapy (MIST) for lupus nephritis

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Conflict of interest: None

[Objectives/Background] In most guidelines for proliferative lupus nephritis (LN), steroid and a single immunosuppressant (IS) are used at a time. Recently, simultaneous use of multiple ISs (especially combination of a nucleic acid synthesis inhibitor and a calcineurin inhibitor) is reported to lead favorable outcome. [Methods] We explored the medical record of our hospital seeking LN patients who took multiple ISs at a time. [Results] Two cases were identified. It is noteworthy that both responded with lower dose MIST. <Case 1> A 43-year old female who had been diagnosed with lupus, because of LN (WHO IV), pleuritis, lymphopenia, dsDNA Ab, was treated with 1500mg of Mycophenolate mofetil (MMF), leading to disappearance of proteinuria. Due to leukopenia, the dose was reduced to 375mg, resulting in recurrence of proteinuria. By Adding of 3mg of tacrolimus, complete remission (CR) was achieved. <Case 2> A 26-year old male with LN (WHO IV) had been treated with 1.5g of MMF subsequently after IVCY exhibited leukopenia. Decrement of MMF to 375mg caused flare of LN. Addition of 3mg of tacrolimus induced CR. [Conclusion] Low dose MIST is a useful option for LN patients who do not respond satisfactorily or who cannot tolerate conventional therapy. It is worth evaluating in further studies.

P3-186

Pathogenesis of systemic lupus erythematosus (SLE) taught by TCR-pMHC bias: Contribution of Self-Organized Criticality Theory

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Conflict of interest: None

[Objectives] Based on recent progress in structural TCR: pMHC study, we study the cause of SLE [Methods] Literatures on TCR: pMHC bias were examined. [Results] TCRα CDR1/2 bind one αhelix of HLA peptide binding groove, TCRβ CDR1/2 bind the other αhelix, where CDR3 binds peptides obliquely. Unrelated peptides can be antigen-presented by the same HLA to the same TCR, and the same peptide can be antigen-presented on non-self HLA and stimulate the same TCR. In such unusual responses, either TCR-HLA angle may change, angle of TCRVα or Vβ may open, or TCR 3D structure may change. Such wobbles in TCR: pMHC guarantee varieties of TCR reactivity thru negative selection. Thymic positive selection, instead, restricts wobbles to inhibit autoreactivity. According to structural study, for autoimmunity to take place, either low affinity antigen may pass thru thymic selection, antigen may not rightly be presented on HLA, or novel antigen may emerge thru cellular process unique out of thymus. Autoimmunity then results in when T cells are activated at periphery in a different fashion either quantitatively (ex. Insulin or MBP) or qualitatively (ex. anti-CCP). [Conclusion] Thus, instead of antigen, novel TCR generated *via* V (D) J recombination may also induce autoimmunity in Self-organized Criticality Theory.

P3-187

Three cases of lupus nephritis that developed in the clinical course of mixed connective tissue disease

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Conflict of interest: None

Case 1: A 70-year-old man with Raynaud's phenomenon (RP) and polyarthritis was diagnosed with mixed connective tissue disease

(MCTD), and treated with prednisolone (PSL). 10 years later, proteinuria (UP) with elevated serum anti-Sm (aSm) and anti-double strand DNA (adsDNA) antibodies (Ab), and hypocomplementemia (hypoC) developed, and renal biopsy revealed class IV-G (A) lupus nephritis (LN) followed by successful treatment (Tx) with PSL + cyclosporine A (CyA). Case 2: A 34-year-old woman with RP, polyarthritis and polymyalgia was diagnosed with MCTD. 5 years later, malar rash and hemophagocytic syndrome with high adsDNA Ab and hypoC developed, and treated with PSL + CyA. 7 years thereafter, UP developed. Renal biopsy showed class IV-G (A/C)+V LN followed by successful Tx with pulse methyl-PSL + tacrolimus (Tac). Case 3: A 39-year-old woman with RP and polyarthritis was diagnosed with MCTD. 6 years later, polyarthritis worsened and PSL was started. The next year, pleuritis with high aSm and adsDNA Ab, hypoC and UP developed, and renal biopsy revealed class IV-S (A) LN followed by successful Tx with pulse methyl-PSL + Tac. Discussion: Renal lesions are rarely seen in MCTD, and the development of lupus nephritis must be suspected if hematuria and/or proteinuria newly develops in MCTD.

P3-188

Benefits of immunosuppressive therapy for lupus nephritis in the tapering of steroids and renal prognosis

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Conflict of interest: None

【Objective】We examined how the concomitant use of immunosuppressant influences the outcome of LN.【Methods】We carried out a 36 months retrospective study comparing the LN patients with the GC and immunosuppressants (IVCY or MMF group or other group) and GC monotherapy groups. All patients perfomed renal biopsy in our hospital between 2000 and 2010 and we examined the amount of GC, the rate of flare and remission of LN.【Results】53 patients (female=43, male=10) were analyzed. The number for each class of the ISN/RPS classification was as follows; class I･VI (n-1), class II (n-5), class III (n-6), class IV (n-33), class･V (n-7). As induction therapy, 43 patients were treated with immunosuppressant (26 patients were IVCY or MMF group), 10 patients were with GC monotherapy. At 6 month the rate of remission was significantly higher in IVCY or MMF group (p=0.01). At 12 month GC was significantly reduced in immunosuppressant group compared to GC monotherapy (8 mg vs 11 mg). At 36 month the flare was observed in 15 patients and 14 of them occurred between 12 and 24 month. All 15 patients was immunosuppressants group.【conclusion】Current immunosuppressive therapy provide early induction for remission and GC tapering, while maintenance therapy needs to be improved from 24 month onwards.

P3-189

Association between blood mizoribine/tacrolimus levels and clinical outcomes in patients with lupus nephritis

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Conflict of interest: None

[Objectives/Methods] At our hospital, multitarget therapy involving a combination of corticosteroids and 2 immunosuppressants (mizoribine and tacrolimus) with different action mechanisms is used to induce remission of lupus nephritis (LN). To develop a better protocol, we retrospectively evaluated the association between blood mizoribine/tacrolimus levels and clinical efficacy/toxicity in 18 LN (mean age, 44.4 years; 17 women; 16 new cases; urinary protein, 4.3 ± 2.6 g/day). The peak mizoribine (C3) and trough tacrolimus levels were measured. [Results] Complete remission was achieved in 72% and 100% cases at 6 and 12 months, respectively. Mean blood mizoribine and tacrolimus levels were 2.13 μg/mL and 5.02 ng/mL, respectively. Complete remission and adverse events did not correlate with blood drug levels, but alleviation of proteinuria and increase in serum C3 levels at 6 months were correlated. Blood mizoribine and tacrolimus levels were associated with lower prednisolone dosage at 12 months; thus maintaining target drug levels (mizoribine, ≥2 μg/mL; tacrolimus, ≥5 ng/mL) seems essential. [Conclusion] Although our treatment protocol is safe in terms of blood drug levels and effective, target drug levels must be considered for reliable corticosteroid reduction at 12 months.

P3-190

Examination of prognosis in biopsy-proven Lupus Nephritis

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Conflict of interest: None

Background: International Society of Nephrology-Renal Pathology Society (ISN/RPS) 2003 classification of lupus nephritis (LN) provides beneficial pathologic information relevant to the renal outcome. We conducted retrospective observational study to investigate the baseline characteristics and the response to treatment between WHO and ISN/RPS classification. Methods: 39 Japanese patients with LN who underwent renal biopsy between 1998 and 2012. Renal biopsy samples were re-classification by WHO and ISN/RPS 2003 criteria. Result: Among WHO type IV, higher number of patients with remaining ISN/RPS class III LN achieved complete response to treatment than those with reclassified class IV LN at 6 month follow-up. 20 patients with previous WHO class IVc LN were reclassified into ISN/RPS class III, III+IV, IV-S, IV-S+V, IV-G and IV-G+V. There were no patients who developed end-stage renal failure requiring dialysis or transplantation. Conclusion: Our results suggest that biopsy-proven LN has an excellent prognosis due to enhance the treatment according to the result of renal biopsy and not do renal biopsy of the patients with poor medical condition. ISN/RPS classification is more useful in predicting renal outcome and guiding treatment when evaluating previously classified by WHO classification.

P3-191

Implication of IL-22 in the renal pathogenesis of lupus nephritis

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Conflict of interest: None

[Objectives] Previous studies have shown relationships between IL-22 and the pathogenesis of autoimmune diseases such as Rheumatoid arthritis. The present study intended to investigate a role of IL-22 in lupus nephritis. [Methods] 25 patients with lupus nephritis were entered in this study. We examined relationships between serum IL-22 level and, renal injuries (Cr, eGFR, urinary protein excretion (UP), NAG and urinaryβ2MG), serological findings (C3, C4, CH50 and ds-DNA) and renal pathological findings (presence of cellar and/or fibro-celluar crescent, or not, intense of tubulointerstitial injury and classification of lupus nephritis). [Results] There were no relations between serum IL-22 level and other parameters. While, serum IL-22 level in moderate to severe reduced renal function group (eGFR<60ml/min) was significantly lower than in eGFR≧60ml/min group (p<0.05). In renal pathology, there were significant differences between of serum IL-22 level between crescents group and non-crescent group (p<0.05), and class IV group and non-class IV group (p<0.05). [Conclusion] IL-22 might implicate the pathogenesis of lupus nephritis, leading to reduce glomerular injury.

P3-192

Efficacy of tacrolimus for maintenance therapy in patients with active lupus nephritis

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Conflict of interest: None

[Objectives] To evaluate efficacy of tacrolimus (Tac) for maintenance therapy with active lupus nephritis (LN). [Methods] We subjected the cases at our hospital as we diagnosed LN, and used Tac for the maintenance treatment. We analyzed the clinical information retrospectively such as WHO pathological tissue classification, treatment, and outcome. [Results] Tac was administered for 34 cases of maintenance therapy phase of lupus patients. Renal biopsy was performed at 18 cases, these were type II (3 cases), type III (1 case), type IV (10 cases), type V (2 cases), and type IV+V (2 cases). Traf level of Tac was 4.9 ng/ml (mean). Remission rate was 85.3% and above all of first nephritis cases were complete remission state. We did not recognize even 1 case for the shifted example of chronic kidney failure and artificial dialysis. [Conclusion] We consider that Tac is effective for maintenance therapy with active LN, especially for initialy onset nephritis.

P3-193

The promising ability of MMF against refractory proteinuria of Lupus Nephritis

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Conflict of interest: None

[Objectives] To assess the efficacy and safety of MMF against refractory proteiuria of lupus nephritis with other immunosupressant failure [Methods] We followed up patients, with refractory proteinuria of lupus nephritis and, who were treated with MMF. During the 6 months' observation period, we checked on urine protein, serum creatinine and albumin, immunological activity, steroid dosing, and complication. [Results] This study included 11patient. 10 were female, 1was male. 3 cases were type IV lupus nephritis, another 3 were V, one was IV+V, and the others were not biopsied. Steroid was reduced during the observational period, serum albumin and urine protein were improved. There was no flare of SLE activity. No severe infection, nor worsening of complication e,g, hypertension nor hyperlipidemia were observed. [Conclusion] MMF would be a promising treatment for lupus nephritis with refractory proteinuria, even for type V nephritis, for which treatment recommendation is not yet established.

P3-194

A case of systemic lupus erythematosus showing a massive finger print in the glomeruli: an electron microscopic observation of a repeated-renal biopsy

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Conflict of interest: None

[Objectives] We present a case of systemic lupus erythematosus showing a massive finger print in the glomeruli by repeated kidney biopsy. [Methods] He was admitted to our hospital with bilateral arthritis and fever in 1993. diagonsed as systemic erythematosus because of positive anti-ds DNA antibody, hypocomplenemia, and prteinuria. Kidney biopsy revealed class V. PSL was prescribed and compete remission was achived. In 2002, proteinuria was recurred and second biopsy was perfoermd. [Results] Electron microscopy (EM) showed a finger print in subepithelial area. Cyclosporine A and intravenous cyclophosphamide was added and proteinuria disappeared. In 2013, third biopsy was done. A massive amount of microstrucure exhibiting a finger print was observed. [Conclusion] The repeated biopsy showed increase of microtubular strucure presenting a finger print over 20 years in LN.

P3-195

Efficacy and safety of the treatment with mycophenolate mofetil for lupus nephritis

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Conflict of interest: None

[Objectives] In this study, we evaluate the effectiveness and tolerability of mycophenolate mofetil (MMF) for lupus nephritis (LN) in a Japanese population. [Methods] We retrospectively investigated the clinical features of 10 LN patients receiving MMF between Jan 2008 and Oct 2013 in our institution. [Results] Oral MMF was administered for the prevention of infertility or adverse effects by intravenous cyclophosphamide (IVCY) in 8 patients, and for the treatment of renal flares after IVCY in 2 patients. In 7 patients who began to receive MMF in our institution, the initial dose of MMF was 1.6±0.4 (2.0, 1.0-2.0) [mean±SD (median, range)] g/day. The dose of prednisolone (PSL) at the initiation of MMF was 39.1±11.6 (42.5, 25-50) mg/day. In 6 patients observed for more than 4 weeks, complement activity and anti-DNA antibody in serum gradually improved. Accordingly, PSL doses could be reduced in the patients. At 4 weeks after MMF initiation, the levels of daily proteinuria significantly decreased (p=0.0313). Although MMF was discontinued in 1 patient at 4 weeks due to cytomegalovirus infection, 9 patients have been treated with MMF for 94.5±110.0 (37.4, 2-206) weeks. [Conclusion] MMF treatment was effective and tolerable for the patients with LN.

P3-196

The efficacy and long term safety of multitarget therapy for lupus nephritis

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Conflict of interest: None

[Objectives] We studied about efficacy and safety of multitarget therapy for induction and maintenance therapy. [Methods] Study population is active lupus nephritis patients or lupus nephritis patients in remission who is treated with multitarget therapy. We extracted a series of change in serum creatinine, serum complement, urine protein creatinine ratio (UPCR), dose of steroid, and other adverse events. [Results] Thirty patients (female:25, male:5) met the definition. The mean age was 36.4 years old. Fourteen patients (female:12, male:2) undergo induction therapy. When we initiated induction therapy, the mean value were UPCR 4.34 g/gCr, serum creatinine 0.74mg/dl, C3 47.4mg/dl, and C4 7.1mg/dl. Within 6 month, 13 out of 14 patients achieved remission. We could decrease the dose of steroid from 59.4mg/day to 12.3mg/day at 3 month and 8mg/day at 6 month. There was one disease flare until 12 months. There was no adverse event requiring hospitalization at all. Also we will report about maintenance therapy with multitarget therapy. [Conclusion] Multitarget therapy for lupus nephritis has a high degree of therapeutic efficacy and safety.

P3-197

Efficacy and safety of rituximab in patients with lupus nephritis

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Conflict of interest: None

[Objectives] B-cell depletion therapy by rituximab (RTX) has been reported to be useful for treatment of lupus nephritis (LN) in many observational uncontrolled studies, and recent ACR/EULAR guideline recommend RTX as an alternative treatment option for refractory LN. To examine efficacy/safety of RTX in LN, a post-hoc analysis was done for subset of LN entered into Japanese phase II clinical study in refractory SLE. [Methods] RTX was administrated at a dose of 1,000mg/body on days 1, 15, 169 and 183. After the first dose of RTX, background steroid was tapered by 20% every two weeks. Pts were followed for 53 weeks. [Results] A total of 34 pts were enrolled and 17 pts had renal involvement with Upr/Ucr >1.0 (median: 2.2, range: 1.0-10.0). Peripheral blood of B-cells depleted after the first RTX in all 17 pts. Overall response rate by ACR and LUNAR criteria were 59% and 53% respectively. Successful steroid tapering achieved in 15 pts who completed the study and median predonisolone dose at week 53 was 5 mg/day. Rituximab was well tolerated and 6 infusion-associated reactions were observed in 3 pts which were all grade 1-2 in severity. Only three grade 3/4 AEs observed in 2 pts. [Conclusion] Rituximab is effective for treatment of LN who were poorly controlled by conventional therapy.

P3-198

A case report of anti-MDA5 antibody -positive dermatomyositis with various clinical manifestations

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Conflict of interest: None

A sixty year-old male was admitted to our hospital because of myalgia of upper limbs. He suffered from low-grade fever, cough and pain of finger joints. He also had erythema on dorsal surface of hands and peripheral circulatory failure of his fingers. Laboratory data showed pancytopenia with elevated ESR, but the anti-nuclear antibody was negative. He also had interstitial pneumonia with pleural effusion and active synovitis of fingers. The electromyogram showed myogenic damage. The histological finding of his finger was compatible with scleroderma. Based on those findings, he was suspected of overlap syndrome of DM, SSc, and SLE. His symptom disappeared immediately after treatment with 40mg of prednisolone (PSL). However, his interstitial pneumonia relapsed when PSL decreased to 25mg/day. We increased PSL to 40mg/day and added intravenous cyclophosphamide. Cyclophosphamide was switched to cyclosporine because of cytomegalovirus infection. PSL have been tapered to 20mg/day without relapsing of interstitial pneumonia. Then, we detected Anti-MDA5 antibody in his sera. We finally diagnosed him as dermatomyositis with anti-MDA5 antibody. It is noteworthy that he presented with a variety of symptoms and signs which were suggestive of other autoimmune diseases.

P3-199

A case of RA patients successfully treated with abatacept accompanying with polymyositis

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Conflict of interest: None

74 years-old woman, who had suffered from rheumatoid arthritis from 2001. Oral administration of methotrexate was effective. In March 2011, she developed proximal muscles weakness, and at August she stopped oral medication of MTX because of liver dysfunction. On November 8, laboratory examinations revealed highly elevated serum CPK and she was admitted to our hospital. Electromyogram of her right triceps showed myogenic pattern and MRI examination showed high intensity lesion in Gluteus maximus. Although anti-Jo-1 antibody test was negative, muscle biopsy from her Quadriceps confirmed her diagnosis as polymyositis. She was started on predonisolone 40mg daily and thereafter added 8mg of MTX weekly. Laboratory data and her symptom of muscle weakness gradually recovered. But in April 2012, she had complained polyarthralgia because of worsening RA. On August 15, we decided to add abatacept 500mg monthly. Fewer new research studies about etiologies and treatments had been conducted on PM/DM, because there was no proper animal model. Recently some groups have reported the efficacy of TNF inhibitors, we also overview the reported efficacy of biologics on PM/DM.

P3-200

Acute/subacute progressive interstitial pneumonia associated with dermatomyositis (DM-IP) treated with Tacrolimus (TAC): 3 cases

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Conflict of interest: None

[Case 1] A 70-year-old female patient. She was admitted with pneumocystis pneumonia (PCP). PCP improved, but skin eruption was present and existing IP was progressing subacutely. She was diagnosed with DM-IP. Anti-MDA5 antibody was positive. She was treated successfully with predonisolone (PSL) and TAC 6mg/day. The average TAC trough was maintained highly at 22.5 ng/ml, but there was no adverse drug reactions. [Case 2] A 51-year-old male patient. He was diagnosed with DM-IP with adverse prognosis factors of anti-MDA5 antibody, high ferritin level and high A-aDO2. He was treated with PSL and TAC 8mg/day, but TAC trough remained low (2.9 ng/ml). IP was progressing and TAC was changed to cyclosporine. We additionally administered 2500mg of intravenous cyclophosphamide, and IP improved. [Case 3] 65-year-old female with subacute DM-IP. Anti-MDA5 antibody was negative. She was treated successfully with PSL and TAC 6mg/day. The average TAC trough was 15.8 ng/ml. [Disucussion] TAC is a drug whose absorption depends heavily on the individual. Dosage adjustment is difficult. Dosage and blood levels that we should aim for are not clear from the point of view of efficacy and adverse effects. We suggest a more useful dose regimen of TAC for DM-IP from our experience.

P3-201

A case of Dermatomyositis and pemphigus vulgaris: successful treatment with high-dose intravenous gammaglobulin

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Conflict of interest: None

A 80-year-old male was admitted to his nearby hospital with myalgia and weakness in his arms and difficulty in swallowing. The levels of Creatinine kinase (CK) and Aldolase (ALD) were both elevated. He was diagnosed as dermatomyositis (DM) and 60 mg/day of prednisolone (PSL) were initiated. His clinical and laboratory findings of DM gradually improved and he was transferred to our hospital 3 months later. He has been in our hospital for 4 months and discharged. PSL was continued to tapered to 10 mg/day during his hospitarization. After 4 years outpatient visit, He was admitted to our hospital with aspiration pneumonia and an-

tibiotics was initiated. He has made an untroubled recovery. On the 7th hospital month, he presented with multiple painful scaly erosions on his arms and legs. Serum anti-desmoglein 3 antibody was positive, but anti-desmoglein 1 antibody and anti BP-180 antibody were negative. On the basis of these findings, he was diagnosed as having pemphigus vulgaris and Cyclosporine A (CSA) was administrated to him. But his epidermolysis bullosa (EB) had developed. Then he was treated with two courses of IVIg therapy (20 g/day × 5 days), and his blisters improved over 1 month. We report a rare case with dermatomyositis and pemphigus vulgaris.

P3-202

A patient with severe myocarditis associated with polymyositis

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Conflict of interest: Yes

【Case】A 42-year-old woman【Past history】32-year-old: Primary biliary cirrhosis【Present illness】She had felt exertional dyspnea since five years ago. She also felt palpitation six months ago, and she consulted a previous doctor. Frequent ventricular premature contraction and poor cardiac functions existed. A cardioangiography didn't show ischemic heart disease. Sarcoidosis was suspected. So she was introduced to our hospital. Bilateral hilar lymphadenitis was not existed and serum angiotensin converting enzyme levels were normal. Serum cardiac muscle enzyme levels were high and cardiac magnetic resonance imaging showed late gadolinium enhancement at left ventricular walls. After electrophysiologic study and cardiac muscle biopsy, she was diagnosed as myocarditis. In addition, mild proximal muscular weakness existed, serum skeletal muscle enzyme levels were high, an electromyogram showed myopathic changes and skeletal muscle biopsy showed fiber size variations.【diagnosis】polymyositis with myocarditis【clinical courses】The treatment included prednisolone and intravenous immunoglobulin made serum muscle enzyme levels normal. On myocarditis, the treatment included β-blocker and antiarrhythmic drugs decreased the frequency of arrhythmia. But the cardiac functions remained poor.

P3-203

A case of effective Batista procedure for dilatative cardiomyopathy associated with polymyositis

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Conflict of interest: None

[Case] Here, we report a 56-year-old female patient with polymyositis, which occurred when she was 49 years old. She did not have any past history was satisfying the diagnostic criteria of polymyositis (PM) that was based on myalgia and weakness of proximal extremity muscle biopsy, EMG, hyper-creatine kinasemia, and high titer of CRP. Simultaneously, she was diagnosed as dilatative cardiomyopathy (DCM) from biopsy of cardiac muscle. Her PM was treated with 1mg/kg prednisolon and tapered to 4mg/day. Her DCM progressed slowly. Thereafter she had severe clonic heart failure (LVDd 79mm, EF 33% on UCG), and hard to be controlled by medication. When she was 56 years old, her DCM was repaird with "Batista procedure". This operation resulted in her heart failure alleviated (LVDd 49mm, EF 42% on UCG).

P3-204

A case of dermatomyositis with severe myocarditis as a initial simptom

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Conflict of interest: None

78-years-old female was admitted because of exertional dyspnea and pedal edema. She was diagnosed as dermatomyositis (DM) because of mechanic's hands, Gottron's sign, elevated serum levels of muscle enzymes, including CK (720U/L), aldolase (22.2U/L), AST (48U/L) and ALT (34U/L), myositis on tight MRI, myopatic changes on electromyography. Chest X-ray showed cardiomegaly and pleural effusion. Chest CT showed no remarkable interstitial shadow change. Arterial blood gas analysis in room air showed PaO2 75.2Torr and PaCO2 33.8Torr. Cardiac ultrasound showed diffuse wall motion decline (EF 21%) and myocardial tissue indicated mild fibrosis. Cardiac MRI showed late gadolinium enhancement (LGE) in left ventricular wall. She was diagnosed as myocarditis with DM and was started to treat with PSL 30mg/day and to manage heart failure. After which the symptoms and laboratory findings were improved, including CK (60U/L), aldolase (2.1U/L), AST (24U/L) and ALT (26U/L). Cardiac ultrasound showed improvement of wall motion (EF 67%). The incidence of cardiac involvement in PM and DM was 9% to 72%. Thirty-seven patients died as adirect result of heart disease. We report a case of DM accompanying severe heart failure with DM myocarditis which showed the improvement of heart function with PSL therapy.

P3-205

A Serious Case of Polymyositis Presenting Fasciitis on Magnetic Resonance Imaging (MRI)

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Conflict of interest: None

In Oct. 2012, a 52-year-old woman presented with swollen hands, puffy fingers and dyspnea. Laboratory data revealed antinuclear antibody 1:160 in a positive speckled pattern; negative other autoantibodies, CK 402IU/l, and KL-6 1113U/ml. Computed tomography demonstrated interstitial pneumonia (IP) and dilatation of esophagus. In Jan. 2013, she presented with Raynaud phenomenon (RP) and polyarthralgia. The diagnosis of scleroderma was supported by the presence of IP, skin hardening, swollen hands, puffy fingers, RP, and dilatation of esophagus. In Mar. 2013, she had proximal extremity myalgias. In Apr. 2013, CK elevated to 1199IU/l, myoglobin to 543ng/ml, and aldolase to23.0IU/l. MRI detected fasciitis in bilateral proximal lower extremity musckles. The diagnosis of polymyositis was supported by muscle biopsy. She received the treatment of prednisolone at a dose of 1.0 mg/kg/day. CPK elevated to 14776U/l, and myoglobin to 4196ng/ml, atrial fibrillation and myocarditis appeared simultaneously. She received methylprednisolone 1g pulse therapy, high-dose intravenous immunoglobulin, and intravenous cyclophosphamide pulse therapy. Fasciitis is a common lesion of dermatomyositis, however, is rare in polymyositis. We experienced a rare case of severe polymyositis with fasciitis on MRI.

P3-206

A case of polymyositis developed after statin use

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Conflict of interest: None

We report a 62-year old woman, who has treated for hyperlipidemia with atorvastatin for a few years. Before two weeks on admission, she had fatigue and low grade fever. She also felt muscle weakness gradually. Finally she was introduced our hospital because of abnormal blood test which showed myogenic enzyme elevation. She had proximal muscle

weakness, an erythema on right inner femoral and nodules of both lungs. We performed biopsies from skin, muscle and lung. The results showed inflammatory change on skin and infiltration of inflammatory cells in muscle and alveoli and alveolar walls in lung. She also had myogenic change of EMG and positive of anti-Jo1 antibody, but lack of skin symptoms on criteria, so we diagnosed polymyositis and treated. We have interested in the mechanism of inflammatory and immune-mediated myophaty in this case.

P3-207

Expression of inflammasomes is different in muscle of dermatomyositis and polymyositis patients

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Conflict of interest: None

[Objectives] To investigate the expression of inflammasomes in muscle of dermatomyositis (DM) and polymyositis (PM) patients. [Methods] Immunohistochemistry was performed to determine the expression of NALP1, NALP3, ASC (apoptosis-associated speck-like protein containing a CARD) and caspase-1 in muscles of 10 newly diagnosed adult DM/PM patients (4 DM and 6 PM) and 5 healthy controls. [Results] In 4 DM patients, ASC and caspase-1 were expressed in the plasma of $CD3^+$ T and $CD20^+$ B cells, while in 2 of them NALP3 was also expressed. Only 1 PM patient in 6 expressed NALP3, ASC and caspase-1. NALP1 was not expressed in any of the 10 patients. No NALP1, NALP3, ASC and caspase-1 were expressed in 5 healthy controls. The positive rate of ASC and caspase-1 in DM group was significantly higher than that in PM and control group ($P<0.01$ and $P<0.05$), while the positive rate of NALP3 in DM group was higher than that in PM and control group but with no statistical significance. The levels of CK, ESR, CRP had no difference between positive and negative groups. [Conclusion] Innate immune may play different role in the pathogenesis of DM and PM. Inflammasome may participate in the inflammation of DM and be activated by NALP3 mostly, while it may not participate in the pathogenesis of most of PM.

P3-208

A case of bladder tumor developed in a patient with microscopic polyantiitis treated with intravenous cyclophosphamide pulse therapy

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Conflict of interest: None

Hemorrhagic cystitis and cancer of the urinary tract are well known adverse events of cyclophosphamide (CPM). Cancer of the urinary tract develops in patients who take CPM for a long time orally, and the total dose is more than 50 g in most of the reports. Here we report a case of bladder tumor developed in a patient with microscopic polyantiitis (MPA) treated with intravenous cyclophosphamide pulse therapy (IVCY). The patient is a 78 years-old woman, in whom MPA with RPGN and IDL developed in 2002. Treatment with PSL (1 mg/kg) and IVCY started in Sept. 2002. IVCY was followed by azathioprine, but in the course the titer of MPO-ANCA increased combined with variety of symptoms including fever, polyarthritis and polyneuripathy, resulting in re-introduction of IVCY. The total dose of CPM was 12.65 g. In Oct. 2013 abdominal CT was done for the assessment of FUO, and a tumor around the orifice of left ureter was found. A wide-based tumor was recognized by a cystoscopy and trans-urethral resection was done. In conclusion, attention should be paid on the development of bladder tumor even if CPM was administrated in the form of IVCY.

P3-209

Efficacy and Safety of Induction Therapy with Pulse Cyclophosphamide for Microscopic Polyangiitis

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Conflict of interest: None

[Objectives] To investigate efficacy and safety of induction therapy with pulse cyclophosphamide (pCY) for microscopic polyangiitis (MPA). **[Methods]** We evaluated 24 patients with MPA (M/F=12:12) who were treated with pCY plus oral daily prednisolone (PSL) between Jan 2005 and Aug 2013, retrospectively. Disease activity was assessed by BVAS, and the remission was defined as BVAS=0. **[Results]** Mean age was 70.6±8.0 years. BVAS was 18.6±4.4 and total follow-up duration was 3.3±2.5 years. All of them had renal involvement. Starting dose of PSL was 0.78±0.23 mg/kg/day. PSL dose at 6 months was 10.9±3.0mg/day, and total dosage of PSL at 6 months was 3262.1±531.7mg. Total dosage of CY was 3.7±2.9g. The remission rate was 95% at 6 months (n=20/21), 72% at 12 months (n=13/18) and 63% at 24 months (n=10/16). The relapsing patients received significantly less amount of CY (1.9±1.2g vs 5.1±2.8g, p=0.004) and higher daily dose of PSL (21.5±8.9mg vs 10.5±4.9mg, p=0.028) at withdrawal of CY. The major reason for withdrawal of CY was remission (n=5/6). Two serious infections were observed in remission group and 3 in relapsing group. **[Conclusion]** The pCY was effective for remission induction of MPA with some risk of serious infections. The higher cumulative dose of CY could prevent relapse.

P3-210

The Effectiveness of Rituximab for Granulomatosis with Polyangiitis (GPA)

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Conflict of interest: None

A 46 year-old-male was diagnosed with Wegener's granulomatosis (Granulomatosis with polyangiitis; GPA) on 2004. And he was treated with corticosteroid (PSL 20mg per day) and oral cyclophosphamide (CPA) (50mg per day). He noticed right exthophthalmos and failing vision in 2005, and was pointed out intraorbitally tumor and sinus abnormality by magnetic resonance image (MRI). He was underwent biopsy of the tumor and diagnosed with GPA recurrence. He was administered methyl-prednisolone pulse therapy (m-PSL: 1gx3 days for four courses) and intra-venous cyclophosphamide (IV-CY: 750 mg per body x 6 courses) as immunosuppressive therapy, and irradiation therapy (total 42 Gy) expected to directly decrease orbital tumor. He repeated light exacerbation of the orbital and paranasal tumors in spite of these combined therapy. He recurred GPA again, he pointed out new lung lesions in 2013, and administered Rituximab (375mg/m^2, once per week for four times). Lung involvement improved after four courses Rituximab administration.

P3-211

A case of refractory granulomatosis with polyangitis (GPA) effectively treated by rituximab (RTX) for induction therapy

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Conflict of interest: None

A 58-year-old man was reffered to our hospital in January 2013 to investigate more than two months history of refractory left middle otitis. Simultaneously the peripheral facial paralysis developed at the left side of his face and urinary retention occurred by prostatemegaly. The histopathologies of biopsy specimens taken from his left middle ear showed necrotizing granulomatous inflammation tissues. Laboratory findings showed positive C-ANCA, high level inflammation and CT scan revealed that many cavity-forming lung lesions. He was diagnosed with GPA and admitted to our hospital for the treatment. After administering predonisolone (PSL) 60mg/day (1mg/kg) and monthly intravenous cyclophosphamide (IVCY), his clinical findings including prostatomegaly improved and we succeeded to maintain low grade disease activity with negative C-

ANCA for a few months. We tapered PSL and continued monthly IVCY. However, 6 months later he relapsed. We increased PSL and switched IVCY to RTX, then disease activity quickly fell down for a month. We report a case of the GPA patient who well responded to RTX after the exacerbation.

P3-212

Safety and effectiveness of rituximab for six Japanese patients with ANCA-associated systemic vasculitides in Japan

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Conflict of interest: None

Rituximab (RTX) has been approved in Japan for the treatment of patients with antineutrophil cytoplasmic antibody (ANCA) -associated systemic vasculitides (AAV) which are resistant or intolerant to the standard therapy with glucocorticoids and/or cyclophosphamide (CY). We used RTX in 6 Japanese patients with AAV since 2011, and report the safety and effectiveness of the treatment. The average age was 38.1 years old and 5 of them were female. The types of AAV were granulomatosis with polyangiitis in 3 cases, eosinophilic granulomatosis with polyangiitis in 2, and microscopic polyangiitis in 1. CY had been used for all of them, but was discontinued because of adverse drug reactions or previously administered dosages. The average Birmingham Vasculitis Activity Score (BVAS) was 14.5±4.2 at RTX administration and was 2.0±4.9 six months later. Two cases were retreated with RTX 6 months later for the maintenance of remission and the other three cases were given RTX again more than 18 months after the initial treatment due to recurrence. Regarding safety, one infusion reaction and one abdominal surgery for intestinal perforation were reported. Infection was not observed. Maintenance therapy after achieving remission of AAV with RTX should be investigated in future.

P3-213

Two cases of Polyarteritis nodosa (PN) successfully treated with Infliximab (IFX)

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Conflict of interest: None

[Purpose] IFX has been reported as an effective treatment for refractory PN. Here, we report two cases of PN successfully treated with IFX. [Case 1] A 37-year-old woman was diagnosed with PN in 2005 with erythema nodosum (EN), arthritis, myositis and fibrinoid necrosis of small-sized arteries revealed by skin biopsy. Despite initial effect with PSL 15mg/day, PN recurred twice during reduction of corticosteroids (CS). Combination of CS, CY and AZ was initiated, resulting in successful discontinuation in 2008. However, PN recurred in 2009 and combination of CS, AZ and MTX was insufficient. Thus, IFX 3 mg/kg was started in 2010. After 6 weeks, Birmingham vasculitis activity score (BVAS) was reduced from 4 to 0. [Case 2] A 56-year-old woman was diagnosed with PN in 2011 with arthritis, EN and necrotizing vasculitis revealed by skin biopsy, and was also diagnosed with RA by bone erosions detected. MTX 6mg/w + IFX 3mg/kg were started, and after 3 months EN healed, but arthritis remained. Ten months after increase of MTX to 16mg/w and of IFX to 10mg/kg, active arthritis was disappeared (BVAS 3→0). [Conclusion] In both cases no recurrences, as well as no adverse events, have been identified to date. These cases suggest that IFX was safe and effective for patients with PN.

P3-214

Refractory eosinophilic granulomatosis with polyangiitis (EGPA) complicated by small intestinal necrosis can be successfully treated with infliximab (IFX): A case report

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Conflict of interest: None

A 38-year-old Japanese woman with EGPA was sequentially treated with prednisolone (PSL), methotrexate (MTX), cyclosporin A (CyA), and IFX 8 years ago after she failed standard therapies. Because she wished to bear a child, we carefully discontinued MTX, CyA, and IFX, and tapered a dosage of PSL to 5 mg/day 5 years ago. EGPA was stable and she got pregnant 2 years ago. Two months later after childbirth, she presented abdominal pain and eosinophilia (11020 cells/μL). Increase in a dosage of PSL to 30 mg/day failed to improve her symptoms and signs. Although receiving steroid pulse therapy, she developed small intestinal necrosis and underwent partial resection of small intestine and jejunostomy a year ago. Pathological findings revealed middle-small vasculitis with eosinophilic infiltration and fibrinoid necrosis compatible with EGPA. Also enhanced CT demonstrated aneurysms of small abdominal arteries. Assessing that EGPA was aggressive, we administered IFX 4 mg/kg and maintained PSL 30 mg/day. EGPA became stable and PSL was gradually tapered to 5 mg/day while using IFX. The patient underwent stoma closure, and EGPA has been stable and the aneurysms have disappeared after the initial surgery. We speculated that IFX might be one of the most effective agents in refractory EGPA.

P3-215

Adjunctive role of recombinant human soluble thrombomodulin for the treatment of thrombotic microangiopathy associated with microscopic polyangiitis

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Conflict of interest: None

Thrombotic Microangiopathy (TMA) is a rare but serious disease. We experienced a patient with microscopic polyangiitis (MPA) who developed from rapidly progressive gromerulonephritis (RPGN) to TMA during remission induction therapy. Following administration of recombinant human soluble thrombomodulin (rTM), the patient's thrombocytopenia and renal failure started to improve. Clinical remission was successfully induced and maintained without renal dialysis. This case illustrated the possible pathogenesis of RPGN and the therapeutic implications of rTM in MPA.

P3-216

Large vessel involvement with refractory granulomatosis with polyangitis successfully treated with rituximab

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Conflict of interest: None

A 60-year-old female developed fever, bloody nasal discharge, and skin ulcers in lower extremities. A contrast-enhanced CT scan revealed sinusitis, multiple lung nodules, and local thickening of vessel walls of aortic arch and abdominal aorta. The diagnosis of granulomatosis with polyangitis (GPA) was made based on positivity for PR3-ANCA and epithelioid granuloma with fibrinoid vasculitis on nasal mucosal biopsy. Although a combination therapy with high-dose prednisolone and intravenous cyclophosphamide was performed for 2 months, several lung nodules were enlarged and the aortic wall thickness was unchanged. Worse still, she developed orbital pseudotumor. Since pulse methylpred-

nisolone therapy (125 mg/day IV for 4 days) was ineffective, treatment with rituximab at a dose of 375mg/m^2 weekly for four consecutive weeks along with initial dose of prednisolone was administered. Levels of CRP and PR3-ANCA were subsequently normalized for the first time, whereas a CT scan examined at 1 month after the first infusion of rituximab demonstrated marked improvement of orbital pseudotumor, lung nodules and aortic wall thickness. We report a case of refractory GPA with large vessel involvement in which add-on therapy of rituximab was markedly effective.

P3-217

A case of IgA vasculitis with obstructive jaundice due to intestinal edema

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Conflict of interest: None

A 25-year-old male had sudden onset of abdominal pains, vomiting, diarrhea, and melena 6 days prior to admission to our hospital. He was admitted to another hospital and abdominal computed tomography showed inflammatory change in terminal ileum, and ascites. Diagnosis of acute terminal ileitis was made. His symptoms were not improved with conservative treatment. Spotty purpura developed on the extremities on the 2nd hospital day. He was transferred to our hospital. Skin biopsy on the purpuric lesion revealed IgA vasculitis. Gastrointestinal features were compatible with GI involvement of IgA vasculitis. Urinalysis on admission showed proteinuria and hematuria. On the 4th hospital day elevation of liver enzyme and amylase developed. Abdominal contrast enhanced computed tomography revealed obstructive jaundice due to intestinal edema. Three doses of methylprednisolone pulse therapy along with recombinant factor XIII were given followed by the oral administration of prednisolone 50mg. Abdominal symptoms and purpura soon disappeared and the liver and pancreatic enzymes were normalized. On the 11th hospital day, renal biopsy was performed, which showed purpura nephritis. The combination of prednisolone, cyclophosphamide and mizoribine were required to reduce proteinuria.

P3-218

A case of Rosai-Dorfman disease complicated with aortic lesions

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Conflict of interest: None

[Background] Rosai-Dorfman disease (RDD) is a rare histiocytic proliferative disorder, typically presenting with cervical lymph node swelling and fever. **[Case report]** A 31-year-old man came to the outpatient otolaryngology clinic of our hospital because of right neck mass, fever, arthralgia and inflamed eyes in Nov., 2012. FDG-PET/CT revealed high uptake in the right neck mass. A biopsy of the mass, performed in Jan., 2013, showed non-neoplastic inflammatory cell infiltrations of unknown etiology. Twenty mg of prednisolone (PSL) ameliorated fever and arthralgia, but failed to reduce cervical mass. In Jun, CT scan showed thickened walls of the aortic arch and the bilateral cervical arteries. He was referred to our outpatient clinic suspecting aortitis. Re-biopsy of the cervical mass was done and the diagnosis of RDD was made, based on accumulation of S-100-positive histiocytes with emperipolesis. PSL at a dose of 55mg was started. Fifty days later, the cervical mass almost disappeared and the wall thickening of both aortic arch and cervical arteries were improved. **[Clinical significance]** A few cases of RDD patients complicated with aortic lesions have been reported. Although very rarely found, RDD should be considered as one of differential diagnosis of aortitis or periaortitis.

P3-219

A case of giant cell arteritis associated with spondyloarthritis

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Conflict of interest: None

A case, 77 year-old woman, taking MTX and prednisolone (PSL) under diagnosis of rheumatoid arthritis for polyarthralgia in extremities lasted for previous four months, was referred to our clinic. She had polyarthritis in extremities, and laboratory findings revealed positive for CRP and ESR, and negative for RF nor ACPA. MRI revealed erosions in left wrist, and we strengthened the treatment for seronegative RA. During follow-up, there were found to have abdominal aortic aneurysm, and she developed cerebral infarction. FDG-PET/CT performed because of difficulty in control of inflammatory markers, revealed FDG accumulation in carotid arteries, brachiocephalic artery, subclavian arteries, abdominal aneurysms, femoral arteries, and popliteal arteries. FDG was also accumulated in multiple enthesis of joints, lumbar interspinous ligaments, and ischial tuberosities, so we finally diagnosed her illness as giant cell arteritis associated with spondyloarthritis. Therefore, we added IVCY therapy on MTX plus PSL, her symptoms and signs clinically subsided. Giant cell arteritis associated with spondyloarthritis is relatively rare and we report some considerations about these conditions.

P3-220

A case of giant cell arteritis (GCA) with hypertrophic pachymeningitis (HP)

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Conflict of interest: None

A 76-year-old woman who had tympanitis in May 2012 complained of fever and appetite loss after a fall. She was treated with antibiotics but her symptoms worsened. She was diagnosed with polymyalgia rheumatica and 40 mg/day of PSL improved her symptoms. When the PSL dose was tapered to 10 mg/day, her symptoms recurred. In August 2013, she was hospitalized because of headache, hearing difficulty, diplopia, jaw claudication and induration of temporal arteries. Based on the criteria, she was diagnosed with GCA, and a temporal artery biopsy was taken. Arterial wall thickening with destruction of the elastic fibers of the tunica intima and media was identified, though inflammatory and giant cell infiltration was absent. Gadolinium-enhanced T1-weighted MRI of the brain showed diffuse pachymeningeal enhancement. We diagnosed her as having GCA with HP and successfully treated her with 20 mg/day of PSL and tacrolimus. There have been few reports on GCA complicated with HP. However, antineutrophil cytoplasmic autoantibodies-associated vasculitis (AAV) is sometimes complicated with HP. We consider that she suffered from not only from GCA but also AAV associated HP.

P3-221

A case of Takayasu arteritis accompanied with recurrent abdominal pain suggestive of acute appendicitis

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Conflict of interest: None

A 22 year-old woman fainted several times since 2011. She had some episode of fever and polyarthralgia since 2012. In April 2013, she admitted to our hospital because of abdominal pain with peritoneal signs. Blood test revealed elevated inflammatory reaction and computed tomography (CT) showed wall thickening of appendix. She was diagnosed with acute appendicitis, treated medically and her clinical symptoms disappeared but results of blood test did not improve. Then images of chest CT suggested thickening of aortic wall. In September 2013, she developed fever and abdominal pain again. Abdominal CT revealed enlarged appen-

dix. She consulted our department. On admission, physical and routine laboratory findings revealed same results as those at the last admission, but abdominal bruit and serologically positive HLA-B52 were newly detected. Ultrasonography, CT, and magnetic resonance images showed wall thickening of thoracic and abdominal aorta, those of carotid and superior mesenteric artery (SMA), segmental enlargement of abdominal aorta, and stenosis of renal and superior mesenteric arteries. She was diagnosed with Takayasu arteritis (TAK) and treated effectively with oral prednisolone (40mg/day). It seemed that recurrent abdominal pain of this case was caused by SMA lesion of TAK.

P3-222

Takayasu's arteritis with an extensive collateral circulation that presented the cerebral ischemic stroke during steroid therpy

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Conflict of interest: None

A 35-year-old woman was admitted to our hospital because of left cervical pain, showing absent radical pulses, carotid bruits, and difficulty in blood pressure determinations. CT angiography revealed a thickened wall of aortic arch with severe stenosis of bilateral common carotid arteries (CCA) and subclavian arteries. She was diagnosed as Takayasu's arteritis (TA) type IIa, and was treated with prednisolone (PSL). 1 week after starting PSL, she had the weakness of her right arm and the syncope. Magnetic resonance imaging revealed the brain infarction of the parietal region. Angiography confirmed the occlusion of left CCA, which had thrombosis in the distal site. The ICAs were perfused with an extensive collateral circulation from the intercostal arteries. To further control the disease, mPSL pulse therapy was performed, followed by oral PSL and azathiopurine. Three months later, percutaneous transluminal angioplasty for stenosis of the innominate and right CCA was successfully performed. 10-20% of patients with TA have ischemic stroke or transient ischemic attacks. This case developed the stroke in spite of well-developed collateral blood flow and negative CRP. This suggests that active inflammatory process could continue during the chronic phase and cause cerebral infarction.

P3-223

Takayasu arteritis (TA) with advanced stenoses of aortic main branches treated with Tocilizumab (TCZ)

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Conflict of interest: None

The patient was a 25-year-old female. In April 2010, she started to have bouts of dizziness and syncope. Her blood pressure decreased in both arms. Ultrasonography revealed advanced stenoses of main aortic branches. She visited our hospital in June 2010. A blood test showed an inflammatory reaction and proved the elevation of serum IgG and negative for autoantibody. 3D-CT angiography and MRA revealed advanced stenoses of main aortic branches. From these findings, we diagnosed Takayasu arteritis and started prednisolone 50mg/day and methotrexate 6mg/week. After 6 months, we performed CAG and detected 90% stenosis of LMT. Although PTCA was performed, restenosis occurred repeatedly. Because of her persistent positive for inflammatory reaction and enhanced aortic wall finding on MRI, we added Infliximab (IFX) to her medication, increasing the dose to 6mg/kg/4weeks. Due to unsatisfactory effect of IFX, we changed IFX to TCZ, after which CRP changed to negative. Despite the effectiveness of steroids and the fact that a good prognosis is expected in TA, some cases are associated with cardiac, renal or vascular complications. We experienced a case in which TCZ was effective, and some studies suggest the effectiveness of biological products in intractable TA.

P3-224

A case of anti-TNF α therapies refractory for Takayasu's arteritis successfully treated by tocilizumab

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Conflict of interest: None

We report a case of anti-TNF α therapies for refractory Takayasu's arteritis (TA) successfully treated by tocilizumab. The patient, a 25-year-old female, was diagnosed as having TA in 2008. She was treated by corticosteroids (CS), methotrexate (MTX), pulsed cyclophosphamide, and tacrolimus. These agents and their combination therapies did not achieve remission or taper CS dosage to less than 10mg prednisolone a day. Therefore, we used infliximab. But we could not taper CS to an opportune dosage. Next, we switched to etanercept. However result was the same. We administered tocilizumab (TCZ) in 2010. After that, she suffered from pyoderma gangrenosum. So we decided to stop TCZ. But we resumed TCZ in combination with MTX when TA flared in March 2013. A subcutaneous abscess in her right heel had occurred during the course. Using antibiotics, we did not totally stop TCZ regimen. With further combinations of tacrolimus, we have achieved proper CS tapering without any symptoms or signs of flare. TCZ and its combination with immunosuppressants could be a promising agent for refractory TA patients.

P3-225

A case of Refractory Takayasu Arteritis for whom Tocilizumab was Effective

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Conflict of interest: Yes

Takayasu arteritis is a chronic type of granulomatous vasculitis of unknown pathogenesis chiefly affecting young females. Glucocorticoids and immune-suppressants are the mainstay of treatment, but relapses are common when treatment is tapered. A 16-year-old woman failed to respond to prednisolone in combination with azathioprine and mizoribine. After the begining of tocilizumab therapy (8mg/kg at monthly infusions), an impressive improvement in the clinical and laboratory parameters of the disease activity occurred, allowing a reduction of the prednisolone dose from 30 to 7 mg/day. No relapse and no severe adverse events were observed. These results indicate that anti-IL-6 receptor antibody, tocilizumab, might be a therapeutic option for Takayasu arteritis.

P3-226

Adalimumab therapy in a patient with refractory Crohn's disease and Takayasu arteritis

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Conflict of interest: None

[Objectives] There are few reports which Takayasu's arteritis (TA) is associated with Crohn's disease. We experienced the TA patient with Crohn's disease. [Case] 18-year-old woman presented to a local hospital with a history of fever in May. Cause of the fever is unknown, she visit to our hospital in October. Clinical examination confirmed the right-and-left difference of blood pressure. The serum CRP level and ESR were high. FDG was accumulated in the left carotid artery in PET-CT. We diagnosed her as aortic syndrome, oral prednisolone was started. FDG accumulation was observed also in the intestinal tract, ulcers were found in colonoscopy. We judged this view to be the ileocecal region nonspecific colitis by

TA. Tocilizumab (TCZ) was started in February next year. Although CRP became negative, melena was observed in April. We colonoscopy again, and we detected an epithelioid granuloma in the biopsy from the lesion. ADA was started in May. After three months, gastrointestinal tract lesions were markedly improved in colonoscopy. [Conclusion] In the present case TCZ which was used for TA did not contribute to the improvement of mucosal symptoms. As a treatment when complicated with both diseases, the possibility that ADA was effective was suggested.

P3-227

Successful Diagnosis of Elderly Onset Takayasu's Arteritis with FDG-PET/CT; 10 cases

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Conflict of interest: None

Recently, elderly onset Takayasu's Arteritis (TA) cases are occasionally reported to be diagnosed using PET. We report the characteristics of elderly onset TA diagnosed using the PET in our department. [Objectives] [Methods] 10 TA patients 40 years-old and above diagnosed in our department using the PET between 2009 and 2013 were studied retrospectively. [Results] Median age at onset was 70.5 years-old. There were 4 males and 6 females. Median disease duration was 29 months, and time from onset to diagnosis was 4 months. Arteriosclerosis factors included 8 hypertension, 1 hyperlipidemia, and 5 diabetes. All had type V. Initial symptoms included 6 fevers, 2 fatigue, 3 joint pains, 3 sore throats, 3 headaches, 1 arm numbness, and 3 easy fatigabilities. Average initial CRP was 7.19±1.04 mg/dl. HLA-B52 was positive in 5 out of 8 patients, and B39 was positive in 1. All males had a positive HLA related to TA. 3 cases had traveled overseas before onset, and all were male. Steroids were used in 8 cases, and initial dosage was 45mg. MTX was used in 8, AZA in 6, and MMF in 1. All were survived [Conclusion] The PET can detect early TA and vascular lesions unnoticed on existing imaging methods. Elderly onset TA cases have strong genetic factors.

P3-228

Case report; A case of the flare of aortitis syndrome in elderly onset diagnosed with 18F-FDG-PET

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Conflict of interest: None

67-year-old female with aortitis syndrome because of dilation of aorta and stenosis of the main branch artery in aorta on chest computed tomography about 1 year ago was treated with prednisolone. When prednisolone was tapered to 12.5mg, laboratory examination revealed a high level of C-reactive protein. Contrast-enhanced CT did not revealed a new change of aorta. But ^{18}F-FDG-PET revealed an accumulation of 18 fluorodeoxyglucose in aorta. Because we thought that aortitis syndrome was flared, prednisolone was increased to 60mg/day and azathioprine 50mg/day was added. C-reactive protein improved to normal levels. We suggest that ^{18}F-FDG-PET is useful to diagnose the activity of aortitis.

P3-229

A case of giant cell arteritis diagnosed by FDG-PET/CT

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Conflict of interest: None

70-year-old woman suffered from double vision on Feb. 2, 2013. She was admitted to a local hospital, and had a diagnosis of right vertebral artery obstruction by MR-angiography. Her double vision was relieved with antithrombotic agents, but she was referred to us because of fever of unknown origin to continue since she was hospitalized. She had slight pain and stiffness around proximal limbs, and laboratory findings showed that high CRP (16.2mg/dl) and ESR (140mm/h). Various culture tests and tumor markers, autoantibodies except for rheumatoid factor were negative. Contrast CT scan and endoscopy did not show any malignant or infectious diseases. But we recognized high accumulation of FDG along the vascular wall of main arteries of whole body by FDG-PET/CT. The tissue obtained from the right temporal artery was revealed that she had giant cell arteritis. PSL 40mg/day was started and her symptoms were improved. This case showed the usefulness of FDG-PET/CT for diagnosis of giant cell arteritis without typical symptoms.

P3-230

Influence of HTLV-I infection toward salivary glands epithelial cells from primary Sjögren's syndrome

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Conflict of interest: None

Objective: To investigate direct influence of HTLV-I infection toward salivary glands epithelial cells (SGECs) in primary Sjögren's syndrome (pSS) in vitro. **Methods:** Cytokine array of supernatant and apoptosis array of cell lysate were employed for samples from co-culture between SGEC obtained from HTLV-I-seronegative SS patients and HCT-5. Expression of HTLV-I-related protein was examined by immunofluorescence (IF) or Western blot (WB). Expression of HTLV-I DNA was determined by in situ PCR by using HTLV-I pX region primers. **Results:** ICAM-1, RANTES or interferon gamma-induced protein 10kDa (IP-10/CXCL10) were observed in HCT-5 only culture supernatant. However, these molecules increased in co-cultured supernatant. Pro-apoptotic such as pro-caspase 3 and Fas and anti-apoptotic molecules including Bcl-2, HO-2, HSP-27 were detected in SGEC lysate with no TUNEL positive staining during 0-96 hour co-culture. HTLV-I-related proteins such as p19, p28 and GAG were detected by WB at least 48 hour co-culture. IF showed appearance of HTLV-I-related molecules along with NF-kB nuclear translocation. HTLV-I DNA was detected within at least 48 hour co-culture by in situ PCR. **Conclusion:** Direct infection of HTLV-I toward SGEC was found in vitro with involvement of relevant molecules.

P3-231

Abnormality of the activated peripheral B cells of patients with primary Sjögren's syndrome

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Conflict of interest: None

[Objectives] It has been suggested that dysregulation of a BAFF/BAFF-R (BR3) system may contribute to the development of primary Sjögren's syndrome (pSS). In this study, we investigated possible abnormalities of peripheral pSS B cells. [Methods] $CD19^+$ B cells were prepared from peripheral blood of pSS patients and normal individuals. The expression of BR3 was analyzed by FACS. The cells were cultured in vitro in the presence or absence of recombinant human soluble BAFF (rhs-BAFF), an anti IgM antibody, CD40 Ligand and rIL-4 for 96 hrs. The production of IgG by the cells were measured by ELISA. [Results] FACS revealed that $CD19^+$ cells of both pSS patients and normal individuals expressed BR3. Notably, among $CD19^+$ cells, the population of $CD38^+$ cells was significantly increased in pSS patients as compared to the con-

trols. The production of IgG by CD19+ cells co-stimulated with an anti-IgM antibody, CD40 Ligand and rIL-4 was significantly increased in pSS patients than that of normal individuals. In addition, stimulation of co-stimulated $CD19^+$ cells with rhsBAFF further enhanced IgG production. [Conclusion] Our results suggest that the abnormality in $CD38^+$ / $CD19^+$cells may account for the increased production of IgG. The dysregulated IgG production may be involved in the pathogenesis of pSS.

P3-232

Salivary metabolomics of primary Sjogren's syndrome

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Conflict of interest: None

[Objectives] Saliva may reflect the pathogenesis of primary Sjogren syndrome (pSS). Metabolomics is the study of the small-molecule metabolite profile. Metabolomics is regarded as the most predictive of phenotype among the other "omics" studies. We conducted the salivary metabolomics to clarify the pathogenesis of pSS. [Methods] We analyzed metabolite profiles of saliva from 14 pSS patients and 21 healthy controls (HC) using by GC-MS. The level of metabolites were calibrated by saliva volume. [Results] 88 metabolites are detected. 32 metabolites are decreased in pSS patients and only one metabolite was increased in pSS. PCA analysis revealed pSS patients lost biodiversity of metabolites compare to HC. The decrease of Glysine, Tyrosine, Uric Acid and Fucose contributed to the biodiversity loss. PCA analysis divided pSS into two subpopulation according to the metabolites profiles. The prevalence of major salivary glanditis was different between two subgroups. [Conclusion] A possible reason for impaired production and biodiversity loss of salivary metabolites is destroy of salivary glands due to chronic sialoadenitis. Meanwhile, two-thirds metabolite levels are not decreased in pSS. Salivary metabolomics of pSS patients is potential approach to figure out pSS pathogenesis.

P3-233

Regulatory mechanisms of BAFF receptor expression on human peripheral monocytes

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Conflict of interest: None

[Objectives] We have already revealed that a BAFF receptor (BR3) is expressed on not only human peripheral B lymphocytes but also human peripheral monocytes, and that the BR3 expression was significantly elevated in pSS monocytes as compared to that in normal monocytes. These results suggest that BR3 upregulation is involved in the development of pSS. Therefore, elucidation of the mechanisms of BR3 upregulation may shed light on the pathogenesis of pSS and identify therapeutic targets of the disease. In this study, we investigated the regulatory mechanisms of the BR3 expression in human peripheral monocytes. [Methods] CD14+ monocytes were prepared from peripheral blood of normal individuals using an autoMACS Pro separator. The cells were cultured with or without rhIFNγ, rhIFNα and rhsBAFF. The BR3 expression on monocytes was analyzed by FACS and RT-PCR. [Results] RT-PCR indicated marked BR3 upregulation in human peripheral monocytes when the cells were cultured in the presence of IFNγ, IFNα and sBAFF for 24 hours. The upregulation was confirmed by FACS. [Conclusion]: The data of the present study suggest that at least IFNγ, IFNα and BAFF are involved in the BR3 expression on human peripheral monocytes and hence in the pathogenesis of pSS.

P3-234

Distinct role of plasmacytoid dendritic cells and mast cells in the pathogenesis of Sjögren's syndrome

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Conflict of interest: None

[Objectives] To study plasmacytoid dendritic cells (PDCs) and mast cells (MCs) in the pathogenesis of Sjögren's Syndrome (SS). [Methods] Lip biopsy specimen (178 SS vs7 Sicca) patients were analyzed. MCs, PDCs, CD68 and CXCL13 were detected by immunohistochemistry and toluidine blue staining. [Results] Significant lymphocytes infiltration, acinar atrophy and intralobular fibrosis were observed in SS compared to Sicca patients with salivary gland destruction. Both, PDCs and MCs were significantly increased in SS compared to Sicca (12.6±10.2 vs 3.4±3.7, 43.7±21.8 vs 21.5±6.9). Positive correlation between density of PDCs with lymphocytes infiltration ($p=0.02$) and density of MCs with intralobular fibrosis ($p=0.03$) was observed in primary SS but not in secondary SS. Within the primary SS, density of CXCL13 positive cells positively correlated with density of PDCs ($p<0.0001$), Macrophages is majority of CXCL13 positive infiltrating cells (51.5±17.9%). No correlation was observed with secondary SS patients. [Conclusion] Our data suggests the specific role of PDCs and MCs in pathogenesis of primary SS. Moreover, CXCL13 expression suggests the involvement of multiple lineage cells in the early stage of the disease. MCs was considered to contribute from mid to late stage of primary SS.

P3-235

The efficacy of glucocorticoid therapy for interstitial nephritis with Sjögren syndrome

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Conflict of interest: None

[Objectives] To investigate the clinical feature and the effect of glucocorticoid therapy to interstitial nephritis (IN) with Sjögren syndrome (SjS). [Methods] Among patients with SjS admitted to Tokyo Metropolitan Komagome Hospital from November 2003 to October 2013, we identified those diagnosed with IN by biopsy. We compared the laboratory data before and after glucocorticoid therapy. [Results] Six patients with SjS had IN. The level of serum creatinine (Scr) was increased in five patients. One patient had normal Scr level and hypokalemia. Two of six patients had hypokalemia ($K<3.0$ mEq/L). The level of blood HCO_3- was less than 20 mmoL/L in one of six patients. Five patients with increased Scr level received oral glucocorticoid therapy. The initial dose of PSL was 31.6±7.43 (average±SD) mg. The level of Scr improved within one month (Scr before treatment 1.51±0.312, four weeks after 1.18±0.248, one year after 1.10±0.081 mg/dL). [Conclusion] In the present report, glucocorticoid therapy promptly improved the renal function of SjS patient with IN. The past study reported that SjS patients with IN receiving only potassium or bicarbonate supplement therapy were likely to develop chronic renal failure. It suggests that the appropriate glucocorticoid therapy is necessary for IN with SjS.

P3-236

Salivary production rate and clinical entities among sicca-associated antibodies

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Conflict of interest: None

Objective: Salivary production rate (SPR) and clinical entities among sicca-associated antibodies were studied. Subjects: 181 females (53 ± 15 years) who had anti-Ro, anti-La, anti-U1RNP, and/or ACA were enrolled. Results: SPR was 1.85 ± 1.57 g/2 minutes; the number of seropositivity for anti-Ro, 113 (62.4%); anti-La, 55 (30.4%); anti-U1RNP, 55 (30.4%); ACA, 66 (36.5%); The number of subject with SS was 109 (60.2%); SLE, 51 (28.2%); SSc, 33 (18.2%); RA, 18 (9.9%); MCTD, 15 (8.3%), respectively. Seropositivity for anti-La was significantly associated with SPR with age correction ($P < 0.01$), whereas those of the other 3 autoan-

tibodies were not. Positivity for SS was significantly associated with SPR with reduction ($P < 0.001$); that for MCTD was also significantly associated ($P < 0.05$), whereas those for SLE, SSc and RA were not. Seropositivity for anti-Ro was significantly associated with that for anti-La. Seropositivity for ACA was negatively correlated with that for anti-Ro ($r = -0.503$, $P < 0.001$). Seropositivity for ACA also had weak negative relationships with those for anti-La or anti-U1RNP. Seropositivity for anti-U1RNP was not significantly associated with those for anti-Ro or anti-La. Conclusions: SPR and clinical entities among sicca-associated antibodies were clarified.

P3-237

Autoimmune autonomic ganglionopathy and Guillain-Barré syndrome observed in a patient with Sjögren's syndrome

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Conflict of interest: None

【Case】A 45 year-old woman with Sjögren's syndrome got diarrhea on March 14, 2013, and after three days she developed progressive muscle weakness of upper extremities, orthostatic hypotension, dysarthria, dysphagia and paresthesia of extremities. The examination of cerebrospinal fluid revealed the albuminocytologic dissociation, suggesting of the presence of Guillain-Barré syndrome. Intravenous immunoglobulin therapy improved the above mentioned neurological symptoms except for orthostatic hypotension. As autonomic dysfunction causes orthostatic hypotension, we checked the anti-ganglionic acetylcholine receptors antibody, which was proved to be positive later. Therefore we diagnosed that orthostatic hypotension was caused by autoimmune autonomic ganglionopathy. Five times of plasma pheresis in addition to the administration of predonisolon and azathioprine dramatically improved orthostatic hypotension.【Conclusion】Autoimmune autonomic ganglionopathy should be considered when autonomic dysfunction persists.

P3-238

A case of Sjogren's syndrome complicated with atypical hemolytic-uremic syndrome

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Conflict of interest: None

A 68-year-old female patient was consulted to our hospital because of fatigue, low grade fever and cervical lymphadenopathy in July 2013. The biopsy specimen of lymph node showed no evidence of malignant lymphoma. She presented decreased saliva secretion and positive Saxon test, and diagnosed as having Sjogren's syndrome based on findings of lip biopsy specimen. She was taken a follow-up as outpatient without medicine, however, in the middle of September, she developed epigastralgia and increase of malaise. Laboratory data showed thrombocytopenia, anemia and impairment of renal function. She was admitted to out hospital on September 20, 2013. Nevertheless, her renal function deteriorated further. She showed marked decrease of haptoglobin and fragment erythrocytes, which took over 3% of peripheral blood smear. Since she showed no decreased ADAMTS-13 activity (76.6%), she was diagnosed as atypical hemolytic-uremic syndrome (aHUS). We started plasma exchange therapy, however, it was effective only transiently. Therefore, we added eculizumab treatment. aHUS is a novel concept of thrombotic microangiopathy, and is reported to be complicated with some autoimmune diseases. Here, we report a case of Sjogren's syndrome complicated with aHUS.

P3-239

A case of juvenile onset Sjogren syndrome with synovitis

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Conflict of interest: None

【introduction】Since many of the patiants with juvenile onset Sjogren syndrome can't subjectively fell dry eye or mouth in the initial step, we sometimes check the presence of this syndrome by MR sialography and lip biopsy when a child with fever of unknown origin and arthralgia has hyper serum IgG, anti SS-A/B Ab or RF.【case】9-year-old girl. She had shown slight fever and arthralgia which disappeared naturally. Because her blood analysis show positive ANA (320 times) and anti SS-B Antibody at former clinic, the doctor suspected her as Sjogren syndrome, then consulted us. Her foot joints were swelling and mild synovitis on contrast-enhanced MRI. Although the anti SS-B antibody was carried out negative, we diagnosed her as Sjogren syndrome, since we observed invasion of lymphocytes and plasma cell in the surrounding of salivary duct by the lips biopsy. We prescribed NSAIDs and soon she got in remission. She has no synovitis and bone destruction in spite of the subclinical detection of synovial fluid by echo.【conclusion】In seronegative arthritis, Sjogren syndrome is important as a diagnostic workup of RA or JIA. Decision of diagnosis by a lip biopsy may allow us avoiding from over treatment.

P3-240

A case of Sjögren's syndrome coexisting with sarcoidosis and diffuse large B-cell lymphoma (DLBCL)

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Conflict of interest: None

A 76-year old man was admitted to our hospital with a one-year history of a low-grade fever and both sides of chest pain. Sjögren's syndrome was diagnosed based on the positivity of both anti-Ro and anti-La antibodies and the results of Schirmer's and rose bengal staining test. Elevated C-reactive protein (11.9mg/dl) and masses in mediastinum on the chest CT scan made us suspect a malignancy. PET-CT demonstrated multiple areas of increased uptake, in particular mediastinum and abdomem, thoracic vertebrae, costal bones, and prostate. A prostate biopsy and an endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) of lymph nodes in the mediastinum showed only non-caseating epithelioid granuloma without evidence of malignancy. QFT-test was positive but the culture in liquid medium after EBUS-TBNA was negative. Typical pathological findings at diffrent sites with elevated serum ACE and Ca made his diagnosis sarcoidosis. One month after he left the hospital, he had a progressive walking difficulty and the MRI scan of the spine revealed there were tumors with spinal cord compression at Th6 and Th10. He underwent spinal tumorectomy and was diagnosed with EBV-positive DLBCL pathologically. We report a rare case of Sjögren's syndrome complicated by sarcoidosis and DLBCL.

P3-241

A case of pulmonary Mucosa-Associated Lymphoid Tissue (MALT) lymphoma in Sögren's syndrome (SjS)

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Conflict of interest: None

A 64-year old woman was admitted to our hospital because of fever and dyspnea in August, 2003. Chest X-ray revealed left pleural effusion. A diagnosis of SjS was made based on elevation of anti nuclear and anti-SS-A antibodies titer in serum in combination with keratoconjunctivitis sicca and dry mouth. In the pleural effusion, elevated lymphocytes were observed. She showed no signs of infection nor malignancy. After an administration of PSL40mg/day, the pleural effusion improved. She complicated with chronic lung abscess and antibiotics administration was started. Prednisolone dose was gradually reduced from 40mg to 3mg over five years. In 2008 chest CT revealed bilateral ground glass shadows and small nodules. From fluid of bronchoalveolar lavage with elevation of

lymphocytes (68%), we diagnosed them as lymphocytic interstitial pneumonia associated with SjS. The shadows and small nodules improved after an administration of PSL30mg/day. In 2009 chest CT showed nodules. FDG-PET/CT also showed the increased FDG uptake associated with the nodules. Trans bronchial lung biopsy specimen revealed MALT lymphoma. She was followed up closely with PSL5mg/day. Four years later, she died from pneumonia. We report a case of pulmonary MALT in primary SjS and review the literature.

P3-242

A case of idiopathic nodular glomerulosclerosis and Fanconi's syndrome complicated with asymptomatic Sjogren's syndrome

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Conflict of interest: None

We would like to report a case of idiopathic nodular glomerulosclerosis and Fnacon's syndrome complicated with asymptomatic Sjogren's syndrome. A 8X-year-old man suffering from nephrotic syndrome and renal dysfunction had no prior history of diabetes mellitus, but had a history of hypertension and smoking. Laboratory findings on admission showed the positive antinuclear antibodies, anti-Ro/AA-S and SS-B. Schirmer's test showed decreased tear secretion and fluorescein staining showed marked bilateral superficial keratitis. A lip biopsy showed infiltration by small round cells. A kidney biopsy showed increased mesangial matrix with Kimmelstiel-Wilson-like nodules, glomerular basement membrane thickening and capillary microaneurysms. Glomerular involvement is much less common than interstitial nephritis in Sjögren's syndrome. We think that a discussion of the pathophysiology of idiopathic nodular glomerulosclerosis would be informative.

P3-243

Central nerve involvement secondary to Sjögren syndrome

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Conflict of interest: None

[Case presentation] A 56-year-old man noticed slurred speech with no precipitating cause. Magnetic resonance imaging (MRI) of brain showed an abnormal intensity in the white matter of the left temporal lobe. He started to take urokinase and ozagrel on a suspicion of cerebral infarction, but two weeks later, MRI showed an increase in the size of abnormal signal. To further investigate the cause of the brain lesion, he was admitted to our hospital. Positive results of anti-SSA/Ro and anti-SSB/La antibodies, pathology of the biopsied lip tissue and impaired secretory function of salivary gland led us to a definite diagnosis of Sjögren syndrome according to the classification criteria of Ministry of Health, Labour and Welfare. Corticosteroid therapy quickly improved his clinical sumptoms in parallel with decrease in the size of the brain lesion on MRI. [Conclusion] The central nerve involvement secondary to Sjögren syndrome is sometimes similar to Multiple Sclerosis with regard to clinical features and image findings. Sjögren syndrome should be considered as a possible underlying disorder in the diagnosis of white matter lesions.

P3-244

Efficacy and safety of Tocilizumab (TCZ) on refractory polymyalgia rheumatica (PMR)

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Conflict of interest: None

[Objective] The objective of this study was to investigate the efficacy and safety of TCZ on refractory PMR. [Methods] We treated 4 refractory PMR patients with TCZ. Disease activity and drug tolerability were assessed clinically, by laboratory tests every month during TCZ therapy. [Results] All patients were female. 2 patients were treated with Methotorexate (MTX). 1 patient were diagnosed with diabete, 1patient with glaucoma, 4 patients with osteoporosis, 1 patient with the liver dysfunction, 2 patients with interstitial pneumonitis. The daily prednisone dosages before and after TCZ initiation were 2-7.5 mg/day and 0-2.0 mg/day. Erythrocyte sedimentation rate declined from 19-59 mm/hour to 2-8 mm/hour. CRP declined from 0.4-2.5 mg/dL to < 0.1 mg/dL. Dr's VAS declined from 1-48 mm to 0-4 mm. Patient's general health VAS declined from 20-41 to 10-26 mm. Health assessment questionnaire (HAQ) declined from 0-0.125 to 0. PMR activity score declined from 3.6-21.7 to 0-2.4. All patients entered and maintained clinical remission during TCZ therapy with no adverse effect. No patient were worsened the comorbidities. [Conclusion] The results of these date suggested that TCZ therapy may be effective and safe in refractory PMR.

P3-245

Cancer in patients hospitalized with polymyalgia rheumatica

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Conflict of interest: None

【objectives】There are some studies reporting cancer risk with polymyalgia rheumatica (PMR). Although several studies have failed to demonstrate any deviation from the expected malignancy rate in patients with PMR, there is a study reporting that patients hospitalized for PMR had an increased risk of cancer. We examined the incidence of cancer in PMR in our hospital.【Materials】We used the records of the hospital patients who were first diagnosed as having PMR from September 2006 until July 2013 in our hospital.【Result】We evaluate a total of 63 patients. Malignancy was registered in 7 patients (11%). The malignancy were: papillary adenocarcinoma of thyroid (n=1), lung cancer (n=1), breast cancer (n=1), and gastric cancer (n=2). One patient had 2 malignancies: malignant lymphoma and squamous cell carcinoma of buccal mucosa 7 years before diagnosis of PMR. We compared the patients with cancer and the patients without cancer about age, gender, laboratory date, and so on. The analysis showed there is not much difference between two groups about laboratory date and their back ground. The former tend to undergo an endoscopic examination and chest~pelvic contrast enhanced CT. We thought that it is important that to make a thorough examination of cancer when we diagnose PMR.

P3-246

An example of RS3PE syndrome caused by DPP-4 inhibitor administration with bilateral pleural effusion

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Conflict of interest: None

(Case) 77y.o. male with Diabetes. DPP-4 inhibitor were used for the treatment. (P.I) The patient felt abdominal pain. For admission in our hospital, bilateral pleural effusion and slight fever were recognized. Inflammation data (ESR, CRP) were recognized high. Recognizing edema and pain of hands and feet, he visited orthopedic department. As collagen disease was suspected he was referred to Department of rheumatology. RS3PE syndrome caused by DPP-4 inhibitor administration was diagnosed for his symptom and laboratory data including increase of CRP, acceleration of ESR, increase of MMP-3, anti CCP antibody negative. DPP-4 inhibitor was discontinued, Prednisolone 10mg per day was started. After starting Prednisolone he recovered rapidly from his complaint and inflammation and pleural effusion disappeared. (Conclusion) RS3PE syndrome has been reported to be associated with VEGF which is vascular permeability factor. There are also reports of an increase in VEGF with diabetic foot caused by DPP-4 inhibitor. We do not measure VEGF in this case, but association with DPP-4 inhibitor and VEGF was suspected. Report of RS3PE syndrome caused by DPP-4 inhibitor administration was seen, but there is no report of case with pleural effusion. We take this case rare and valuable one and report here.

P3-247

Assessment of predictive factors in pulmonary arterial hypertension associated with connective tissue disease

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Conflict of interest: None

[Objective] Pulmonary arterial hypertension (PAH) associated with connective tissue disease (PAH-CTD) had poor prognosis. We evaluated screening rate, diagnosis and treatment of PAH in our department and assessed useful screening of PAH. [Methods] Among outpatinets in our department from April 2011 to April 2013, we retrospectively reviewed 19 patients, performed right heart catheterization (RHC) after screening by transthoracic echocardiogram (TTE), if Right ventricle systolic pressure (RVSP)≧40mmHg. PAH was defined by a mean pulmonary arterial pressure of ≧25mmHg with a pulmonary capillary wedge pressure of ≦ 15mmHg. [Results] 14 systemic sclerosis, 4 mixed connective tissue disease, 1 systemic lupus ertthematosus patients were performed RHC. Although RVSP and serum NT-ProBNP had statistical significance, %diffusion capacity carbon monoxide (DLCO), %vital capacity (VC) and ratio of both had not statistical significance. Receiver operating characteristic analysis on PAH was performed, sensitivity and specificity on RVSP≧ 50mmHg was 83.3%, 76.9%, NT-ProBNP>250 pg/ml was 100%, 84.6%, %DLCO<60 was 80.0%, 53.9%, %VC/%DLCO>1.4 was 60.0%, 76.9%. [Conclusion] RVSP≧50mmHg and NT-ProBNP>250 pg/ml may be useful parameter as to PAH-CTD screening.

P3-248

Abatacept may be effective and safe in patients with AA amyloidosis secondary to rheumatoid arthritis

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Conflict of interest: None

[Objectives] To examine the efficacy and safety of abatacept (ABT) in patients with amyloid A (AA) amyloidosis secondary to rheumatoid arthritis (RA), and to speculate about the immunologic association of ABT with AA amyloid deposit regression. **[Methods]** We administered ABT to 70- and 65-year-old Japanese women with RA and AA amyloidosis, quantified serum cytokine concentrations, and analyzed regulatory T lymphocytes (Treg cells). We also studied AA amyloid deposits via histo- and immunopathology. **[Results]** ABT improved rheumatoid inflammation and AA amyloidosis. Serum levels of interleukin-6 and tumor necrosis factor a decreased, but serum interleukin-2 concentrations did not change. $CD4^+CD25^{++}FoxP3^+$ Treg cells gated on T lymphocytes and $CD4^+$ T lymphocytes decreased. One case still had AA amyloid deposits despite normalized rheumatoid inflammation, with polymorphonuclear leukocytes and macrophages infiltrating tissues containing AA amyloid. **[Conclusion]** ABT demonstrated efficacy and safety in AA amyloidosis secondary to RA and affected Treg cells and inflammatory cytokines. AA amyloid fibril turnover in these patients may involve an immunologic mechanism. Phagocytes seemed to have an important role in AA amyloid fibril regression, which suggests an immunologic interaction.

P3-249

Tocilizumab treatment for Sweet's syndrome initially presented with eosinophilia complicated by refractory hepatitis

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Conflict of interest: None

A 66-year-old man developed erythematous papules accompanied by eosinophilia and increased levels of C-reactive protein (CRP). A skin biopsy revealed eosinophil infiltration and he was diagnosed as hypereosinophilic syndrome. Twenty mg of prednisolone was initiated with immunosuppressive agents, such as CyA. Although eosinophilia was improved, some papules continuously developed. A second biopsy showed neutrophil and lymphocyte infiltration. Therefore, he was diagnosed as Sweet's syndrome (SS). Because of persistent liver enzyme elevation and elevated CRP level, steroid dose was increased. However, liver enzymes were not improved. A liver biopsy showed periportal and pericentral vein infiltration predominantly with neutrophils, suggesting liver damage associated with SS. Tocilizumab (TCZ) was started based on high levels of serum IL-6. This is an atypical case of SS, which initially accompanied with eosinophilia and was complicated by persistent hepatitis. Previous studies have shown the effectiveness of biologics for SS including IL-1 receptor antagonist and TNFα inhibitors. This report firstly describes the clinical use of TCZ in patients with refractory SS. Considering that some cases of SS indicated high serum levels of IL-6, TCZ could be a candidate therapy for refractory SS.

P3-250

A male case of Lögren syndrome diagnosised by video-assisted thoracic surgery

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Conflict of interest: None

A 34-year-old male had low back pain and some large joints arthralgia. He was admitted because of fever, poryarthralgia and panniculitis of both lower extremities. Blood tests gave no clue of the diagnosis. Because CT revealed a large number of lymphadenopathy including the pulmonary hilar region, inguinal lymph node biopsy was performed. But there was no evidence of malignancy nor inflammation. Biopsy of the panniculitis of legs was performed, and it coincided in erythema nodosum. Without any treatment, the CRP level decreased, and even CT confirmed the reduction of the lymph node, but the abnormality accumulation to bilateral hilar lymph nodes (BHL) was recognized by Ga scintigraphy. So BALF, TBLB under a bronchoscope were performed, but the meaningful views were not provided. The biopsy under the video-assisted-thoracic surgery was performed, it led to a diagnosis of the sarcoidosis in acknowledgment of a noncaseating epithelioid granuloma to hilar lymph nodes, intrapulmonary lymph node. We diagnosed this case as Löfgren syndrome. The Löfgren syndrome is acute sarcoidosis assume BHL, arthritis, erythema nodosum 3 signs. It is often seen in North Europe and a British woman, but there is extremely few in Japanese men. This is second male Löfgren syndrome in Japan.

P3-251

A case of Takayasu arteritis complicated with occlusion of pulmonary and coronary arteries

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Conflict of interest: None

A 45 years old woman visited our hospital for consolidation on chest radiography in 2008. Although she was treated for a diagnosis of organizing pneumonia, serum level of C-reactive protein (CRP) remained high. In 2013, Computed tomography (CT) showed thickening of the vessel

wall of aorta, its branches and pulmonary arteries. The left subclavian artery and main pulmonary artery were fully occluded and the left lung was atrophic. CRP was elevated to 6.02mg/dl, and the result of human leukocyte antigen (HLA) typing analysis was B52 positive. Angiography showed severe aortic valve regurgitation (Sellers classification III/IV). Right coronary artery and left main pulmonary artery was completely occluded, and the collateral circulations were developed from the left coronary artery. She had no symptoms such as angina and syncope. She was diagnosed with Takayasu arteritis (TA) and treated with PSL40mg daily, resulting in immediate improvement of CRP. TA is a large vessel vasculitis that primarily affects aorta and its major branches, coronary arteries, pulmonary arteries, and so on. Here we report a rare case of TA presenting with multiple arterial involvement.

P3-252

A case of Churg-Strauss syndrome (eosinophilic granulomatosis with polyangitis) with small intestinal bleeding and sigmoid colon perforation

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Conflict of interest: None

We report a case of Churg-Strauss syndrome in a 53-year old woman, who was complicated with small intestinal bleeding and sigmoid colon perforation. In September 2010, she admitted to our hospital with a chief complaint of upper and lower limb numbness. We diagnosed her Churg-Strauss syndrome. She received steroid, cyclophosphamide pulse therapy and intravenous immunoglobulin therapy concomitant with oral corticosteroid treatment. In December 28, 2012, she readmitted to our hospital due to appetite loss and persistant fever. We increased the amount of corticosteroid to 40mg/day (1mg/kg/d). In January, 2013, she recovered appetite loss and became afebrile. In Feburary 6, she suddenly had massive melena. In Feburary 21, enhanced CT scan showed a fresh small intestinal bleeding and transarterial embolization was carried out. In March 3, she had acute abdomen. At the operation, we found a perforation of the sigmoid colon and colostomy was performed. The part of small intestine resection was also necessary. In pathological study, a perforation of necrosis of the sigmoid colon and necrosis and ulceration of the small intestine were seen. It is important to be careful for complication of intestine in treatment of Churg-Strauss syndrome.

P3-253

Osseous sarcoidosis diagnosed by bone biopsy treated with golimumab: a case report

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Conflict of interest: None

A 40-year-old woman was referred because of erythema on her nose and pain of right thumb with 3-years duration. Erythema was diagnosed lymphadenosis cutis benigna by a community dermatologist and treated with laser, but was ineffective. Erythema was re-diagnosed suppurative and glanulomatous dermatitis on skin biopsy. Prednisolone and antibiotics were prescribed, with little effect. Right thumb pain was diagnosed dischondroplasia by a community orthopedist based on hypertransradiancy on first proximal phalanges. She had a pathological fracture on right thumb and biopsy revealed noncaseating granuloma. Chest X-ray showed bilateral hilar lymphadenopathy and serum ACE was 35.4U/mL. She was diagnosed salcoidosis and admitted to our hospital. Chest CT showed small diffused nodules on both lungs. Bone scintigraphy showed high absorbers on right thumb and tarsal bones. Foot MRI (T2) showed high signal intensity on talus and cuboid bone. Right thumb lesion infiltrated to flexor pollicis longus. Since granuloma formation is promoted by TNF-a, TNF-a inhibitor golimumab was administered and osseous lesion was markedly contracted. This is the first case of osseous sarcoidosis which was successfully controlled by golimumab.

P3-254

The case of neurosarcoidosis that presented a mononeuritis multiplex pattern and nodular lesion of lung

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Conflict of interest: None

[Case] 27 years old, male. [Chief Complaint] Fever, numbness of extremity. [Present illness] Numbness of his fingers appeared from February, 2009, and general fatigue and difficulty of movement presented at the beginning of August. He had fever at 37°C, and leg edema and numbness of both lower limbs from middle of August. He consulted our hospital on August 31 and hospitalized for the purpose of a close inspection. [Progress] The cutaneous sensation presented a mononeuritis multiplex pattern, and the chest X-rays revealed bilateral hilar lymphadenopathy and nodular lesion of lung. We performed biopsy from sural nerve, hilar lymph node, and lung, and he was diagnosed with neurosarcoidosis. After the dose of predonisolone (PSL) was tapered to 5mg/day gradually, peripheral neuropathies have been well controlled for 4 years with no severe adverse events. [Consideration] e experienced a case of sarcoidosis involved in peripheral nerves. After oral administration of 1mg/kg/day of PSL was started, the neurologic findings improved and nodular lesions of lung reduced.

P3-255

A case of Addison's disease due to sarcoidosis

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Conflict of interest: None

The patient was a 52-year-old male. In the course of four months, limb muscle pain, cough, wheeze, general fatigue, skin brown change and loss of appetite appeared. For serum ACE and lysozyme elevation and accumulations in FDG-PET/CT scan in swollen hilar and mediastinal lymph nodes, skin and muscles, sarcoidosis was suspected. Biopsy of gastrocnemius muscle that had accumulation in FDG-PET proved epithelioid cell granulomas. Further, endocrinological examination showed peripheral adrenocortical insufficiency; plasma ACTH 1240pg/ml (7.2-63.3), serum cortisol (CS)<1.0pg/ml (4-18.3), aldosterone<10.0pg/ml (29.9-159), urinary CS<4.5mg/day. Pituitary function was normal. Therefore, He was diagnosed as sarcoidosis and Addison's disease. We started treatment with PSL40mg (0.8mg/kg)/day. He developed steroid psychosis on the fourth day, and PSL was reduced to 10mg/day. Steroid psychosis subsided promptly thereafter. ACE, aldosterone, urinary CS and symptoms improved in two weeks. In summary, although cases of pituitary dysfunction due to sarcoidosis have been often reported, the case of Addison's disease due to sarcoidosis is extremely rare. In addition, it is speculated that upregulation of steroid receptors caused by Addison's disease enhanced both effects and side effects of PSL.

P3-256

A Case of Sarcoidosis with Acute Onset of Arthritis

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Conflict of interest: None

A-52-year-old female had suffered from bilateral digital pain, swelling and morning stiffness for about 4 years. She visited our hospital for the left digital pain lasting for one week. Her multiple digital joints

showed the swelling with tenderness including left their MP joint. The serum C-reactive protein was 0.12 mg/dl, and the erythrocyte sedimentation rate was 23 mm/hour. Rheumatoid factor and anti-CCP antibody were both negative. The joint ultrasonography revealed the presence of an active synovitis. Hand X-ray revealed cystic and lacy lytic patterns. The chest X-ray and CT showed bilateral hilar and mediastinal lymphadenopathy. The serum levels of angiotensin converting enzyme, lysozyme, and calcium were within normal limits. T-SPOT was negative. The examination on bronchoalveolar lavage fluid revealed an increased lymphocytic proportion and elevated CD4/CD8 ratio (4.87). Although a histological study on specimens obtained by transbronchial lung biopsy didn't reveal the present of granuloma, skin biopsy from erythema of the left eyebrow showed the epitheroid granuloma. The hand MRI showed small nodule and marrow signal changes. Taken together we diagnosed this case as bone sarcoidosis. [Conclusion] Sarcoidosis should be recognized as a possible cause of polyarthritis.

P3-257

A Case of Felty's syndrome with autoimmune pancytopenia

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Conflict of interest: None

A 60-year-old female with a history of rheumatoid arthritis for 25 years was admitted to our hospital with neutropenia. She had been treated with methotrexate and etanercept. Her blood test showed pancytopenia (WBC 1000/μL [neutrophil 100/μL], Hb 9.4/dL, Plt 9.9×10^4/μL) and positive anti-ds DNA antibody. Although methotrexate and etanercept were discontinued and folic acid was administered, pancytopenia was getting worse. Splenomegaly was recognized in abdominal CT and bone marrow examination showed hyperplastic bone marrow and did not show dysplasia. In addition, anti-neutrophil antibody, anti-platelet antibody and Coombs' test were all positive. We diagnosed her with Felty's syndrome with autoimmune thrombocytopenia and autoimmune hemolytic anemia. By steroid pulse therapy followed by oral predonisone 40mg/day and low-dose cyclosporine A, neutrophil was increased and anemia and thrombocytopenia were improved. She had similar characteristics to SLE, however, she did not fulfill the ARA diagnostic criteria for SLE. Although patients of Felty's syndrome often have various autoantibodies, it is rare to have anti-platelet antibody. This is the first report, to our knowledge, of a case of Felty's syndrome associated with autoimmune hemolytic anemia and autoimmune thrombocytopenia.

P3-258

Tocilizumab is useful for treating polymyalgia rheumatica (PMR): five cases of intractable PMR ameliorated by tocilizumab treatment

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Conflict of interest: Yes

[Aims] To clarify the efficacy and safety of tocilizumab (TCZ) for intractable PMR. **[Method]** We evaluated all the PMR patients who had been treated with TCZ from April, 2008 to November, 2013. **[Results]** Five PMR patients (2 males and 3 females) were treated with 8 mg/kg TCZ every 4 weeks. Mean age was 69.4 (65-80) years. All patients had complications such as osteoporosis, diabetes mellitus, and hypertension. None had temporal arteritis. Mean observation period was 10.2 (3-18) months. TCZ promptly improved PMR symptoms; proximal muscle pain disappeared in 11 (4-23) weeks on average; duration of morning stiffness decreased from 450 min (0-1440) at baseline to 60 (0-180) min at 3 months. Patients' pain VAS and general VAS were improved from 51 (25-92) and 57 (33-90) at baseline to 9 (0-27) and 15 (0-31) at 3 months, respectively. Mean HAQ-DI was improved from 1.1 (0-2.75) at baseline to 0.6 (0-1.75) at 3 months. Mean CRP level and ESR were improved from 4.65 (0.86-14.72) mg/dL and 56.4 (20-99) mm/h at baseline to 0.29 (0.01-1.37) mg/dL and 1-23 mm/h at 3 months. PSL dose decreased from 7.4 mg/d (0-14) at baseline to 4.4 mg/d (0-9) at 3 months. All patients continued TCZ treatment without adverse events. **[Conclusion]** TCZ is effective and well-tolerated in patients with intractable PMR.

P3-259

Case report; A case of Epstein-Barr Virus-Induced Hemophagocytic Lymphohistiocytosis with posterior reversible encephalopathy syndrome

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Conflict of interest: None

A 51-year-old female with Adult Onset Still's Disease was transferred to our hospital for insufficient response to high dose predonisolone in her previous hospital. After increasing a steroid in quantity, fever and the impaired liver function were improved temporarily. But on 15th day in our hospital, fever and liver function were recieved and pancytopenia was revealed. As there were EBER positive cells in bone marrow biopsy, we diagnosed EBV-HLH (Epstein-Barr Virus–Induced Hemophagocytic Lymphohistiocytosis) and changed prednisolone 50mg/day to betamethason 5mg/day, added cyclosporin, plasmapheresis, and IVIG. On the 27th day in our hospital disturbance of consciousness and left side paralysis were occurred suddenly and head MRI diffusion emphasis image showed multiple high intensity area. However, the neurologic symptoms were improved from the next day without additional any treatment, and the high intensity areas in the head MRI were disappeared over time and improved pancytopenia. It was possible that she developed posterior reversible encephalopathy syndrome (PRES) due to EBV-HLH and PRES was improved by immunosuppressive therapy.

P3-260

Two cases of myelitis with taking immunosupressants

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Conflict of interest: None

Case 1: 63years old woman with Rheumatoig Arthrilits for 4years. 4weeks before admission, she started to feel abonormal sense from sole of her right foot and reached to her right hip after 2 weeks. She had high intensity region from Th11 to L1 in MRI, and had 338/3 cell counts of cerebrospinal fruid. We cannot catch the cause of myelitis and presume inflammatory cause. We performed mPSL pulse, then did 50mg/day PSL. Her symptoms and MRI high intensity area disappeared. Case 2: 47 years old woman emerged diagnosed SLE 6months before, and took 10mg of PSL, 3mg of Tacrolimus, 300mg of Mizoribine. She had right Th4-5 VZV infection 4weeks before admission. 4days before, she realized loss of pain of her left leg. She lost left leg's thermal nociception under Th4-5 and rihgt leg's and had right leg's muscle weekness. mPSL pulse was performed for 3days and she took 1mg/kg/day PSL, but symptoms did not improve. It should be noted myelitis under imunosuppression.

P3-261

Clinical characteristics of a case with HTLV-1 associated arthropathy (HAAP)

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Conflict of interest: Yes

A 63-year old woman was admitted to our Department because of polyarthralgia. Ten years before admission, she felt weakness of her left leg with left gonalgia. Though HAM was suspected by a local neurologist first, that was denied by a specialized hospital. Three years before admis-

sion, she started having joint pains on her wrists with swelling. Because polyarthritis developed gradually, she was referred to our Department. On examinations, her joints of extremities were swollen symmetrically and the numbers of tender and swollen joints among 28 assessed were 3 and 7, respectively. Serum anti-CCP antibody level was 125.0 U/ml. The blood and the synovial fluid anti-HTLV-1 antibody tests were positive, HTLV-1 proviral DNA in her blood was detected, and atypical lymphocytes with clover-leaf nucleus were found in her synovial fluid. An MRI of her wrist showed mild synovitis but very little erosive change. Taken together, she was diagnosed as HAAP without RA. She was also diagnosed as HAM by the neurological examination. Considering unknown effects of MTX or biologics on HTLV-1 infection, SASP was administered. Although the signs and symptoms of this HAAP case were similar to RA, it was hard to conclude the coexistence of long-lasting RA without typical joint destruction.

P3-262

HTLV-1-associated arthropathy: a case report

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Conflict of interest: None

A 59 year-old male had suffered from bilateral shoulder pain for 1 year before his first visit to a hospital. Since atypical cells in peripheral blood and a positive HTLV-1 antibody were found, he was referred to our hospital. He had arthritides in wrist, knee and ankle joints as well as slight swelling in finger joints. Lab exams showed elevated CRP and marginal ESR levels with negative RF and ACPA. Although high level of HTLV-1 provirus in PBMCs was detected by RT-PCR, proviral integration assessed by Southern blot analysis was polyclonal, suggesting that definite ATL was negated. X-ray findings lacked those of RA, while MRI of his wrist and knee joints disclosed the presence of synovitis. Histological findings of synovial tissues from his knee joint demonstrated massive invasion of lymphocyte-like cells having a nuclear atypism. Based on the immunohistochemistry of surface antigens expressed in these cells, he was diagnosed as HTLV-1-associated arthropathy (HAAP) rather than RA. Treatment with methotrexate and prednisolone effectively ameliorated the disease activity. HAAP is closely related to high frequency of HTLV-1 provirus integration into peripheral lymphocytes. It should be noted that the symptoms are often difficult to be distinguished from those of RA.

P3-263

A case of primary cutaneous cryptococcosis which was developed during treatment of rheumatoid arthritis

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Conflict of interest: None

An eighty-two-year-old woman, who had developed rheumatoid arthritis at 68 year old and was treated with PSL 8 mg/day, MTX 6 mg/week, and CyA 100 mg/day, admitted to the hospital due to the left lower leg swelling and pain. She had bitten by a cat before the symptom developed, so we prescribed an antibacterial drug for bacterial cellulitis. However, her general condition didn't improve despite the use of antibacterial drugs, and all cultures were negative. We started a TNF-I because rheumatoid vasculitis was thought be the cause, and switched to an anti-IL-6 agent because of TNFI ineffectiveness. After that, her condition was getting better and discharged. But symptoms relapsed and re-admitted. Although there were no lung lesion, Cryptococcus neoformans was identified from skin tissue culture and we prescribed an antifungal drugs. She died in 4 months since she first developed symptoms. Generally, primary cutaneous cryptococcosis has good disease prognosis, however, we think it should be important for us to consider this disease as one of the differential diagnosis of cellulitis.

P3-264

Study on exacerbation non-tuberculous mycobacterial disease (NTM) in collagen disease patients of our hospital

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Conflict of interest: None

5411 cases of collagen disease patients in 10 years, we analyzed the course of the 10 cases that had a NTM. We were compared with seven cases of non-exacerbation characteristics with three cases that progression. All 10 cases, 5 cases of RA, MPA2, GPA1, SS1, DM1, use steroid of 6 cases, it was in use MTX in 3 cases. Of the exacerbation group, rather than the use of immunosuppressive drugs, including steroids and SS 1 cases. 2 cases, has had a causative organism MAC in three cases of exacerbation group M. kansasii was one case. MAC2, intracellular1, absessus1. Cavity type in 2 cases with NTM onset, breakdown was 1 case in both cases of non- exacerbation exacerbation. Low-dose macrolide has been administered in 4 cases in 10 cases of. 2 cases 3 cases of exacerbation cases is included and was administered from NTM after diagnosis. Administration had been started in NTM diagnosis before two cases of non- progression cases. In one example multiple drug therapy. There were also cases regardless of the treatment of the underlying disease, showed improvement in antibiotic treatment exacerbation group NTM. May result in deterioration of the NTM is treatment with low-dose macrolide monotherapy

P3-265

Milliary tuberculosis with highly elevated neutrophil CD64 in a patient with dermatomyositis

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Conflict of interest: None

[Case report] A 78-year old woman with generalized muscle weakness was admitted to the hospital. She was diagnosed as dermatomyositis with typical rash, elevated CK, positive anti-Jo-1 antibody and myogenic electromyography pattern. Prednisolone therapy of 1mg/kg daily improved her condition. Before starting the steroid, there was no sign of tuberculosis with chest CT and negative interferon-gamma releasing assay (IGRA). On the 58th day of admission, subcutaneous abscess of left arm appeared. M. tuberculosis was cultured from abscess and blood. Chest CT showed disseminated nodules in bilateral lung, which led to a diagnosis of milliary tuberculosis. At this time IGRA result was indeterminate. The number of CD64 on neutrophil was increased to 16674 molecules/cell (normal range <2000). After the tuberculosis treatment, neutrophil CD64 was improved. [Discussion] One of the most important complications in immunosuppressive therapy is infection. The number of CD64 molecule on neutrophil is a useful marker for infection. CD64 expression in tuberculosis infection tended to be much higher compared to any other type of pathogen in our hands as others reported elsewhere. This case illustrates the usefulness of neutrophil CD64 in immunosuppressed patients in whom IGRA can be indeterminate.

P3-266

Mycobacterium intracellulare-induced spondylodiscitis in a patient with rheumatoid arthritis

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Conflict of interest: None

A 76-year-old woman who was diagnosed with RA 20 years previously had been taking prednisolone 7.5 mg/day and methotrexate 6 mg/week. She was admitted to the hospital with a 1-year history of low back pain and a 3-month history of high fever. A MRI scan showed L4/5 discitis. Cultures prepared after lumbar puncture of the intervertebral disk were negative. PET-CT showed high accumulation in Th6 and Th-10, L4/5, and the left sacroiliac joint, and she was referred to our hospital. Results for blood culture, tuberculin test, and QuantiFERON were negative. Chest CT showed no evidence of old tuberculosis (TB). Because she had a familial history of TB, anti-TB therapy was administered. However, back pain and low-grade fever persisted 1 month after admission. Therefore, an MRI was performed again, which showed an epidural abscess. She then underwent a CT-guided needle biopsy. The tissue sample showed granuloma with necrosis. PCR indicated the presence of *M. intracellulare*. We diagnosed the patient with *M. intracellulare*-induced spondylodiscitis. Cases of *M. intracellulare*-induced spondylodiscitis in patients without HIV infection are very rare. When clinicians encounter a case of spondylodiscitis of unknown etiology, CT-guided needle biopsy may help with establishing diagnosis.

P3-267

Mycobacterium intracellulare infection of the bilateral knee joints: a case report

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Conflict of interest: None

[Objectives] To report a case of mycobacterium intracellulare infection in the bilateral knee joints. [Case] We report a 49-year-old male with an eight year history of polymyositis treated with steroid therapy. He had bilateral knee pain for recent three years and invasive tenosinovitis in the bilateral knee joints and popliteus bursa. He underwent arthroscopic synovectomy and popliteal bursa excision of the bilateral knee joints. He received biological therapy in a diagnosis with an acute exacerbation of rheumatoid arthritis, but didn't lead to improvement in the knee arthritis. After mycobacterium intracellulare infection of the bilateral knee joints was detected, he received chemotherapy and lead to improvement in the knee arthritis. [Conclusion] It is important to distinguish mycobacterium avium-intracellulare infection from rheumatoid arthritis in recurrent tenosinovitis of compromised patients.

P3-268

A case of polyarthritis caused by *Mycobacterium abscessus* infection which required the differential diagnosis with rheumatoid arthritis

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Conflict of interest: None

A 66-year-old man suspected of having rheumatoid arthritis was referred to our hospital. He developed the right wrist and the left knee pain and swelling for 2 years, and the joints swelling had been diagnosed with cellulitis at the time of the onset. 4 months before admission, he had been diagnosed with rheumatoid arthritis and prednisone 20 mg/day had been administered. On physical examination, skins over the swelling joints were edematous and the ulnar deviation was observed. His white blood cell count was 9400/μl and C-reactive protein was 0.43mg/dl. RF, FANA, ACPA, and other disease specific autoantibodies were negative. X-ray examination showed periosteal reaction in the metaphysis of the right radius and the left metatarsal bones, and the narrowing of the right radiocarpal joint and the left tarso-metatarsal joint was observed. Synovectomy of the right wrist joint and the left Lisfranc's joint was performed, and *Mycobacterium abscessus* was identified in the purulent effusion and the synovium obtained from the joints. Joint inflammation caused by non-tuberculous mycobacterial infection is important as a differential diagnosis of rheumatoid arthritis.

P3-269

Arteriosclerosis in Patients with Rheumatoid Arthritis

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Conflict of interest: None

Objective: Patients with rheumatoid arthritis (RA) *are at increased* risk of cardiovascular (CV) events compared to the risk in the healthy population. The present study aimed to compare the risk of arteriosclerosis between patients with RA and those with lifestyle diseases (hypertension, diabetes, and dyslipidemia) by measuring the maximum intima-media thickness (max IMT) and pulse wave (ABI and baPWV). **Patients and Methods:** This study included 32 patients with RA (mean age, 64.9 years) and 117 patients with lifestyle diseases (mean age, 65.3 years). IMT and pulse wave were measured using SSA-660A (Xario™) and Form™, respectively. **Results:** The mean values of max IMT, ABI, and baPWV were 1.35 mm, 1.08, and 1754 cm/s in the RA group and 1.30 mm, 1.14, and 1753 cm/s in the lifestyle diseases group, respectively. The max IMT values in patients aged≤ 65 years and those aged ≥66 years were 1.17 and 1.50 mm in the RA group and 1.19 and 1.39 mm in the lifestyle diseases group, respectively. **Discussion:** There were no significant differences in IMT values between the RA and lifestyle diseases groups. However, patients with RA aged ≥66 years had high IMT values, suggesting that particular attention should be paid to the risk of CV events in older RA patients during treatment.

P3-270

Maintenance of Long-term efficacy with entecavir in rheumatoid arthritis patients who have shown reactivation of hepatitis B under immunosuppressive therapy

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Conflict of interest: None

Reactivation of hepatitis B virus (HBV) is a frequent complication of immunosuppressive therapy in patients with HBV infection. Entecavir has been known to provide sustained viral suppression with minimal resistance in long-term treatment of chronic hepatitis B (CH-B). But the benefits of long-term treatment of entecavir for rheumatoid arthritis (RA) patients with chronic HBV infection who are under the immunosuppressive treatment are not known. We present three RA cases with chronic HBV infection: one is a HBV carrier while the other two show evident reactivation of HBV infection with abnormal liver function tests. While under the sustained immunosuppressive therapy over more than five years, they all have maintained normal liver function with sustained suppression of HBV-DNA with entecavir.

P3-271

Successful treatment of a severe Castleman disease with mediastinum mass, marked pleural effusion and ascites, disturbance of consciousness and DIC by using Tocilizumab

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Conflict of interest: None

A 45-year-old man was admitted to our hospital because of chest pain, an anterior mediastinal mass and marked bilateral pleural effusions and ascites. The patient was diagnosed as multicentric Castleman disease (MCD) with a mixed type of hyaline vascular type and plasma cell type

by biopsy of the mass. At the time of diagnosis, C-reactive protein (26mg/dL) and plasma IL-6 level (457pg/mL) were very high levels. Additionally, the patient showed a serious condition with disturbance of consciousness, DIC, and renal dysfunction. Although the patient was started methylprednisolone pulse therapy, no clinical response was observed. Tocilizumab was administered, because of refractory steroid therapy. About 2 weeks later, general condition tended to improve. The marked pleural effusions and ascites were remarkably improved, so the patient lost 27 kilograms in weight for 3 weeks. Five month later, plasma IL-6 level was decreased to the normal and the mass was remarkably reduced. Recently some cases of Castleman disease with thrombocytopenia, pleural effusions, ascites, and renal dysfunction were reported. We report this case with discussion from literatures.

P3-272

Cardiac involvement in EGPA patient

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Conflict of interest: None

【case】A 38-year-old woman was diagnosed with Eosinophilic Granulomatosis With Polyangiitis (EGPA) because of based upon the symptoms of bronchial asthma, eosinophilic pneumonia, peripheral blood eosinophilia, and palpable purpura on lower leg. she had chest pain and dyspnea. Complete right bundle branch block (RBBB) and negative T waves was seen on 12-lead electrocardiogram and biomarker of heart disorders were elevated. Coronary angiography and endomyocardial biopsy perfomed in this patient results nothing particular. They are with peripheral blood eosinophilia. We diagnosed the patient as EGPA with cardiac involvement and started to treat with high dose corticosteroids and addmition immunosuppression. After initiation of therapy, she have resolution of symptoms, peripheral blood eosinophilia, biomarker of heart disorders, 99mTc-tetrofosmin myocardial scintigraphy, and exhaled NO. 【discussion】althou ther are many cardiac involvement with EGPA, sometimes endomyocardial biopsy cannot get a typical pathological findings. To get a typical pathological findings, we have to do biopsy for the right site at the right time. At the other extreme, myocardial scintigraphy can reveal microlesion. In this case, we cannot see the lesion by biopsy, but can see it by myocardial scintigraphy.

P3-273

The study of autoimmune related data for Fibromualgia

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Conflict of interest: None

[Objectives] Patients diagnosised for Fibromyalgia (FM) were anayized with some data as one of autoimmune diseases. The objects of this examination is to include FM into some autoimmune diseases. [Methods] In 126 patients who have some pain as FM, some labo data were checked. These dataes include ESR, CRP, FDP, FDP-D dimmer, ANA, Anti-DNA antibody, Anti-SS-A antibody. Gd enhanced MRI of hands was examined for all patients of FM diagnosised to exclude early RA. [Results] 126 patients are fulfilled criteria of FM. But 16 patients (12.7%) can be diagnosised as early RA. To partial patients who have dataes including FDP, FDP-D dimmer, TAT wer elevated, low dose of steroid can be effective to decrease their FM's pain. In 78 patients (61.9%), ANA is positive, and in 12 patients (9.5%), anti SS-A antibody is positive. [Conclusion] Some labo data of FM are similar to the data of autoimmune disease. Some species of inflammation data are recognized and low dose steroid can be effective for some case of FM. So we must take FM as autoimmune disease and check some inflammation data to exclude other autoimmune disease as RA.

P3-274

Methotrexate-induced pneumonia in a rheumatoid arthritis patient manifesting peripheral edema as an initial symptom: a case report

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Conflict of interest: None

Methotrexate (MTX) has been frequently used as an anchor drug in rheumatoid arthritis (RA) treatment. It has become possible to select carefully the subject of administration in recent years because experience of MTX treatment is rich. Therefore an opportunity to encounter serious adverse events is decreasing. However it is still necessary to pay attention to the emergence of adverse events constantly. A 71-year-old woman had developed RA in 1981. She was prescribed MTX from June 2012 for RA disease activity is increased. Though her articular symptoms has improved, peripheral edema appeared from November, and then she was hospitalized with the interstitial pneumonia complained of respiratory discomfort. She recovered by treatment of steroid and diuretic. We sometimes experience the interstitial pneumonia as an adverse event by MTX. In this case it has developed with oliguria, peripheral edema and pleurisy, and involvement of heart failure was also considered from mild rise of BNP level and echocardiographic findings.

P3-275

Two cases of osseous sarcoidosis

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Conflict of interest: None

Symptomatic osseous sarcoidosis is rather rare affecting 1 -2 % of sarcoidosis. We report 2 cases of osseous sarcoidosis. The first case is a 44 years-old woman who was referred to us in Feb. 2013 because of polyarthritis. She had been diagnosed as sarcoidosis in 2009 based on chest CT, BAL finding, etc. A hand X-ray film showed cystic changes in proximal, middle and distal phalanges, which showed low density in T1weighted images. The diagnosis of osseous sarcoidosis was made and she is being followed up without treatment. The second case is 63 years-old woman who visited our hospital because of polyarthritis. Based on the character and distribution of arthritis, positive ant-SSA antibody, and sicca symptom, she was diagnosed as RA and SjS. In 2005, another attending physician doubted that she is not RA because there was a cystic change in a middle phalange and the joint surface was rough. The diagnosis of sarcoidosis was made from the chest CT findings (small nodules, reticular shadows), BAL findings (CD4/8 = 3), negative STS, elevated serum lysozym level, and a granuloma in a skin biopsy specimen. Although the frequency of osseous sarcoidosis is not high, sarcoidosis should be taken into consideration when cystic changes are present in digit bones.

P3-276

Analysis of clinical features of pseudogout in our hospital

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Conflict of interest: None

[Objectives] Psedogout occurs as acute arthritis, and some cases show as recurrence. The related factors of recurrence of acute arthritis is uncertain. To elucidate the related factors for the recurrence of peudogout attack, we studied clinical features of pseudogout cases in our hospital. [Methods] The subjects were 62 cases in Aki-Ohta Hospital from January 1st 2010 to June 30th 2013 (25 for male and 37 for female, mean age was 83.8 ± 7.5 years old.). Clinical findings including trigger, complication, and blood chemistry data were retrospectively compared. [Results and conclusion] Period showing arthritis was 7.8 ± 5.0 days. Most cases improved after received single injection of corticosteroid into joint-space. Single arthritis for 41 (66.1%) and triple arthritis for 3 (4.8%) were rec-

ognized. Triggers of onset of arthritis were injury/surgery for 16 (25.8%), infection for 10 (16.1%), cerebrovascular disease for 4 (6.5%), and heart failure for 5 (8.1%). 13 cases (21.0%) showed recurrence and the average period was 8.7 ± 9.0 months. The clinical features related to recurrence were advanced age and episode of sudden onset. Gender, length of the symptoms, WBC count, serum CRP, and complication did not showed statistically significant difference.

P3-277

An example of a protein S deficiency developed severe leg ulcers

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Conflict of interest: Yes

22-year-old man. He had fever and polyarthritis and skin lesion of the lower leg in 2005. They examined him because of suspected collagen disease but did not diagnose. In skin biopsy recognize the findings of vasculitis vein center. While undiagnosed, immunosuppressant and steroid is administered. It was calm in warfarin and PSL5mg the past 5 years. Our hospital dermatology introduction complained ulcer appeared later insect bites leg in 2012, there is no improvement. We went in our department the scrutiny of the presence or absence of collagen disease that lead to leg ulcer. We showed a decrease in protein S activity in blood collection (<10%). Was re-examination by switching to heparin in order to deny the possibility of protein S reduced activity by warfarin orally, but protein S activity was as low as 11% also, and protein S deficiency was diagnosed. Is an enforcement plan to skin grafting for future ulcer part. Association with clinical symptoms collagen disease in 2005 was suspected is unknown, intractable leg ulcers this is considered primarily due to venous stasis due to protein S deficiency, was a valuable case-provoking.

P3-278

The pain killers for fibromyalgia associated with obesity via ER stress

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Conflict of interest: Yes

Fibromyalgia (FM) is a chronic pain syndrome with unknown etiology. In addition to chronic pain, FM also accompanied by other symptoms such as the widespread musculoskeletalchronic pain, depression, fatigue and inflammatory and known one of the rheumatic disease. Since biomarkers for diagnostic and pathogenesis of FM have been unclear, the decisive treatments for FM have not been established. It was shown that new drugs, pregabalin and gabapentin which have the structural similarity to the inhibitory transmitter GABA, have clinical efficacy in neuropathic pain. However in addition to antipsychotics these drugs were reported to increase body weight as the side effect. Although it is thought that they affect on the central nervous system and promote appetite, that mechanisms could not explain the phenomenon well enough. Recently it is revealed that obesity associates with inflammatory, insulin resistance and endoplasmic reticulum (ER) stress. As E3 ubiquitin ligase Synoviolin functions in ER-associated protein degradation (ERAD) pathway and has important roles in inflammation and rheumatoid arthritis. We also found that Synoviolin implicated in obesity. In this study we assessed effects of the drugs on ER stress to clarify the mechanisms of obesity by the drug in FM patients.

P3-279

Assessment of psychological state and pain in patients with fibromyalgia and rheumatoid arthritis

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Conflict of interest: None

[Objectives] Assessed the correlation of psychological state and pain in FM or RA. **[Methods]** Depression was assessed with CES-D and STAI. Pain was evaluated by JFIQ in FM and pain-VAS in RA, respectively. Wilcoxon rank-sum or Peason chi-square test were used for significant difference test. Pearson correlation coefficient was used for the relevance of mental and pain. Stratified and covariance analysis were used for age compensation. **[Results]** 75 pts (M/F=9/66, Av. 46 yrs old) in FM and 128 pts (M/F=22/106, Av. 55 yrs old) in RA. Depression rate (CES-D: 16≤) and STAI (State) were significantly higher in FM compared with RA, while there was no significant difference in STAI (Trait) between FM and RA. There was significant correlation between CES-D and pain-VAS in RA. With or without the psychotropic agents in FM, the relevance of JFIQ and CES-D was not observed. On the other hand, the tendency in the association of pain-VAS and CES-D was observed in RA without biologics, but not in RA with biologics. **[Conclusion]** Depression and anxiety state were significantly stronger in FM. There was a significant correlation between depression and pain in RA especially without biologics.

P3-280

A case of Castleman's disease complicating with renal involvement and cerebral infarcts

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Conflict of interest: None

We report a case of multicentric, hyaline vascular variant of Castleman's disease (CD) complicating with renal thrombotic microangiopathy (TMA) and multiple cerebral infarcts. A 47-year-old male was admitted to our department due to prolonged fever and malaise. Laboratory data showed elevated WBC, CRP, and hyperkalemia. Antinuclear antibody, immunoglobulins were not remarkable. CT scan showed enlargement of axillary, paraaortic, inguinal lymph nodes. From the day 8, he showed disorientation and right hemiplegia. CSF showed albumin-cytological dissociation, and brain MRI revealed multiple cerebral infarcts of left hemisphere. Pathological examination of inguinal lymph node revealed hyaline vascular variant of CD, and renal biopsy showed TMA. After diagnosis of multicentric CD, treatment of high-dose corticosteroid and tocilizumab was started, but no improvement was obtained. He died on the day 62. Autopsy revealed systemic lymphadenopathy, renal TMA, and arterial stenosis around the circle of of Willis.

P3-281

Study on the characteristics of patients with rheumatoid arthritis and diabetes, and problems on treatment

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Conflict of interest: None

[Objectives] We sometimes find rheumatoid arthritis (RA) patients with diabetes mellitus. [Methods] We selected 10 RA patients with diabetes and 60 RA patients without diabetes in our department. We evaluated the difference clinical characteristics between two patient groups. [Results] All case composed of 1 male and 9 females, age is 69.1 ± 9.5 and duration 9.2 ± 9.0. In the stage classification Stage I is 2, Stage II is 5, Stage III is 1, Stage IV is 2, and the function classification Class 1 is 6 Class 2 is 4. Treatment for RA is infliximab 1, MTX alone is 2, MTX+SASP is 1, MTX+Tacrolimus and SASP is 1, SASP only is 3. MTX dose is 10.7±3.5 (6-10) mg/week. PSL is used in 2 cases and average usage is 4.3±4.6 (1-7.5) mg/day was. DAS28-CRP 2.02±0.99 (1.09-4.08), DAS28-ESR 3.44 ±1.35 (2.14-5.61), MMP-3 is 87.06±71.66 (33.6-272.2) ng/ml were. Compared to non-diabetic patients aged (v. s66.8±12.2 no age, no significant difference), staging of advanced patients (Stage II over 80%v.s68.6%). About drug for diabetes mellitus, insulin was used by 4 patients, 5 cases are taking oral drug. Average HbA1c (NGSP) of all cases is 6.8±1.1 (6.1 to 8.9) %. 5 cases were good controlled less than 7.0 %. [Conclusion] Many patients with diabetes complications more elderly in the active DMRADs must be considered.

P3-282

A case of rheumatoid arthritis presented generalized lymphadenopathy with caseating granuloma, and diagnosed with Hodgkin lymphoma after repeated biopsy

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Conflict of interest: None

[Case] A 71 year-old man with a history of rheumatoid arthritis (RA) for 15 years, who had been treated with methotrexate and a biologic agent, hospitalized for cellulitis of the right lower leg. The cellulitis was resolved with antibiotics, but intraperitoneal and bilateral inguinal lymphadenopathy were noted by ultrasound. Biopsy of the left inguinal lymph node revealed caseous granulomas with giant cells; he was started to administer anti-tuberculosis drugs as tuberculous lymphadenitis but high fever with chill persisted for 3 months. The PET-CT showed FDG uptake in many bones, liver, spleen, and lymph nodes in the intraperitoneal and inguinal areas. Biopsy of the right inguinal lymph node revealed Reed-Sternberg cells co-existing with caseating granuloma; the patient was diagnosed with Hodgkin lymphoma and transferred to another hospital for the treatment of lymphoma. [Conclusion] Tuberculosis and lymphoma must be listed in the differential diagnosis if the RA patient has fever with generalized lymphadenopathy. Aggressive examinations, including repeat biopsy and PET-CT, are required to confirm the diagnosis.

P3-283

Case report: A 76-year-old female with rheumatoid arthritis had treated with methotrexate (MTX) and prednisolone, developed intravascular lymphoma (IVL)

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Conflict of interest: None

In August 2011, Lactate dehydrogenase (LDH) showed an increase, but decreased naturally. LDH was increased again in August 2012, then we stopped MTX because LDH and soluble interleukin-2 receptor (sIL-2R) values were very high (LDH>1000 U/l, IL-2R: 4390 U/ML) and hepatosplenomegaly appeared. We did bone marrow biopsy and splenectmy to identify lymphoproliferative diseases, but these examination was normal. LDH and sIL-2R were naturally decreased again. In August 2013, she had hypoxia and impairment of consciousness, with LDH elevating again. This time, her both lung showed diffuse ground-glass shadow in chest CT. TBLB was done, it was diagnosed as intravascular lymphoma (IVL). About 2 years after the beginning of LDH elevation, we first time diagnosed it as IVL from lung shadow.

P3-284

A Real Survey for Collagen Disease Patients with Gastroesophageal Reflux Disease (GERD) our Institution

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Conflict of interest: None

[Objective] To clarify prevalence of gastroesophageal reflux disease (GERD) symptom and the effects of proton pump inhibitors (PPIs) in patients with collagen disease (CD). [Method] In this survey, 674 CD patients (M: 114, F: 560, mean age: 62.5 y.o.) were enrolled. We investigated patients' background and GERD symptom using GerdQ and evaluated factors that affected PPI therapy. [Result] As the underlying disease, 86.8% of patients had rheumatoid arthritis (RA), 15.1% of patients had other collagen disease (CD) except RA/ OA and 9.8% of them had osteoarthritis (OA) (there is overlap). More than half, 50.9% of patients were prescribed PPIs, 47.0% of them were Non-steroidal Anti-inflammatory drugs (NSAIDs) and 28.9% of them were steroid drugs. Regarding remission of symptom, 20.1% of all patients and 24% of patients taking PPIs had GERD symptom at least once a week. Sex ($p<0.01$), CD except RA/ OA ($p=0.028$) and hyperlipidemia ($p<0.01$) showed significant differences. [Conclusion] Though one-quarter of patients taking PPIs had remain GERD symptom, it is considered that more patients with GERD symptom were prescribed PPIs than those who with no GERD symptom. Our survey has suggested that patients with GERD symptom need more effective treatment.

P3-285

Survival and causes of death in Japanese patients with rheumatic diseases in a single university hospital

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Conflict of interest: None

[Objectives] To determine survival and causes of death in Japanese patients with rheumatic disease. [Methods] Major rheumatic disease patients who were under care at Center for Rheumatic Diseases Yokohama City University Medical Center in 2002 were included in this study. Based on clinical charts, mortality rates and causes of death were retrospectively reviewed in a total of 651 rheumatic disease patients (RA (1) 229, SLE (2) 132, SjS (3) 106, SSc (4) 73, vasculitis syndrome (5) 34, Behcet Disease (6) 23, APS (7) 19, PM/DM (8) 19, MCTD (9) 16). [Results] Among 651 rheumatic disease patients (85.6% women, mean age at entry 56.8 years), 54 (8.3%) died during the follow-up period. The 10 year survival rates were (1) 87.3%, (2) 94.3%, (3) 95.5%, (4) 83.7%, (5) 89.0%, (6) 94.4%, (7) 92.0%, (8) 80.1% and (9) 93.3%, respectively. Causes of death were infection (n=12), malignant neoplasm (n=8), cardiovascular disease (n=8), interstitial pneumonia (n=6), and cerebrovascular disease (n=4), respectively. [Conclusion] The long term survival of patients with rheumatic diseases in our cohort was comparable with those previously reported in the literature.

P3-286

A study of inpatients of collagen diseases recent in our community hospital

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Conflict of interest: None

[Objectives] To investigate the recent trend of what is the hospital medical needs in collagen disease around our community hospital. [Method] Collagen disease patients who were admitted to our hospital for medical treatment in these three years. We investigated number of patients. We devided the admission purpose, disease activity (A group) or

complications (C group). We compared the number of patients with each disease prevalence. [Results] 129 total. RA 82 A group / C group 31/51, SLE 4 2/2, PSS 9 4/5, PM / DM 2 1/1, vasculitis syndrome PN 9 5/4, SjS 8 2/6, et al 15 9/6. RA is the majority of hospital admissions, Infectious diseases such as Herpes zoster and pneumonia, cerebral infarction, lumbar compression fracture and femoral neck fracture is often group C of RA, these are seem to derive from the older, but complications cases relevant to the MTX or interstitial pneumonia is suspected also observed. Number of cases of PN were more than expected. In patients with fever of unknown, we measured all cases ANCA, leading to early diagnosis, and early treatment. [Conclusion] We shold note complications elderly, interstitial pneumonia, use of MTX in patients with RA. PN has become possible in the early diagnosis and can be treated at the community hospital.

P3-287

Cytomegalovirus disease of the stomach demonstrated by biopsy in rheumatoid arthritis patient with gastric ulcer

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Conflict of interest: None

(Case) Fifty eight year-old female developed rheumatoid arthritis (RA) in 1987. Her illness was complicated by the right ischiatic nerve palsy in 2009. She has been given etanercept 50mg once a week, methotrexate 8mg per week and prednisolone 15mg per day. She developed pneumocystis pneumonia in November 2011. Both etanercept and methotrexate were stopped. Five hundreds of methyl-prednisolone was give intravenously for 3 days and switched to oral prednisolone. Trimethoprim/sulfamethoxazole was administered orally. She responded with this therapy and recovered. After this, cytomegalovirus antigenemia developed. This antigenemia became negative after administering ganciclovir. She complained of gastrointestinal symptoms, was examined by upper gastrointestinal endoscopy in January 2012. This examination revealed multiple ulcers in the antrum of the stomach. The biopsied specimens demonstrated inclusion body and immunohistochemically stained cytomegalovirus antigen in the cells, which indicated cytomegalovirus disease. (Conclusion) We must evaluate Cytomegalovirus disease of the upper gastrointestinal tract by endoscopy and biopsy if patients with rheumatic diseases under immunosuppressive therapy develop gastrointestinal symptoms even if antigenemia is negative.

P3-288

Efficacy of low dose pregabalin medication for fibromyalgia and chronic pain patients

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Conflict of interest: None

[Objectives] Pregabalin (Lyrica®) is effective for fibromyalgia and chronic pain patients. This usual dosage is initially 150mg and graduate increase to 300mg. Some patients are difficult to take pregabalin by its adverse effects such as drowsiness. In this study, we estimated efficacy of low dose pregabalin using less than 150mg dosage. [Methods] We estimated efficacy of less than 150mg dosage pregabalin medication for outpatients with fibromyalgia and chronic pain. [Results] Efficacy of less than 150mg dosage pregabalin medication for fibromyalgia and chronic pain patients was found in 14 patients. The dose of pregabalin were five 100mg, three 50mg as required and six 25mg as required. [Conclusion] Efficacy of pregabalin was found not only low dose but also as required drug for fibromyalgia and chronic pain patients. The low dose pregabalin is promised for patients who are difficult to take pregabalin by its adverse effects at usual dosage.

P3-289

A patient with paraneoplastic polyarthralgias and fever resulting from teratoma and acute lymphocytic leukemia (ALL)

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Conflict of interest: None

A 21-year-old woman initially noted pain in her hip joints and femoral regions three months before admission. A month before admission, pain in her shoulders and fever developed. She presented to outpatient department. The level of CRP was 2.2mg/dL, with 5% atypical lymphocyte. A CT scanning revealed a left ovarian teratoma. A scintigraphy revealed 68-Ga citrate was accumulated in joints of elbow, shoulder and knee. She was admitted because of severe polyarthralgias which limited her ability to walk. The level of CRP was 4.7mg/dL. The white-cell count 7140 /μL with 10% atypical lymphocyte. Given several examinations, infectious endocarditis, lymphoma, tuberculosis or rheumatic diseases is an unlikely diagnosis, leading to a possibility of paraneoplastic syndrome in teratoma. The tumorectomy was conducted. On the next day of the operation, she could walk with no joint pain. The level of CRP was normalized and atypical lymphocyte disappeared. However, the white-cell count decreased to about 2000 /μL. Pathological findings of bone marrow puncture led to a diagnosis of ALL. In this case, the clinical course suggested paraneoplastic symptoms of teratoma. Though the relationship between teratoma and ALL is unknown, this is a rare and atypical case of paraneoplastic syndrome.

P3-290

Three cases of Elderly-onset Rheumatoid Arthritis

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Conflict of interest: None

[Objectives] The rheumatoid arthritis that developed in over 65 years old is called elderly-onset rheumatoid arthritis (EORA), and it is known to take the atypical onset style. I report here three cases of EORA without typical arthritis. [Methods] Clinical course of the three cases of EORA were analyzed. [Results] There are one male patient and two female patients. The age at the onset was 76 years old - 92 years old. There is no typical arthritis in all cases. In serological studies, CRP level was a high as 5-7 mg/dl. The anti-CCP antibody was high as 114-519 U/ml. Although all cases were initially treated be low dose steroid, there was not the curative effect. All three cases were therated by the biological formulation (Tocilizumab 2cases, Adalimumab 1 case). All cases [Conclusion] were remitted be the biological formulations without any side effect. Treatment with biological formulation from an early stage is recommended.

P3-291

Study of the anticoagulant effects of edoxaban in patients undergoing total knee arthroplasty

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Conflict of interest: None

[Objectives] Patients undergoing total knee arthroplasty (TKA) are at particularly high risk of venous thromboembolism (VTE). Therefore, prophylaxis for VTE has been of great concern to surgeons. Edoxaban is an anticoagulant drug which acts as a direct factor Xa inhibitor. In the clinical trials, administration of edoxaban showed efficacy superior to subcutaneously administered dalteparin or enoxaparin. Edovaban also produced a concentric-dependent prolongation of PT ratio and aPTT in

the in vitro study. We investigated the anticoagulant effects of edoxaban in patients undergoing TKA. [Methods] 27 patients who were diagnosied osteoarthritis of knee were received one of two doses (15, 30 mg) of edoxaban orally once daily for 14 days after primary TKA. The patient that with moderate renal impairment (creatinine clearance 30–50 mL/minute), low body weight, 50 kg, a daily dose of 15 mg were received. PT (%) and aPTT (sec.) at 1PO, 4PO, and 11PO were measured. [Results & Conclusion] Symptomatic deep vein thrombosis was detected in no patients in the patients, and there were no deep vein thrombosis-related deaths or symptomatic pulmonary embolism. PT (%) were decreased, and aPTT (sec.) were prolonged with administration of edoxaban in patients undergoing TKA.

P3-292

Minimally invasive plate osteosynthesis (MIPO) for periprosthetic supracondylar femur fractures following total knee arthroplasty (TKA): report of two cases

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Conflict of interest: None

Two cases of periprosthetic supracondylar femur fractures above TKA were managed with MIPO method, and comparatively good results were acquired, it reports. The first patient was a 78-year-old woman who was operated TKA eight years ago. She was injured after falling down. The X-ray showed supracondylar fracture above TKA (Rorabeck type II). We treated this fracture using the locking plate with MIPO method. After six months from operation, bone union was achieved and this patient regaind pre-operative activity level. The second patint was a 89-year-old woman who was operated TKA five years ago. She was injured after falling down. The X-ray showed supracondylar fracture above TKA and distal to THA (Rorabeck type II, Vancouver type C). We treated this fracture using so long plate with MIPO, that the plate overlapped the stem region of the THA to minimize the mechanical stress between these two implants. After twelve months from operation, bone union was achived and this patient regained almost pre-operative activity level. (Conclusion) This fracture was associated with several problems, such as osteoporosis, small distal fragment and proximal implant of hip joint. However, MIPO method for this fracture was considered to be one of the management which can solve those problems.

P3-293

A case of idiopathic neuropathic elbow arthropathy complicated with rapid destructive coxopathy

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Conflict of interest: None

(Case) A 44-year-old female had received total hip arthroplasty due to rapidly destructive coxopathy. This time she was injured bilateral elbow by falling down. Her elbow X-ray showed neither fracture nor dislocation. Then she was initially diagnosed with bruise. However her elbow joint pain and swelling persisted for 4 months and finally elbow instability was observed. Her elbow X-ray demonstrated severe destructive findings. Laboratory data showed no sign of rheumatoid arthritis. Aspirated synovial fluid from right elbow was bloody serous, and showed no crystal. Culture exam was negative, suggesting neither crystal-induced arthritis nor suppurative arthritis. Both tabes dorsalis and diabetes mellitus were ruled out. Her cervical MRI showed no syringomyelia. Finally she was diagnosed with idiopathic neuropathic elbow arthropathy. Functional elbow brace was applied. She spontaneously complained of paresthesia in her right little finger. She was diagnosed with right cubital tunnel syndrome. Neurolysis of ulnar nerve was performed. Three months after surgery, she neither complained of paresthesia nor pain. She was able to perform activities of daily living. (Clinical significance) Neuropathic elbow arthropathy was very rare. We concluded that she was diagnosed with "idiopathic".

P3-294

Rheumatoid nodule in the heel without arthritis. A case report

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Conflict of interest: None

Rheumatoid nodule is thought to occur in the relation with activity of rheumatoid arthritis (RA) and rheumatoid factor. We report a case of rheumatoid nodule in the heel without any joint symptoms. 56 years old female. 1month before she came to our hospital, she felt pain on her left heel when she walked. Heel pain was getting worse and mass lesion was found in subcutaneous of the left heel by MRI. The tumor showed low intensity in both T1 and T2 MRI and containing some liquid inside. Open biopsy was performed and clear yellow color liquid and white-yellow color tissue were obtained. Pathological diagnosis was palisade granuloma and it suggested rheumatoid nodule. After that, Blood test showed rheumatoid factor level was 92u/ml and Anti-CCP antibody level was 104.9U/ml. However, CRP level was 0.01mg/dl and any tender and swelling of joints ware not seen. X-ray photographs of the hands and feet did not show any sign of RA. It was reported that in few RA patients rheumatoid nodule occurs before arthritis. We need systemic observation about joint and extra-joint symptoms in our case. Treatment of this patient should be considered carefully.

P3-295

A questionnaire surveying for rheumatoid arthritis at a public program

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Conflict of interest: None

[Objectives] We report a questionnaire surveying for rheumatoid arthritis patients who attended a public program for citizen in Nara prefecture. [Methods] The public program for RA took place every year since 2010. We designed a questionnaire-based study to examine patient behaviors regarding how they seek information about treatments for RA, and their health conditions and treatment. Participants answered a questionnaire regarding sources of RA treatment information and their usefulness, and scales (VAS; visual analogue scale) regarding their attitudes. [Results] A total of participants was 150 to 200 RA patients and their family. Major participants were their age of over 60 years and around 80% of those were women. The proportion of RA participants with therapy of any biologics was similar (30%) at both the first and recent programs. The VAS of participant's global assessment of disease activity indicated 38/100 for those with conventional DMARDs therapy, and 34/100 for those with biologics therapy. In particular, the participants' motivation for further seeking information about RA was increased after the public programs. [Conclusion] The public programs for RA gave a variety of valuable information and enhanced motivation to seek information for the participants.

P3-296

The approach of RA treatment by the cooperation between hospital and clinic at the area where RA specialists are absent

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Conflict of interest: None

[Background] Patients have widely different prognosis whether appropriate treatment is performed or not. However, in Shimane, many RA patients still have been treated with pyramid therapy at the specialists absence area. [Purpose] In Hamada city (Shimane) which is the RA specialists absence area, family doctors and RA specialists (Hamada medical

center; HC) begun to work in collaboration to perform adequate treatment for RA. We introduce an approach of supporting treatment for RA throughout the region. **[Method]** RA specialists gave the family doctors RA lectures and have started collaboration of treatment from 2009. At HC, the specialists have charge of activities which are hard to perform for family doctors; such as diagnosis, choice of therapy on evaluating patient's general status, response to appearing critical complications, etc. After starting treatment, the specialists re-introduce RA patients to family doctors at once. And they examine regularly and the specialists check once per 3-6 months at HC. The specialists and the family doctors share information with rheumatic note. **[Conclusion]** Even if the area of few medical specialists, it's possible to perform appropriate treatment for more patients by division of each roles and cooperation.

P3-297

Survey on the degree of satisfaction in RA patients treated with biologics

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Conflict of interest: None

[OBJECTIVE] We conducted a survey of RA patients treated with biologics, to clarify and satisfaction actual conditions of treatment to help improve satisfaction. **[METHODS]** Questionnaire was carried out to 201 patients in our hospital. Questionnaire contents, 28 survey items. **[RESULTS]** Questionnaire sheets were distributed to 201 RA patients and recovered from 174 patients (86.6%). Questionnaires revealed that satisfaction with RA treatment was "very satisfied (Group A)" in 41%, "satisfied" in 52%, "dissatisfied" in 3% and "not sure" in 4% patients. There was not a person that answered very dissatisfied. Classified as Group B other than Group A. There was no difference in age and gender between the two group. The percentage of the intravenous was A group 38.6%, B group 52.0%, subcutaneous was A group 61.4%, B group 48.0%. Percentage of subcutaneous used was higher in group A slightly. Percentage that the employment was 44% A group, 25% B group. The proportion who think that it's high health care costs, B group was 63% compared with 40% A group. **[CONCLUSION]** The satisfaction of the treatment with biologics was high. In addition, it was suggested that the satisfaction depended on the situation such as the operation situation.

P3-298

MRI studies of sacroiliac joints in patients with axial spondyloarthritis

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Conflict of interest: None

[Objectives] The prevalence of spondyloarthritis (SpA) was reported to be similar to that of rheumatoid arthritis in an investigation of the Wakayama prefecture in 2010. We reported the proportion to the patients with non-radiographic Axial SpA (nr-AxSpA) among the patients with SpA in our hospital, which was similar to the French reports. [Methods] MRI studies were implemented using coronal short τ inversion recovery (STIR) for the patients with SpA in our clinic. [Results] 117 cases (91 females, 26 males) were investigated; the average age was 51 years old; MRI STIR revealed 46 cases (39.3%) with positive findings. There are 20 cases (43.5%) of ankylosing spondylitis (AS) for nr-AxSpA, on the other hand, 43 cases (60.6%) of AS for SpA without STIR of sacroiliac joints. [Conclusion] As these treatments can achieve an excellent outcome in patients with SpA when biologics is administered if the diagnosis is made early in the course of the disease, it is important to make the definitive diagnosis and initiate treatment early on.

P3-299

Clinicopathological characteristics of 13 patients with rheumatoid arthritis and lymphoproliferative diseases

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Conflict of interest: None

[Objectives] We peformed a clinical analysis in rheumatoid arthritis (RA) patients complicated with lymphoproliferative disease (LPD). [Methods] We assessed the clinicopathological characteristics of 13 patients with RA and LPD. [Result] The mean age at the diagnosis of LPD was 67.6±10.7 years, with a male:female ratio of 3:10. The median disease duration of RA was 10 years. Methotrexate (MTX) is used in 11 out of 13 patients. 3 patients received biologics. Pathological findings revealed that 6 patients were diffuse large B cell lymphoma, 3 B cell lymphoma, 3 Hodgkin lymphoma and 1 mucosa associated lymphoid tissue. The outcome was that 12 patients were alive and 1 patients was died. Spontaneous regression occurred in 3 patients in whom MTX was discontinued. 8 patients received chemotherapy, and 1 radiation. They achieved remission and no recurrence. The median of survival period was 22 months. The treatment for RA after developing LPD was prednisolone and DMARDs except MTX. TCZ was used in combination in 2 patients. [Conclusion] The outcome of RA-LPD in our department was relatively good. However, there is no consensus of the treatment for RA after developing LPD and the careful consideration is required.

P3-300

Nontuberculous mycobacterium tenosynovitis in the hand treated as rheumatoid arthritis : Two case reports

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Conflict of interest: None

[Objectives] We present our experience with 2 cases of nontuberculous mycobacterium tenosynovitis in the hand treated as rheumatoid arthritis. [Methods, Results] Case 1: A 57-year-old female was aware of rash in her left index finger, but it was disappeared spontaneously. Five month later, she consulted rheumatologist and was treated with oral prednisolone and bucillamine as RA. 7 months later, she visited our hospital because of swelling, ulceration, and pain in her finger worsened after steroid injection. Tenosynovectomy was performed two times. Mycobacterium marinum was isolated from mycobacterial cultures. Case 2: A 66-year-old man was injured his right middle finger by crashed flowerpot in a water tank, but he did not visit medical institution. Six month later, marked swelling of his middle finger was developed. He consulted rheumatologist and was treated with bucillamine as RA. He was referred to our hospital and tenosynovectomy was performed two times. The pathological examination showed acid-fast organism in resected tenosynovium. [Conclusion] The characteristics of our two cases were chronic disease course and local trauma associated with water and fish. Delay in diagnosis or misdiagnosis may result in inappropriate treatments, and may worsen the course of the infection.

P3-301

Joint ultrasound findings of two cases of reactive arthritis

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Conflict of interest: None

[case1] 38 year old man, had been aware of the discomfort during urination in early June 2013. There was a history of sex with other partner the four weeks before the acute onset polyarthritis in interview. He had showed swelling and tenderness joint both hands, both sides MCP, on both feet joint center as joint finding. Revealed a tendon sheath syno-

vitis in his right hand third finger flexor tendon right ulnar extensor tendon and ECU in joint ultrasound. He was diagnosed with reactive arthritis associated with chlamydial urethritis, and 30mg/day of prednisolone and NSAIDs in addition to Chlamydia infectious diseases. [Case2] 75 -year-old man, had been medical treatment at our hospital dermatology suffering from hand, foot and mouth disease in early September in 2013. He also had pain and swelling of both hands finger joint. He showed swelling and tenderness on both sides wrist, tendon sheath synovitis on both sides ECU in joint ultrasound. He was diagnosed with reactive arthritis associated with Coxsackie A group virus infections were initiated at the medical treatment salazosulfapyridine and NSAIDs. We experienced two cases of reactive arthritis this time. We report joint ultrasound findings of reactive arthritis including the considerations of literature.

P3-302

A case of methotrexate associated lymphoproliferative disorder complicated with hemophagocytic syndrome in a patient with rheumatoid arthritis

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Conflict of interest: None

A 68-year-old woman with rheumatoid arthritis had been treated with methotrexate (MTX) since 2008. Infliximab was started in 2009, but discontinued because of palpitation. Then adalimumab (ADA) was started with MTX and tacrolimus (TAC) and prednisolone in 2010. She acheived clinical remission. She started complaining of abdominal pain and nausea in June 2013. But her symptom was persistent. She was admitted to the hospital with general fatigue in July 2013. CT scan showed multiple swelling of mesenteric lymph nodes. Their findings suggested MTX associated lymphoproliferative disorder (LPD), therapies of MTX, TAC and ADA were withdrawn. Laboratory examination showed pancytopenia and increased of LDH, ferritin and sIL2-R. She had diagnosed hemophagocytic syndrome with bone-marrow. An intraabdominal lymph node biopsy revealed diffuse large B cell lymphoma. Immunohistochemical staining showed these cells were positive for EBV and EBV DNA determination in the serum was elevated. Only discontinuation of MTX and ADA without chemotherapy resulted in improvement of pancytopenia and regression of lymph node swelling. Based on the clinical course and pathological results, we made a diagnosis of EBV-associated LPD due to immunodeficiency related to immunosuppressive therapy. MTX-LPD with HPS is rare, so we report.

P3-303

Successful treatment of knee synovitis and osteochondral defect accompanied by ankylosing spondylitis with infliximab: a case report

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Conflict of interest: None

[Introduction] We encountered a case in which both the knee synoivitis from ankylosing spondylitis (AS) was accompanied by multiple osteochondral defect. And AS is classified into two division, axial AS (spine) and peripheral AS (Joints). Infliximab has recently been proved to be effective in the treatment of AS. [Case] Miss. KM, 31-year-old female, was reffered for right gonalgia and knee swelling. X-ray of both knee joints revealed multiple bone erosions, and X-ray of the spine showed bamboo spine. Investigations revealed normal RF and anti-CCP antibody. We diagonosed knee synovitis and osteochondral defect accompanied by ankylosing spondylitis. In September, 2012, Synovectomy to the both knee joints were performed and the severe synovitises were found. We decided to start infliximab treatment. The patient responded well to infliximab and, bone degfects were rebuilt. [Conclusion] Infliximab is effective on synovitis from the periipheral AS.

P3-304

Systemic lupus erythematosus (SLE) mimicking *Kikuchi-Fujimoto disease (KFD)* presenting lymphadenopathy

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Conflict of interest: None

A 60-year-old woman presented with persistent slight fever and dry mouth 5 months before the admission. She was referred to our hospital because of positive antinuclear antibody. Laboratory findings revealed of WBC 2050 and anti-dsDNA antibody of 84.8IU/mL. She had a spike fever. Physical examination showed lymphadenopathy of bilateral anterior cervical lymph nodes. Examination of bone marrow smears disclosed a normal morphological appearance. A biopsy of the right axillary lymph node showed lymphadenits, abundant histosytes and necrosis that are the characteristic features of KFD. We continued observation of her course with no medication because of no complications. After a month, she developed sudden severe abdominal pain and bloody feces. CT scan of her abdomen showed diffuse edema and wall thickening of the ascending, transverse colon with ascites. Based on the above findings, she was diagnosed with lupus enteritis and treated with prednisone 50mg and tacrolimus 1mg daily. Her fever resolved and abdominal symptoms improved. We presented a case of lupus enteritis presentinglymphadenopathy as an initial symptom and review and discuss differential diagnosis of SLE and KFD.

P3-305

What to learn from four cases with rheumatoid arthritis who were not able to visit outpatient clinic

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Conflict of interest: None

[Objectives] Public health policy is going to promote home medical care. And increasing number of RA patients with disability of visiting outpatient clinic are concerned. In my clinic, four patients with RA are followed by home care medicine. Several problems emerged. [Case Report] All of the patients are elderly and seriously disabled. In the first case, aggressive treatment with MTX and home rehabilitation were successful in relieving pain and keep her ADL. In the second case, immunosuppressants could not be used because of her past history of Pneumocystis pneumonia, but combination tablet of acetaminophen and tramadol hydrochloride and home rehabilitation relieved her low back pain In the third case, DMARDs or NSAIDs were contraindicated because of renal dysfunction. The last case needed rehabilitation and home nursing care, but she cannot afford to pay for those services. [Conclusion] Although MTX was helpful for one patient's ADL, drug therapy was limited due to patient's organ failure and lack of monitoring chest X-ray and other exams in home medical care. Home rehabilitation and nursing care were also great help to keep patients' ADL and QOL, but the burden of their family and care managers were heavy.

Luncheon Seminar

LS1-1

Basic aspects of anti-IL-6 receptor inhibiting therapy and promises for future treatment strategy

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Conflict of interest: Yes

Rheumatoid arthritis (RA) is a systemic autoimmune disease, which is accompanied by progressive, and often rapid joint destruction and following irreversible physical disability. Receptor activator of NF-κB ligand (RANKL), which induces osteoclastogenesis as well as matrix metalloproteinase (MMPs), which degrades the cartilage, are both considered to play key roles in the pathology of RA. It has been shown that the upregulation of these molecules are driven by inflammatory cytokines in the RA joints. Tocilizumab (TCZ) – an IL-6 receptor inhibitor is an effective treatment option to suppress RA. IL-6 induces the RANKL expression by synovial fibroblasts and MMP expression by cartilage cells through STAT3 and ERK pathways. It also induces ICAM-1 expression of endothelial cells and MMP-3 production by chondrocytes, showing that IL-6 has multiple targets. These facts are probably reflected by the results of the clinical trials that demonstrated superiority of TCZ over methotrexate, and over TNF blockade without concomitant use of methotrexate in inhibition of arthritic symptoms and progression of bone and joint destruction. For the future treatment, since TCZ has multiple immunosuppressive effects, it should be a good partner of treatment with a cyclin-dependent kinase (CDK) 4/6 inhibitor, which controls cell cycle progression of synovial fibloblasts. Actually, CDK 4/6 inhibitor and TCZ cooperated well to suppress animal models of RA. In this seminar, I would like to discuss basic aspects of IL-6 inhibition in RA pathology, and future combination treatment with cytokine blockers and the CDK4/6 inhibitor for complete suppression of RA.

LS1-2

The effectiveness and safety of tocilizumab in real clinical practice in RA patients -FIRST BIO study-

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Conflict of interest: Yes

The therapeutic strategy followed in the treatment of rheumatoid arthritis (RA) has dramatically changed with the advent of biologic DMARDs, and the treatment goal has shifted from "improving the signs and symptoms of RA" to "preventing joint damage and maintaining activities of daily living (ALD)". Joint destruction occurs from an early stage in the development of RA; therefore, in 2010, EULAR advocated a new set of classification criteria to allow classifying of RA in its early stages. Furthermore, a new standard of remission criteria - which is a stricter treatment target than previously advocated - was set, and a "treat-to-target" medical guideline was proposed. Tocilizumab (TCZ), an anti-IL-6 receptor antibody, is known to be effective in patients who have failed to respond adequately to synthetic DMARDs and other biologic DMARDs. Moreover, TCZ shows high efficacy without concomitant use of MTX. Recently, EULAR recommended that TCZ can be used as a first-choice biologic DMARD, the same as TNF inhibitors, in patients who have failed on synthetic DMARDs. Because TCZ has a mode of action completely different from that of TNF inhibitors, studies to determine which patients will show a good risk/benefit balance during TCZ treatment are needed. In Japan, the FIRST-BIO postmarketing surveillance study is ongoing with 881 biologic-naïve RA patients. The aim of the study is to examine the safety and effectiveness of TCZ in real clinical practice in patients who met the new RA classification criteria. In this seminar, I would like to present the results of an interim analysis of the FIRST-BIO study and to discuss the benefits of TCZ as the first choice of biologic DMARD in RA patients.

LS2-1

Golimumab, a drug chosen as a 1st Bio - On the ground of experience with Bio's in 107 cases

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Conflict of interest: Yes

With the advent of biological drug preparations, treatment strategies for RA have undergone marked changes. Currently, seven biological drug products are available, viz., IFX, ENT, ADA, GLM, CZP, TCZ and ABT. A wide range of choices adoptable in using these drugs according to the disease state and lifestyle of patients, e.g., route of administration, dose level and dosing interval, is indeed a great advantage but at the same time it is also a fact that appropriate practical use of these biological drugs entails difficulty. In the case of a human anti-TNFα monoclonal antibody GLM approved as of September 2011, treatment requires only simple, once-in-every-4-weeks subcutaneous administration, even at dose levels up to 100 mg approved only in Japan. It is a drug available for treatment of all varieties of RA disease state. An approximate total of 400 patients have been treated with the biological products at our hospital, including own experience with GLM in 107 patients (91 naïve cases; a 50 mg dosage group of 103 patients, and a group of 4 patients with the dosage raised to 100 mg). The present study represents an attempt to analyze results of the treatment in 100 patients, with attention focused upon GLM, using changes in DAS28CRP, DAS28ESR, SDAI, and HAQ and percentage of patients continued in GLM therapy as evaluation variables. The mean DAS28CRP was 5.13 before treatment (at baseline) and 2.64 at week 48 of treatment, the mean DAS28ESR was 5.36 and 2.77 at week 48, the mean SDAI was 22.8 at baseline and 4.7 at week 48, the mean HAQ was 1.5 at baseline and 0.6 at week 48, and the percentage of patients continued in the therapy was 92% of those attaining the 48th week. The present therapeutic results were comparable with or even superior to results with other biological products, indicating that GLM may prove a biological preparation capable of being a useful choice of drug as a "1st Bio".

LS2-2

Effective therapy to continue golimumab in patients with rheumatoid arthritis

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Conflict of interest: None

There are established evidences for efficacy and safety of golimumab in patients with rheumatoid arthritis (RA). However it is not well known how to elucidate the good efficacy of golimumab in daily practical level. The clinical efficacy including the van der Heijde-modified Sharp (vdH-S) score was analyzed regarding to DAS28 (CRP), SDAI, serum TNF-α, IL-6 every month for 52 weeks in naïve vs switch and MTX plus or minus. In Results, MMP-3 and disease duration were significant collated with DAS24 (CRP) at 24 weeks. Remission rate was higher in naïve and MTX plus group at 52 weeks. We focus on the rapid radiographic improvement (RRI) of golimumab showing 44.8% (13/29 cases). RRI of golimumab tends to increase meaning that continuous golimumab therapy is effective for improvement of bone damage. A case of bio-free remission showing negative CRP, negative MMP-3 and low titer of RF more than 3 months was no flare 6 months after bio-free with 6 mg/weeks of MTX. We found new procedure to elucidate efficacy in switching biologics named K-method. We introduce this K-method with golimumab this time. Histological examination treated with golimumab showed CD20 correlated with CRP and serum IL-6 significantly. Therefore golimumab works with not only TNF-α but also inhibit B-lymphocytes to decrease serum IL-6 in RA.

LS3

Present Status of NSAIDs-induced Gastrointestinal Injury

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Conflict of interest: None

Helicobacter pylori (*H. pylori*) and nonsteroidal antiinflammatory drugs (NSAIDs) are two major causes of peptic ulcers. Recently, the rate of *H. pylori* infection have been decreasing. As the aging society, the prescription of low-dose aspirin (LDA) and NSAIDs are increasing in elderly patients with multiple diseases. NSAIDs- and LDA-induced ulcers lead to bleeding at high rates and deterioration in the general condition of the patient. We conducted a survey to evaluate the changes in the causes of ulcers in 1500 patients from 2002 to 2011 and found that LDA-induced ulcers increased doubly whereas non-aspirin NSAIDs-induced ones showed little change. The risk factors for bleeding ulcers caused by NSAIDs include a recent history of bleeding, old age, high dose, and a concomitant use with antithrombotic drugs, *H. pylori* infection, and other comorbidity. A case-control study conducted on *H. pylori* and NSAIDs indicates that the risk of upper gastrointestinal bleeding was 5.5-fold and 6.1-fold higher for aspirin and other NSAIDs respectively than for people without these drugs. Also, LDA showed the risk of bleeding to be the same as with NSAIDs, and *H. pylori* and NSAIDs increased the risk of bleeding ulcersadditively. Bleeding occurs mostly within 14 days after receiving NSAIDs, on the other hand bleeding often occurs in case of long-term administration of LDA. *The Japanese Guideline for Peptic Ulcer Treatment* (2003) recommends proton pump inhibitors (PPIs) or prostaglandins (PGs) for ulcer treatment in continuous NSAID users, and PPIs, PGs, and high-dose H2 blockers for prevention. PPIs are the most highly recommended because of less adverse events and better medication compliance. The risk of gastrointestinal bleeding in elderly patients should be reviewed carefully because they often receive drugs from multiple clinics. Here, we present recent reports on gastrointestinal events both in Japan and abroad as well as cases from our own experience.

LS4-1

The action and effect of tofacitinib

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Conflict of interest: Yes

Tofacitinib is a small molecule compound that targets Janus kinase (JAK), a tyrosine kinase that resides in the cytoplasm. While biological products target a single cytokine or a cell surface molecule, targeting JAK will result in inhibiting multiple cytokines or cell surface molecules affecting its biological activity or expression in a direct or indirect manner. This enables this oral compound to exert anti-rheumatic activity resembling biological products. Clinical efficacy can be observed from the early stage of treatment and is known to sustain. In this seminar, the results from 3 clinical trials, ORAL Standard/Scan/Step and our own experience with tofacitinib will be presented.

LS4-2

Safety from the evidence of tofacitinib

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Conflict of interest: Yes

Tofacitinib, Janus kinase (JAK) inhibitor developed as a therapeutic drug of rheumatoid arthritis (RA), is an orally-available small molecule compound indicating similar treatment effect as biologics. The high effectiveness is shown around two weeks. These things mean that the treatment strategy of the rheumatoid arthritis can go in the new era. Tofacitinib was approved by adaptation of RA in United States and Japan, but there is room for the examination about the safety of this drug. In Europe, tofacitinib has being approved at present with a negative opinion from the viewpoint of benefit risk balance. There are not many serious adverse events in Phase II and III trials, but patients by whom safety is collateralized are registered using exclusion criteria. So enough consideration of the safety is necessary for daily clinical practice and post-marketing survey (PMS) is now ongoing in Japan. In guideline for the use of tofacitinib in PMS, this drug should be available for RA patients with poor control, which is more than moderate disease activity even if we continue the dose more than MTX 8 mg/week for at least three months. The precautions are similar to guidelines about the use of biologics, we should be careful about a white blood-cell count and the number of the lymphocytes particularly because there are side effects such as the cytopenia and the viral infection including herpes zoster. The incidence of malignant tumor is shown to be almost same as biologics by the latest results from the long-term examination of the Phase II and III trials. But the kind of the malignant tumor in Japanese is different from Westerners, and we had better examine the safety in Japanese. In this seminar, I would like to give an outline mainly on safety of tofacitinib, while introducing the data of the past clinical trial.

LS5

Early Diagnosis and Treatment in Connective Tissue Disease associated with Pulmonary Arterial Hypertension

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Conflict of interest: Yes

Pulmonary arterial hypertension (PAH), defined as mean pulmonary arterial pressure (PAP) ≥ 25mmHg and mean pulmonary artery wedge pressure ≤ 15mmHg at rest as assessed by right heart catheterization, is a fatal disease caused by small pulmonary artery obstruction due to vascular proliferation and remodeling. PAH is characterized by elevated PAP and increased pulmonary vascular resistance (PVR), frequently leading to right-sided heart failure and death. As the effective tool for early diagnosis of PAH has not been developed, the symptoms of PAH are important for the early detection, although the symptoms are non-specific, such as shortness of breath, fatigue, weakness, angina, syncope, and abdominal distension. Echocardiography is highly reliable to assess the dynamic morphology of cardiac and vascular structures and to measure flow velocities using pulsed and continuous-wave Doppler. Cardiac catheterization is required not only to diagnose PAH and to exclude other causes but also to evaluate the disease severity and prognosis assessment. It is widely accepted that immunological and inflammatory mechanisms contribute to the initiation and progression of PAH in patients with connective tissue disease (CTD-PAH), such as systemic sclerosis (SSc), systemic lupus erythematosus (SLE) and mixed connective tissue disease (MCTD). Indeed, inflammatory cells (e.g. macrophages and lymphocytes) were detected in the plexiform lesions of the lung from CTD-PAH patients. Our recent study has demonstrated that the intensive immunosuppressive therapy combined with cyclophosphamide and glucocorticosteroid on the top of conventional pulmonary vasodilator therapy, such as prostacyclin, endothelin receptor antagonist, and PDE-5 inhibitor, markedly improved pulmonary hemodynamics and long-term prognosis of patients with CTD-PAH except SSc-associated PAH. The effects of the intensive immunosuppressive therapy are evident when it is started immediately after diagnosis of CPAH at early stage.

LS6

Reactivation of Hepatitis B virus in Patients Receiving Immunosuppressive Agents - Messages through the Analyses by Study Group of the Ministry of Health, Welfare and Labour and a Deceased Patients in Our Hospital -

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Conflict of interest: Yes

Hepatitis B virus (HBV) prevails among populations in eastern Asia; more than 20% of populations aged greater than 50 years old have been resolved HBV infection in Japan. In such patients, serum HBV-DNA may become detectable following immunosuppressive therapies leading to development of liver damage, since cccDNA of HBV inevitably remains in hepatocytes after HBV infection. The most hepatologists have been speculated that severe hepatitis seldom develops in patients with resolved HBV infection during immunosuppressive therapies, since such therapies also attenuate the extent of liver inflammation. Also, economical issues

should be taken in our mind to establish the appropriate guideline for prevention of HBV reactivation, since the therapies for rheumatoid diseases are required to be continued for lifelong periods. The study group of the Ministry of Health, Welfare and Labour revealed that HBV reactivation developed in frequent in patients with rheumatoid diseases especially within 6 months after the initiation of immunosuppressive therapies. Thus, the guideline was revised in 2013; serum HBV-DNA measurements should be done every month within 6 months following the initiation and/or modification of the therapies, but the duration of the examination can be prolong up to 3 months. In contrast, mortal cases with acute liver failure due to HBV reactivation seen between 2010 and 2012 were still enrolled in the nationwide survey by the study group. Also, we recently experienced a deceased patient with acute liver failure in whom immunosuppressive therapies for collagen diseases were done without the screening examinations of serum anti-HBc and ant-HBs. In the present seminar, clinical features of patients showing HBV reactivation following immunosuppressive therapies were discussed based on the analysis by the study group.

LS7

Use of IGRA in screening and prophylaxis for latent tuberculosis prior to initiating biologics

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Conflict of interest: Yes

Biologics are more effective than conventional therapy in inducing remission in RA and have revolutionized the management of RA. In biologics era, guidelines for RA treatment have been revised to achieve optimal use of this therapeutics. Attention needs to be paid to adverse events related to biologics, especially opportunistic infection because of strong immunosuppressive effect. In 2001, Kean et al. reported that the estimated incidence of tuberculosis in patients receiving infliximab was 24.4 cases per 100,000 patient-years. Accumulating data indicate that infliximab poses a greater risk of reactivating latent tuberculosis than etanercept. Several hypotheses based on differences in drug properties have been advanced to explain the differential risk. TNF is essential for granuloma maintenance, which are key components of host defenses against intracellular mycobacterium. TNF induces maturation of mycobacteria-containing phagosome, resulting in increased intracellular killing by macrophage. A major subset of antimycobacterial effector cells (CD8+TEMRA cells) is selectively depleted by anti-TNF monoclonal antibody. Screening should take place for both active and latent tuberculosis prior to initiating biologics. The tuberculin skin test (TST) has been used to support the diagnosis of latent tuberculosis for almost a century. However, false-positive TST responses may occur after contact with Nontuberculous mycobacteria or after BCG vaccination. Recently IFN-γ release assay (IGRA) have been introduced to compensate for the drawbacks of TST. QuantiFERON-GIF and T-Spot are available for diagnostic aids in Japan. There are many investigations assessed specificity and sensitivity of IGRA, and there are some reports that T-spot sensitivities are considered better compared to those for TST. In 2010, CDC published updated guideline for using IGRA to detect Mycobacterium tuberculosis infection. We must be cautious about screening and prophylaxis prior initiating biologics.

LS8-1

Diagnosing Ankylosing Spondylitis: An overlooked early phase symptom and update of treatment

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Conflict of interest: None

Ankylosing spondylitis (AS) is generally recognized as a rare disease and often underdiagnosed even by rheumatologists. According to a survey, it took average of 9 years for patients to receive the diagnosis of AS, while receiving different treatments under different diagnosis through the time. The survey highlighted that AS patients occasionally wander looking for help and they require an accurate diagnosis at early stage of the disease. In general, the modified New York criteria are used to make a diagnosis of AS. The conditions presented in the criteria, however, are symptoms that can be observed only after ankylosis has already progressed. Outside of Japan, diagnostic criteria have been repeatedly reviewed and revised to overcome this problem. In recent years, the ASAS criteria for classification of axial spondyloarthritis (SpA) have been widely used, and there is also a report that the time required to make a diagnosis of axial SpA, including AS, has been shortened to about 3 months, similar to that for rheumatoid arthritis. The ASAS criteria for classification are helpful in making an early diagnosis of AS, or more specifically, the criteria help diagnosing physicians to focus on inflammatory back pain (IBP). Rudwaleit et al. reported that 14% of patients who had IBP received a diagnosis of axial SpA, including AS. Paying attention to the presence or absence of uveitis, psoriasis, inflammatory bowel disease, etc. other than IBP is also helpful for making a diagnosis. I would like to introduce the remarkable advance in the the treatment of AS. Therapeutic exercise and NSAIDs are fundamental in the treatment of AS. In Japan, there have been few reports of large case studies because the absolute number of patients with AS is small. Although, the analysis of cases accumulated at our hospital suggests that the usefulness of TNF inhibitors can be enhanced by using them primarily in patients with a short duration of illness and a low score on BASFI.

LS8-2

Manaemeng of psoriatic arthritis: updating information

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Conflict of interest: None

Psoriatic arthritis has been reported to be developed in 10 to 30% of patients with psoriasis. In Japanese, the prevalence of psoriasis is lower than that in Caucasian. However, recently, the prevalence of psoriasis in Japan is getting increased, indicating the recognition of psoriatic arthritis is important in the rheumatology in Japan. Psoriatic arthritis is classified among spondyloarthritides. Although previous descriptions indicated that psoriatic arthritis was a mild disease, recent examinations showed that psoriatic arthritis led to increased morbidity and mortality, and joint damage occurs early in the course. Psoriatic arthritis has various rheumatological presentations; peripheral oligo-to-polyarthritis, dactylitis, enthesitis, DIP arthritis and axial involvement. The recognition of these domains is important for diagnosis and treatment of psoriatic arthritis. In most patients, skin lesions are antecedent to joint manifestations. However, in 10 to 15% of patients, arthritis may develop without skin disease. The concept of psoriatic arthritis sine psoriasis is useful in the diagnosis of psoriatic arthritis Imaging studies are also important for the diagnosis of psoriatic arthritis. MRI and ultrasonography provide interesting findings in terms of pathophysiology of inflammation in psoriatic arthritis, radiographic findings are useful for the diagnosis of psoriatic arthritis. Practically, patients with obvious skin disease see dermatologists and patients with predominant arthritic symptoms visit rheumatologists. Therefore, collaboration between dermatologists and rheumatologists are necessary. For treatment, DMARDs such as methotrexate are used without definite evidence. Although TNF inhibitors are expensive compared with DMARDs, evidence and clinical experience support their use in the management of psoriatic arthritis.

LS9

Focus on challenges in diagnosis and evaluation of systemic vasculitis

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Conflict of interest: None

The systemic vasculitides are uncommon diseases characterized by inflammation of blood vessels and if untreated, can result in end organ damage or death. Immunosuppressive therapy has improved outcomes, but long-term morbidity occurs, due to flares, chronic low-grade disease activity, or cumulative damage. A delay in diagnosis is common. There are no diagnostic criteria and physicians have to rely on their own experi-

ence together with classification criteria and disease definitions. With the increased understanding of the pathophysiology of vasculitis and newer diagnostic tests, we propose to revise the classification criteria for primary vasculitis. The widespread availability of anti-neutrophil cytoplasm antibody (ANCA) testing and improved imaging techniques now enable clearer distinction between different forms of vasculitis. Updated criteria should include these newer diagnostic tests, in order to improve clinical practice and allow progress to be made in clinical trials. Mortality remains a significant issue for very severe disease especially for ANCA positive patients presenting with renal failure or pulmonary haemorrhage, with 26% early mortality despite treatment. For those who survive, assessment of morbidity can be used to distinguish between different treatments and also to determine if treatment is sufficient. Morbidity can be classified as due to disease activity (Birmingham Vasculitis Activity Score), due to damage (Vasculitis Damage Index), or morbidity affecting the patient's ability to perform activities of daily living, Together they provide a rational approach to standardise patients at diagnosis and evaluate and stage them for disease severity in order to select the best therapy. Guidelines recommended by the European League Against Rheumatism and more recently the updated for ANCA vasculitis British Society for Rheumatology suggest regular monitoring of disease activity and damage to allow a clear definition of patient progress.

LS10

Mechanism of cartilage destruction and current treatment strategy for osteoarthritis

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Conflict of interest: Yes

The development of osteoarthritis (OA) is related to genetic factors, environmental factors, metabolic disorders, and biochemical and/or biomechanical abnormality of the joint. It is clear that the protein catabolic enzymes such as MMPs and ADAMTSs play key roles in the degradation of cartilage. We have previously demonstrated that catabolic mechanical stress (CTS)-induced MMP-13 and ADAMTS-5 expressions were regulated by RUNX-2 transcriptional factor via p38 MAPK pathway in SW1353 cells. CTS-induced RUNX-2, ADAMTS-5, and MMP-3 mRNA expression by human chondrocytes were downregulated by treatment with hyaluronic acid (HA), partly by suppression of NF-kB activation and subsequent IL-1 expression. With regard to the development of new DMORDs, several studies have failed to demonstrate efficacy of anticytokine therapies, including blockade of IL-1 and TNF in the treatment of OA. Tanezumab, a monoclonal antibody to NGF, intra-articular injections of platelet-rich plasma (PRP), or strontium ranelate, approved for the treatment of postmenopausal osteoporosis have demonstrated efficacy in OA. MicroRNAs (miRNAs) are small noncoding RNAs that have recently been recognized as important regulators of gene expression in human cells. Accumulating evidences suggested the involvement of miR-125b, 146a, and 199 in the pathogenesis of OA. Overexpression of miR-145 in articular chondrocytes reduced the levels of SOX9 and the cartilage matrix components COL2A1 and Agc1, and significantly increased RUNX-2 and MMP-13. MicroRNA-140 (miR-140) is shown to target histone deacetylase 4 (HDAC-4), a known corepressor of RUNX-2, and is highly, and selectively expressed in cartilage. As miR-140 is demonstrated to be a mechano-sensitive miRNA in chondrocytes, and HDAC inhibitor suppress the mechanical stress-induced RUNX-2 and MMP-13 expression, the regulation of miRNA expression might be a new therapeutic strategy of the management of OA.

LS11

Topics on diagnosis and treatment in patients with Sjögren's syndrome

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Conflict of interest: Yes

Sjögren's syndrome (SS) is an autoimmune disease that affects exocrine glands including labial salivary glands (LSGs) and lacrimal glands (LGs), resulting in dry mouth and dry eyes. In patients with SS, there are a lot of autoantibodies such as anti-nucliear antibodies, rheumatoid factors, anti-SS-A antibodies, anti-SS-B antibodies, and anti-M3 muscarinic acethylcholine receptor (M3R), and autoreactive T cells in LSGs and LGs. The surveys on epidemiology of SS demonstrated that the mean age of SS patients is 60 years old, the ratio of male:female is 1:17.4, and the number of SS is about 70,000 persons. In Japan, the criteria for the diagnosis of SS was determined by the revised Japanese Ministry of Health criteria for the diagnosis of SS in 1999. In this criteria, there are four factors as followings: 1) Histological findings in LSGs or LGs. 2) Oral examination such as sialography or scintigraphy and Gam test or Saxon test. 3) Ophthalmological examination such as Shirmer test and staining test. 4) anti-SS-A antibodies or anti-SS-B antibodies. The positivity of more than two items is necessary for diagnosis of SS. The validation of Japanese criteria, American-European Consensus Group classification criteria for SS (AECG) and ACR criteria in Japanese patients showed that the sensitivity and specificity of Japanese criteria was the highest. In treatment of patients with SS, there are two approaches. One is to improve QOL and eye drops for dry eyes and pilocarpine hydrochloride and cevimeline hydrochloride for dry mouth. The other is to therapy against systemic organ involvement. In this case, adrenocortical steroid and/or immunosuppressive drugs should be necessary to control inflammation. Near future, biologics against B cells (rituximab, belimumab) and T cells (abatacept) will be approved for SS therapy. In this luncheon seminar, I would like to review the topics on diagnosis and therapy in patients with SS.

LS12

Guidelines for glucocorticoid-induced osteoporosis

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Conflict of interest: Yes

In the last decades, several guidelines for the management of glucocorticoid-induced osteoporosis from different countries have been developed. Unfortunately, these guidelines demonstrated relatively large differences regarding the thresholds of daily glucocorticoid dosage and of BMD values which are regarded as cutoff values for initiating anti-osteoporotic drugs in subgroups of glucocorticoid-treated patients. Recently, an update of the American College of Rheumatology recommendations for the prevention and treatment of glucocorticoid-induced osteoporosis was published. Patients are subcategorized into fracture risk categories using the FRAX tool or tables provided by the ACR. The FRAX calculator uses only bone density at the hip. Patients with glucocorticoid-induced osteoporosis frequently lose bone mass first in trabecular bone (the spine) which may lead to an underestimation of vertebral fracture risk. Also, many of the clinical risk factors in FRAX are dichotomous (yes/no) and do not take into account of dose response (for example, dose of glucocorticoid, number of previous fractures, etc). Current Japanese guidelines indicated that the treatment objectives are patients that are using or planning to use oral glucocorticoids for 3 months or longer with a fragility fracture, with less than 80% BMD of young adult mean, and with 5mg predonisolone equivalent or higher doses per day. We are now working on the revision of Japanese guidelines. Current Japanese guidelines recommended bisphosphonates as first-line drugs and active vitamin D3 or vitamin K2 as second-line drugs. Now in Japan, alendronate or risedronate provide the front-line treatment option in the majority of patients with glucocorticoid-induced osteoporosis.

LS13

Musculoskeletal ultrasound improves the management of rheumatoid arthritis

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Conflict of interest: Yes

Imaging techniques in rheumatoid arthritis (RA) have been substantially advanced along with the modern therapeutic strategies. The utility

of musculoskeletal ultrasound in the management of RA has been extensively studied since research showed that ultrasound can visualize both synovitis and bone lesions. This caused a paradigm shift in the imaging for RA because direct assessment of the activity of synovitis is impossible with plain radiograph. In the diagnosis of RA, ultrasound is more accurate than patients' symptoms or joint examination to detect the presence of synovitis. In addition, ultrasound is more sensitive than plain radiograph to detect bone erosion. Furthermore, ultrasound is useful in the diagnosis of conditions which can mimic RA, such as osteoarthritis, crystal arthropathy, and enthesopathies. Thus, ultrasound not only allows for sensitive diagnosis of RA, but also excludes differential diagnoses, and enables accurate diagnosis at an early stage before characteristic joint damages occur. In monitoring disease activity in RA, frequently used composite measures are not necessarily accurate due to the wide variability of joint examination skills, the influence of non-inflammatory pain, or the non-specific elevation of inflammatory markers. It is especially difficult to evaluate the activity of synovitis in atypical cases, at lower levels of disease activity, or under corticosteroid use. Ultrasound, on the other hand, can visualize the activity of synovitis and more accurately predict joint damage progression. Utilizing ultrasound in monitoring disease activity in equivocal cases can improve the clinical outcome of RA. In addition, ultrasound can assist arthrocentesis and injection. Furthermore, direct visualization of joint structure helps rheumatologists to understand pathophysiology of RA, improve joint examination skills, and have smooth communication with patients, which all contribute to better quality of the management of RA.

LS14-1

Prediction Markers in the treatment of RA by MTX and Bilogics

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Conflict of interest: Yes

Early diagnosis, early treatment and Treat to Target (T2T) are well prevalent dogmas of the current rheumatoid arthritis (RA) therapy. Based on the three recent systematic reviews, EULAR recommendation for the management of rheumatoid arthritis was updated in this year. In this updated version, EULAR recommended to change therapy if there is no improvement by at most 3 months after the start of treatment or the target has not been reached by 6 months. Therefore, it will be helpful for the practice for T2T if we can predict the efficacy of treatment before or soon after change the treatment. Moreover, because of the high-costs of biologic agents, early predictions of the therapeutic effects are also important for the medical economy. Previously, we reported that serum concentration of TNFa before treatment correlates with the clinical effect of Infliximab and serum concentration of IL-6 before treatment correlates with the clinical effect of Tocilizumab. These results suggest that serum concentration of these cytokines should be the prediction factors for the therapeutic effects of these agents. In addition, it has been also reported that the disease activity 12 weeks after treatment is a predictive factor for the induction of clinical remission and inhibition of radiographic progression. This seminar reviews the recent studies about identification of predictive factors of biologic agents for RA therapy. Furthermore MTX, this has been positioned as anchor drug in treatment of RA, should be reconsidered at this seminar. MTX dose and its intracellular concentration would be very important factor to predict its efficacy and safety in case of either mono-therapy or combination-therapy with biologic agent. This seminar tries to clarify critical prediction markers in the treatment of RA by MTX and biologics, and that should lead to more efficient and also safe achievement of the clinical remission for our RA patients

LS14-2

Inhibition of structural damage by TNF blockade

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Conflict of interest: Yes

Recent progress of treatment for rheumatoid arthritis (RA), such as combined treatment of MTX and biologic agents enable us to target clinical remission in the RA therapy. Moreover, long term maintenance of clinical remission results the induction of structural and functional remission. Currently, 5 TNFa inhibitors including 4 S.C. injectable agents are available in Japan. Among them, Golimumab is unique in its flexibility of treatment doses. Patients who are inadequately controlled with 50mg golimumab with MTX can increase dose 100mg. In addition, since Japanese phase III studies (GO-FORTH, GO-MONO) demonstrated the efficacy of golimumab 100mg monotherapy in reducing disease activity and inhibiting radiographic progression, Golimumb 100mg monotherapy is approved in Japan, ahead in the world. The efficacy of Golimumab 100mg in inhibition of radiographic progression of patients with different disease activities were re-analyzed from data of GO-FORTH study (261 RA patients inadequately controlled with MTX). When Golimumab 100mg showed similar efficacy with Golimumab 50mg on changes in TSS (⊿TSS) in patients with low disease activity (LDA: DAS28 (ESR)>3.2~≦5.1, CRP<1.5mg/dL), Golimumab 100mg was superior to Golimumab 50mg in in patients with high disease activity (HDA: DAS28 (ESR)>5.1, CRP≧1.5). These results suggest the clinical benefit of high dose Golimumab (100mg) therapy for the achievement of structural remission in patients with HDA. This seminar reviews the critical issue about progression of structural damage in RA and several approaches about inhibition of it.

LS15-1

Clinical Characteristics and Structural Damage Inhibition of Abatacept for Patients with Rheumatoid Arthritis

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Conflict of interest: Yes

Several clinical studies have indicated the usefulness of abatacept (ABT) in the treatment of patients with rheumatoid arthritis (RA). In Japan, the results of postmarketing survey of RA patients treated with ABT confirmed same superior clinical results. Interestingly, comparison between treatment with and without concomitant MTX showed no remarkable differences between two groups in clinical efficacies. However, whether there was a difference between the groups in suppressive effect on the progression of joint damage has not been clarified. We developed the FIT-RA (Fukui, Ishikawa, Toyama-Rheumatoid Arthritis) registry composed of many institutions in three prefectures in the Hokuriku District of Japan, and a retrospective multicenter study was conducted using this registry. All patients, except those without baseline radiographs, who started treatment with ABT were enrolled in the study. We analyzed the registry data to evaluate the clinical results of treatment with ABT and its suppressive effect on joint damage. The 48 patients with RA consisted of 27 patients treated with concomitant MTX and 21 patients treated without concomitant MTX. At week 52, 37% and 33.3% of patients with or without concomitant MTX achieved clinical remission, respectively. There was no significant difference in achievement of remission by the concomitant use of MTX. Rates of the structural remission at week 52 in patients with and without concomitant MTX were 58.3% and 68.4%, respectively. The radiographic changes were not also significantly affected by the concomitant use of MTX. ABT is a biologic that can be expected to show excellent efficacy for patients with RA, and it appeared possible to expect clinical efficacy and an inhibiting effect on the progression of joint damage whether administered concomitantly with MTX or not. In this seminar, we would like to talk about the clinical characteristics and inhibiting effect on the progression of joint damage of ABT in RA.

LS15-2

Expected role of abatacept ~Immunogenicity and effect estimation~

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Conflict of interest: Yes

Abatacept (ABT) has a characteristic action mechanism as a T cell selective costimulatory modifier. Post marketing surveillance (PMS) and

various clinical studies have revealed the effectiveness and safety. Recently, subcutaneous (SC) injection preparation became available, so we can chose an intravenous (IV) and SC preparation considering the situation of patients. In the results of PMS, there is not a big difference of the safety and effectiveness of ABT regardless of MTX combination and its dose. On the other hand, various arguments for the influence of MTX on the effectiveness and safety of TNF inhibitors have been done. The problem of immunogenicity is known to be able to explain this phenomenon. MTX can inhibit it to some degree. However, some patients have a difficulty of MTX use. It is expected that ABT suppress the production of anti-drug antibody (ADA), because ABT have the indirect action to B cells by acting to the T cell which is the upper stream of the function of immunity. In comparison with other biologics, the production of ADA of ABT is low and do not influence the effectiveness and safety? Also there is not a difference of the production by the route of administration? I want to do consideration to solve these questions. In addition, the indirect action to the B cells may become the signpost to an effect prediction of ABT. We conducted the ABROAD (ABatacept Research Outcomes as a first line biological Agent in the real worlD) study that examined the effectiveness and safety of ABT for biologic naïve rheumatoid arthritis (RA) patients. We examined 179 out of 230 RA patients with moderate and high disease activity, and suggest that autoantibody may be a predictor for good response to ABT. In Japan, I can use seven kinds of biologics now. How do you choose the best medication in consideration of various conditions? In this seminar, I would like to give an outline about a role of ABT in the treatment of RA from the knowledge of various clinical trials.

LS16

Choice of treatment for patients with rheumatoid arthritis based on the immunogenicity of biologics

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Conflict of interest: Yes

Rheumatoid arthritis (RA) is a multiple synovitis of unknown origin, and persistent inflammation causes destruction of joints, disability, decreased quality of life and reduced life expectancy. Accordingly, the earliest resolution of the synovitis has been considered the best treatment philosophy for RA to inhibit progression of joint destruction and permanent damage. However, remission as a goal in treating RA was not realistic because conventional csDMARDs had limited effectiveness for synovitis control. TNF-alpha blockers, which have become available in Japan since 2003, have made it possible to have remission as a treatment goal for RA in daily clinical practice. Both early intervention based on the new classification criteria for RA and tight control following treat to target are very important to achieve remission as defined by composite measures in current RA therapy. In patients responding insufficiently to oral csDMARDs, biologics such as TNF-alpha blockers should be started with methotrexate (MTX). Clinical trials and a few meta-analysis have recently demonstrated no significant heterogeneity among the biologics with respect to remission outcome. However, maintenance of remission is a prerequisite for inhibiting progressive joint destruction. Therefore, the biologic showing the least secondary failures and the highest safety would result in a better outcome for RA patients. The maintenance rate is an important point for selecting biologics. In particular, there have been many reports regarding the maintenance rate with TNF-alpha blockers. Although it is difficult to compare precisely, the maintenance rate of etanercept (ETN), TNF receptor: Fc fusion protein, tends to be higher than that of anti-TNF monoclonal antibody due to both the low immunogenicity of ETN and the low incidence of opportunistic infection such as tuberculosis with ETN treatment. The indications and choice of biologics for RA therapy are considered on the basis of their immunogenicity.

LS17

Pain management in rheumatoid arthritis

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Conflict of interest: Yes

Rheumatoid arthritis (RA) is a systemic disorder characterized by inflammatory synovitis. When the disease progresses, it results in the joint destruction and attenuates ADL and QOL of the patients. Patients with RA identify pain as one of their most troublesome problems, and pain adversely impacts on disability and psychological distress of the patients. Therefore, pain control is quite important for the treatment of RA. Pain in RA patients is caused by joint inflammation, and nociceptive mechanism is considered to play a central role. Prostaglandins and bradykinins produced by inflammatory synovium directly activate sensory nerves within the synovium, capsule and bone. Proinflammatory cytokines such as TNF-alpha, interleukin (IL)-1and IL-6 make the nerve more sensitive to the stimuli. In addition, nerve growth factor is produced by synovium and subchondral bone, and is at least partly involved in the pain in RA patients. Recent studies demonstrated that synovitis causes the biochemical changes in spinal cord and brain. Synovitus not only promotes the production of GABA and CGRP but also increases the expression of their receptors in the spinal cord. Production of TNF-alpha, IL-1 and IL-6 in microglia is also observed. The control of disease activity by disease-modifying anti-rheumatic drugs and/or biologics is critical for the pain management in RA patients. In addition, acetaminophen and opioid are also recommended to control pain. NSAIDs are also effective in reducing pain in RA patients, but the side effects such as gastrointestinal disturbance should be carefully monitored.

LS18-1

Biological disease-modifying anti-rheumatic drug use for achieving 'Treatment Holiday' in patients with rheumatoid arthritis

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Conflict of interest: Yes

Recently, some helpful guidelines for treatment strategy in patients with rheumatoid arthritis (RA) have been published in the international journals. Recently, the 2013 EULAR recommendation for the management of RA has been updated in Madrid. In *Overarching Principles* of the recommendation, 'RA incurs high individual, societal and medical costs, all of which should be considered in its management by the treating rheumatologist (item C)'. Also, in *Recommendation*, 'If a patient is in persistent remission, after having tapered glucocorticoids, one can consider tapering biological disease-modifying anti-rheumatic drugs (bDMARD), especially if this treatment is combined with a conventional synthetic (cs) DMARD (item 12)' and 'In cases of sustained long-term remission, cautious reduction of csDMARD dose could be considered as a shared decision between patient and physician (item 13)' are stated. These statements strongly suggest a possibility of 'Treatment Holiday' in a certain subset of RA patients. It is, however, difficult to achieve DMARD-free remission in real world. Until now, although clinical evidences of bDMARD-free remission have been reported in patients with RA, the drug discontinuation criteria and follow-up period are different among the previous studies. Additionally, inappropriate discontinuation of biological DMARD may result in bone destruction. There are not so many patients who could discontinue ant-rheumatic treatments including csDMARD. In such situation, anti-TNF-α antibody including adalimumab may be the most useful agent for achieving bDMARD-free remission. We, rheumatologists, should make efforts of maintaining maximum level of patient's quality of life and labor productivity as well as of considering economical issues. More sensitive biomarkers for optimization of RA treatment may be required for considering 'Treatment Holiday'.

LS18-2

Prediction of the achievement of "treatment holiday" of biological treatment using ultrasound

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Conflict of interest: Yes

Primary goal of the management of rheumatoid arthritis (RA) is to maximize patients' social participation and long-term QoL. Although bio-

logical treatment is a potent strategy to achieve this goal, its high cost is a substantial burden for both individual patients and society. Therefore, achieving "treatment holiday" can be extremely beneficial and encourage patients who newly start biological treatment. Recently, data on the treatment holiday of anti-TNF-alpha agents have been accumulated. However, not all patients who achieved clinical remission on biological treatment can achieve treatment holiday. Although some studies have shown that the deep remission at discontinuation can be a predictive factor for the achievement of treatment holiday, its accuracy is not necessarily high. We investigated whether the comprehensive ultrasonographic assessment of synovial inflammation predicts relapse after discontinuation of biological treatment in patients with RA. In a prospective blinded study, 42 RA patients in clinical remission (DAS28<2.6) receiving biological treatment who agreed to discontinue the biological treatment underwent a comprehensive ultrasound scan and were prospectively followed up for 6 months. The difference in DAS28 at baseline between patients who had and did not have a relapse was not statistically significant, whereas both total GS and PD scores were significantly higher in patients who had a relapse. Using the optimal cut-off values determined by ROC analysis, PPV and NPV were 80.0% and 73.3% for the total GS score and 88.9% and 74.2% for the total PD score, respectively. In RA patients in clinical remission receiving biological treatment, residual synovial inflammation detected by comprehensive ultrasound assessment predicts relapse within a short term after discontinuation of the biological treatment. Tight control aiming at true deep remission determined by ultrasound may enable the achievement of treatment holiday of biological treatment.

LS19

Role of non-biologic disease-modifying anti-rheumatic drugs (DMARDs) in the treatment of rheumatoid arthritis (RA) -Iguratimod as a new option of oral DMARDs-

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Conflict of interest: Yes

Disease modifying anti-rheumatic drugs (DMARDs) have a central position in RA treatment. DMARDs have capacity to reduce or improve symptoms and signs, disability, impairment of QOL, progression of joint damage, and cardiovascular comorbidity. Among DMARDs, MTX is considered as the first line drug and anchor drug since this drug has greater effectiveness than other non-biologic DMARDs and equivalent effectiveness to biologic agents, as well as greater tolerability and safety in most RA patients. In addition to effectiveness as monotherapy, MTX is highly effective in combination with other synthetic DMARDs and biologic agents. In the 2013 update of EULAR recommendations for the management of RA, MTX should be the first DMARD used in patients with active RA unless contraindicated. However, about 20% to 40 % of patients experience incomplete response to MTX and require further therapy, with several options including other non-biologic DMARDs, glucocorticoids, and biologic agents in combination with MTX. Non-biologic DMARDs, such as iguratimod (IGU), tacrolimus (TAC), and bucillamine (BUC), in combination with MTX may provide greater efficacy. In the results of Japanese phase III trial, IGU in combination with MTX was efficacious in active RA patients despite stable doses of MTX. In cases of MTX contraindications or early intolerance, salazosulfapiridine, BUC, leflunomide, TAC or IGU might be alternative DMRARDs by using alone or in combination. Furthermore, initial combination therapy with DMARDs could be a reasonable option in patients with poor prognostic factors. In this lecture, I discuss the role of oral synthetic DMARDs in the treatment of RA, especially focused on MTX and IGU.

LS20-1

Diagnosis and treatment of Eosinophilic granulomatosis with polyangiitis

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Conflict of interest: None

Eosinophilic granulomatosis with polyangiitis (EGPA; also known as Churg-Strauss syndrome) was defined as eosinophil-rich and necrotizing granulomatous inflammation often involving the respiratory tract, and necrotizing vasculitis predominantly affecting small to medium vessels, and associated with asthma and eosinophilia in Chapel Hill Consensus Conference 2012. In the five-factor score (FFS) 2009, elder age onset more than 65 years was elder age onset more than 65 years was the mortality and prognosis of EGPA in addition to cardiac and gastrointestinal involvement of FFS1996 and FFS2009. The etiology and mechanism of EGPA was unknown. We reported that, at onset of disease, EGPA patients had a lower frequency of T_{reg} cells and the frequency of T_{reg} cells increased at remission, and the percentages of $CD4^{+}CD25^{+}$ T_{reg} cells producing IL-10 and of Th17 cells reflect the disease activity of EGPA (JACI 2008;122:610, IAAI 2009;149:61). The mainstay of treatment for EGPA is systemic corticosteroid (CS) therapy. Additional treatments with immunosuppressive agents, such as cyclophosphamide or azathioprine, may be used in some patients. Other new treatment options include rituximab, anti-IgE therapy, anti-IL-5 antibodies, and intravenous immunoglobulin (IVIG). We reported the percentages of T_{reg} cells increased after the combination of IVIG and conventional therapy in EGPA patients. The increase in T_{reg} cells may promote induction of remission in EGPA and make it possible to reduced CS intake (JR 2012;39:1019). Whether the clinical and immunologic efficacy of IVIG is affected by disease phase (during initial treatment or at relapse after remission) is unknown. In addition, what characteristics of patients' disease condition influence whether remission is achieved after single or multiple courses of IVIG has not previously been assessed. We evaluated whether the frequency of T_{reg} cells varied depending on when IVIG was provided after the start of conventional therapy for EGPA.

LS20-2

The relationship among vasculitis, anti-lysosomal-associated membrane protein-2 (LAMP-2) antibodies, and anti-phosphatidylserine-prothrombin complex (PSPT) antibodies

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Conflict of interest: None

Lysosomal-associated membrane protein-2 (LAMP-2) was identified as part of a systematic search for antineutrophil cytoplasmic antibody antigens. Kain R et al. suggested that autoantibodies against LAMP-2 are closely linked to a subset of primary vasculitides. Anti-LAMP-2 antibodies bind to LAMP-2 on the surface of neutrophils and endothelial cells, and lead to ANCA-associated systemic vasculitis. Cutaneous arteritis (CA) and IgA vasculitis are known as representative cutaneous vasculitis. We found significantly elevated serum anti-LAMP-2 antibody levels in patients with CA and IgA vasculitis compared to healthy persons. A transgenic rat model, env-pX rats, has various types of necrotizing vasculitis including cutaneous vasculitis. Serum anti-LAMP-2 antibody levels were significantly higher in morbid env-pX rats than in wild type normal rats. In addition, the levels in the cutaneous vasculitis group of the morbid env-pX rats were significantly higher than the no cutaneous vasculitis group. Intravenous anti-LAMP-2 antibody injection into female premorbid env-pX rats under 3 months old induced cutaneous vasculitis. Anti-LAMP-2 antibody-binding neutrophils were detected in the cutaneous vasculitis. LAMP-2 and anti-LAMP-2 antibody could be involved in the pathogenesis and development of cutaneous vasculitis in env-pX rats. Anti-phosphatidylserine-prothrombin complex (PSPT) antibodies are one of antiphospholipid antibodies. Anti-PSPT antibodies were detected in all of CA patients and Anti-PSPT antibodies IgA were found most of IgA vasculitis patients. Serum anti- PSPT antibody levels were significantly higher in morbid env-pX rats than in wild type normal rats. In addition, the levels in the cutaneous vasculitis group of the morbid env-pX rats were significantly higher than the no cutaneous vasculitis group. It is important for clinicians to recognize these titers to permit early accurate diagnosis and treatment regarding vasculitis.

LS21

Denosumab, a monoclonal antibody against RANKL for osteoporosis treatment

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Conflict of interest: Yes

The interaction of RANKL with RANK is critical for the formation and function of bone-resorbing osteoclasts. Denosumab, a fully human monoclonal antibody against RANKL, is an anti-resorptive drug that acts by preventing RANKL from interacting with RANK on the osteoclast precursor cells. This inhibits the differentiation and function of these cells and is associated with fracture prevention at multiple sites. In 2010, denosumab (60 mg, subcutaneous injection every 6 months) was licensed by the FDA for use in postmenopausal women who are at high risk of osteoporotic fracture and for those that have been nonresponsive to other osteoporosis therapies. In 2012, it was approved by the FDA for treatment of osteoporosis in men with high risk of fracture, and also approved for treatment primary osteoporosis in Japan. When the effectiveness of denosumab and alendronate treatment in postmenopausal women was compared, denosumab was at least as effective at increasing BMD at the hip and lumbar spine. Although clinical effectiveness was maintained for up to 6 months following a single injection of denosumab, cessation of treatment was associated with a more rapid reduction in BMD compared with bisphosphonate therapy, since unlike bisphosphonates, denosumab is not incorporated into the structure of the bone itself and therefore resolution of denosumab-associated ONJ may be more rapid than bisphosphonate-induced ONJ if treatment is stopped.

LS22

Pathogenesis and new developments in therapy of systemic lupus erythematosus

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Conflict of interest: None

Systemic lupus erythematosus (SLE) can be a severe and potentially life-threatening disease that often represents a therapeutic challenge because of its heterogeneous organ manifestations. Pathogenesis of Systemic Lupus Erythematosus is not resolved. A variety of new experimental data suggest that a dysfunction of apoptosis might be involved in the initiation of autoimmunity finally leading to SLE. This includes signalling alterations in activated lymphocytes (leading to premature apoptosis), defects in the clearance of apoptotic material and genetic defects in the complement system. These mechanisms lead to an increased onflow of apoptotic (like apoptotic microparticles) or secondary necrotic material which will be recognized by immunocompetent cells especially if infections in the context of genetic variations like Fcg- or IL-8 polymorphisms occur. This will lead to T- and B-cell activation, synthesis of ANA or anti-ds-DNA antibodies, and finally to the precipitation of the disease. Estrogens might directly modulate the immune response and therefore favour a shift to a lupus-prone state. Only glucocorticoids, chloroquine and hydroxychloroquine, azathioprine, and cyclophosphamide, and very recently belimumab, have been approved for SLE therapy in Germany, Austria, and Switzerland. Dependence on glucocorticoids and resistance to the approved therapeutic agents, as well as substantial toxicity, are frequent. Therefore, treatment considerations will include “off label” use of medication approved for other indications. In this overview we will discuss the options and limits of the current therapy for SLE, including treatment with various biologics and innovative non-biologic DMARDs like Deoxyspergualin.

LS23-1

Biological versus conventional combination treatment in early aggressive rheumatoid arthritis. - JaSTAR Study-

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Conflict of interest: None

The use of biologics began to spread around the world within several years of their clinical introduction as drugs that exert rapid action and are expected to improve long-term prognosis and to allow patients with RA to maintain physical function. Nonetheless, there are still several open issues involved in the use of biologics. Guidelines in Western countries (EULAR, ACR and NICE) permit moving to therapy with biologics in cases that are poorly controlled despite attempts of treatment with DMARD combination therapy including MTX, even at the highest possible dose levels. In recent years, several reports have been published in the United States and Europe providing data intended to serve as evidence for the view that treatment with a combination of 3 small molecule DMARDs (MTX+SASP+HCQ) is expected to improve long-term prognosis of RA to an extent comparable with biologics. In the TEAR study and RACAT study, the outcome as to DAS28-ESR did not differ between the oral triple therapy and the etanercept plus MTX combination therapy. Swefot trial demonstrated significant reduction in the biologics plus MTX combination therapy group, with the inter-group difference being 1-2 in terms of total Sharp Heijde score, but no difference in improvement of clinical symptoms or loss of labor between both groups. The three drug combined therapy (MRX + SASP + HCQ) is not practically possible in Japan. We thus started a multicenter comparative clinical study on treatment of early stage RA with three small molecule DMARD combination therapy (MTX, SASP and Bucillamine) and biological TNF antagonists plus MTX combination therapy, involving nationwide 32 facilities of rheumatologist in Japan (JaSTAR study: Japan Strategic Treatment of Aggressive RA). Results of analyzed data during the 12 months revealed a similar DAS28 remission rate between the three DMARDs combination therapy group and the biological TNF antagonists plus MTX combination therapy group.

LS23-2

Trend of DMARD utilization

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Conflict of interest: Yes

Conventional disease modifying anti-rheumatic drugs still play a major role in treatment of rheumatoid arthritis. In the past several years combination therapy, particularly triple disease modifying anti-rheumatic drugs, are becoming more common as the equivalent effectiveness to biologics has been reported. In appropriate settings, preceding triple combination therapy to introduction of biologics seems to be beneficial in particular from economic stand point. In the non-erosive era, it is imperative to treat rheumatoid arthritis to target, and timely adjustment of medical treatment should not be postponed solely because of financial reason. However, early escalation of disease modifying anti-rheumatic drugs dose and initiation of disease modifying anti-rheumatic drug combination therapy can be a reasonable approach.

LS24

Clinical and histopathological features of IgG4-related disease

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Conflict of interest: None

IgG4-related disease (IgG4-RD) is a systemic disease of unknown etiology whose concept was not established until this century. This disease has long been diagnosed as a subtype of Sjögren’s syndrome or other autoimmune disease because it is often accompanied by hypergammaglobulinemia and hypocomplementemia. In addition, for many decades, patients had been treated under separate diagnostic monikers such as Mikulicz’s disease, autoimmune pancreatitis (AIP), and retroperitoneal fibrosis because of the lack of recognition of it as a systemic disorder. However, after the discovery of a close relationship between IgG4 and AIP, the diagnostic value of IgG4 attracted attention from specialists in many medical fields, and numerous medical conditions have been diagnosed as a part of the IgG4-RD spectrum using immunohistochemical

method. Until now, diverse lesions of a variety of organs have been recognized as organ manifestations of IgG4-RD. Frequently involved organs include the pancreas, lacrimal glands, salivary glands, kidneys, and aorta. Each lesion has the common histopathological feature of dense lymphoplasmacytic infiltration with abundant IgG4 positive plasma cells. Another pathological feature is storiform fibrosis. Obliterative phlebitis and eosinophilic infiltration also support the diagnosis. IgG4-immunostaining revealed that some cases of Churg-Strauss syndrome, granulomatosis with polyangiitis, and Castleman's disease also show IgG4-positive plasma cell infiltration in their affected organs. Therefore, IgG4 is not a perfect tool but merely a marker, and prudent consideration based on extensive clinical and laboratory data is mandatory before a diagnosis of IgG4-RD can be made with certainty. In this lecture, I will provide an overview of the most up-to-date clinical features of this disease and key points to differentiate it from other mimickers such as ANCA-associated vasculitis and Castleman's disease.

LS25-1

Basic and clinical considerations of bone destruction and repair in rheumatoid arthritis

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Conflict of interest: Yes

During the clinical course of rheumatoid arthritis (RA), inflammation is the key trigger for progressive local and systemic bone damage. Important roles of interleukin-6 (IL-6) in joint inflammation and bone homeostasis have been suggested in experimental studies, whereas IL-6 receptor (IL-6R) blockade by Tocilizumab (TCZ) improves the signs and symptoms of rheumatoid arthritis (RA) and retards bone damage. Receptor activator of NF-κB ligand (RANKL) is an essential factor for osteoclastogenesis and expresses in synovial fibroblasts (RASF), Th17 cells and B cells. IL-6 induces the expression of RANKL in RASF in the presence of soluble IL-6R. Interestingly, recent data suggest that bone loss may already starts during the preclinical disease phase of RA before joint inflammation starts. IL-6 promotes the differentiation of Th17 cells from naïve $CD4^+$ T cells, and IL-6R blockade is known to suppress the differentiation of Th17 in experimental model of RA. It has been recently reported that IL-6 stimulation significantly decreased sphingosine-1-phosphate (S1P) -directed chemotaxis of osteoclast precursor cells (OCPs). IL-6 increased the number of OCPs in the bone marrow via up-regulating S1PR2, thus playing a crucial role in systemic bone loss induced by inflammation. It has been recognized that radiographic healing occurs even in patients with longstanding RA when clinical remission has been achieved. After two monthly infusions of TCZ, osteoprotegerin (OPG)/RANKL ratio increased, Dickkopf-1 (DKK-1) decreased and sclerostin increased comparing to baseline. More recently, micro CT examination on bone erosions in the metacarpo-phalangeal joints of 20 patients revealed that TCZ can induce limited repair in a subset of erosions, particularly in large lesions with sclerosis. These in vivo and in vitro evidences might reflect the favorable impact of TCZ on local bone destruction and remodeling in patients with RA.

LS25-2

Rheumatoid Arthritis from the Bone Perspective: Bone Destruction Inhibiting Effects of Tocilizumab

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Conflict of interest: None

One important goal of treatment for rheumatoid arthritis (RA) is suppression of bone destruction. We are conducting clinical study at 34 facilities in the Tohoku region to investigate the clinical efficacy including inhibition of bone destruction and safety of tocilizumab (TCZ) in clinical practice (Michinoku Tocilizumab Study Group). The subjects are 270 patients who began TCZ treatment until 2010, and the disease activity of the registered patients was evaluated continuously for 3 years. Bone changes were examined by modified Total Sharp Score (mTSS) in 130 of these patients. The overall continuation rate was 80.4% at 1 year and 59.1% at 3 years. This study revealed the following characteristics of inhibiting bone destruction by TCZ in actual clinical use. (1) The rate of structural remission (ΔmTSS$\leq$0.5) was 69.2% at 1 year. (2) Previous use of biological agents was identified as a factor which statistically makes structural remission difficult to attain. (3) Whether or not MTX was used during TCZ treatment was unrelated to structural remission. (4) High RF, anti-CCP antibody positive and high disease activity before beginning treatment were unrelated to achieve structural remission during TCZ treatment. (5) In the first year of evaluation there were cases of rapidly progressing bone destruction instead of achieving clinical remission. (6) The rate of structural remission in the TCZ continuous administration group from year 2 to 3 was 88.9%, showing that bone destruction could be suppressed even in patients who could not achieve structural remission in the first year by continued TCZ treatment thereafter. (7) The number of swollen joints was the most relevant factor in the progress of joint destruction. These results indicate that TCZ can greatly improve joint prognosis of RA even as a single agent with measures to reduce swollen joints early in treatment, and long-term continuous administration while using swollen joints as an index.

LS26

The treatment specific for connective tissue disease-related pulmonary hypertension

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Conflict of interest: Yes

Pulmonary arterial hypertension (PAH) related to connective tissue disease (CTD) is a rare complication which is one of the intractable disorders. However, the frequency of PH complication is approximately 10% in patients with systemic lupus erythematosus (SLE), mixed connective tissue disease (MCTD), or systemic sclerosis (SSc), which are not rare conditions. In PAH with SLE, immunosuppressants are effective for reducing pulmonary arterial pressure, as well as in PAH with MCTD. Conversely, an immunosuppressive therapy can not improve PAH with SSc. These difference in treatment between SLE and SSc is explained by the distinction of the pathogenesis of those diseases. The treatment of PAH with SSc should be started using vasodilators specific for pulmonary artery including PDE5 inhibitor. In particular, PH related to interstitial lung disease (ILD) was frequently complicated with patients with SSc. We select PDE5 inhibitor as the first line therapy for PH related ILD. In this seminar, I summarized the therapy for PH in various situations of CTD.

LS27

T cell target therapy in autoimmune diseases

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Conflict of interest: Yes

Rheumatoid arthritis (RA) and Sjögren's syndrome (SS) are thought to be autoimmune diseases, because there exist a lot of autoantibodies in the serum and autoantigen-reactive T cells in inflammatory organs. To clarify the pathogenesis in RA and SS, T cells infiltrating in rheumatoid synovitis from patients with RA and labial salivary glands (LSG) from patients with SS and their autoantigens have been analyzed as followings. 1) The majority of T cells in rheumatoid synosium from RA patients and LSG from SS patients were CD4+ T cells. They were mainly polyclonal but some were clonal. 2) Clonal T cells function as autoreactive T cells and triggered chronic inflammation. 3) Some of autoantigens recognized by T cells in rheumatoid synovium were type II collagen (CII) and glucose-6-phosphate isomerase (GPI), and autoantigens in LSG from SS patients was M3R muscarinic acetylcholine receptor (M3R). 4) T cell epitope of CII, GPI, and M3R were elucidated and analogue ligand peptides (APLs) were also selected. 5) Each APL suppressed and/or prevented CII induced arthritis (CIA), GPI induced arthritis (GPI), and M3R induced sialadenitis (MIS) mice, respectively. In contrast, CD28-CD80/CD86 interaction is also necessary to active T cells as a second signal pathway in addition to TCR-antigen-MHC interaction. CTLA4 is also expressed on

T cells, bind CD80/CD86 on antigen presenting cells (APCs), and regulate T cell activation by negative signal. Therefore, CTLA4-Ig (abatacept) was developed as T cell inhibitory molecule and used as biological therapy against RA. Recently, there are several reports on the therapeutic effect on SS patients with RA. In this luncheon seminar, I would like to present the above experimental and clinical review.

LS28-1

A personalized medicine approach to biologic treatment of rheumatoid arthritis

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Conflict of interest: None

In Japan, TNF inhibitors available for clinical use include infliximab, etanercept, adalimumab, golimumab and certolizumab. In addition, tocilizumab (IL-6 inhibitor), abatacept (T lymphocyte antagonist) and rituximab (B lymphocyte inhibitor) are now used clinically. The guidelines in western countries, however, do not show define criteria for identifying which of biologics as the 1st Bio is recommended for each cases. According to ACR recommendation, the first biologics (1st Bio) recommended for treatment of early rheumatoid arthritis with disease duration of less than 6 months is a TNF inhibitor. According to the NICE Guidance, abatacept and rituximab (non-TNF inhibitory biopharmaceuticals) are unsuitable as the first-line 1st Bio. In this situation, to reveal which of biologics as a 1st Bio is best selection for individual patients is important for rapid remission and reduction of care costs. Comparison of TNF and IL-6 shows mostly the same pharmacological effects due to cytokine redundancy. Examples of this include the induction of synovial proliferation, induction of inflammatory cytokines, and articular destruction. However, a characteristic effect of IL-6, which is stronger than that of TNF, is the induction of peripheral platelets in bone marrow megakaryocytes. The effect of IL-6 to induce C-reactive protein in hepatocytes is also thought to be stronger than the effect of TNF. When the outcomes of cases in which tocilizumab was selected as the 1st Bio were compared in rheumatoid arthritis patients stratified by pre-treatment platelet levels, improvement in rheumatoid activity due to tocilizumab was found to be more marked in patients with high pre-treatment platelet levels (≥400,000 /μL of blood) than in those with normal platelet levels. From these results, the effects of IL-6 are stronger than the effects of TNF in patients with rheumatoid arthritis of high activity and high platelet levels, which might be a good indication for the use of tocilizumab.+

LS28-2

Treatment target for RA patients and the EBM of IL-6 inhibition ~ The perspective from a hospital physician ~

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Conflict of interest: Yes

Rheumatoid arthritis (RA) is a systemic inflammatory autoimmune disease which originates primarily in the synovial tissue. Early diagnosis and aggressive therapy for RA is essential since irreversible functional damage occurs with the progression of joint destruction. Due to the introduction of biologics that target the inflammatory cytokines such as TNFα and IL-6, RA therapy has advanced dramatically and increased patient satisfaction. This development has led us to aim for a higher treatment goal as the "Treat to Target" concept states the importance of tight disease control to achieve and sustain remission. The new ACR/EULAR classification criteria and stringent remission measures have triggered a paradigm shift in RA treatment over the last ten years. Comprehensive therapeutic strategy has been developed by the new 2013 EULAR treatment recommendation. Tocilizumab (TCZ), a humanized anti-Interleukin-6 receptor monoclonal antibody, developed in Japan. EULAR recommendations recommend TCZ as one of the first-line biologics and many scientific evidences have been accumulated. In the REACTION study, approximately 40% of patients achieved clinical remission and 60% achieved structural remission with TCZ after one year albeit many refractory and severe RA patients were enrolled in this study. Consistent safety data from 7,901 patients were obtained from post marketing surveillance. In addition, subcutaneous (SC) injection of TCZ was approved in Japan last year ahead of other countries. Having both intravenous (IV) and SC injections offer convenience for institutions with limited bed spaces and also for patients who cannot regularly visit the hospital. In this symposium, I'd like to explore the optimal treatment for RA patients and discuss the updated scientific evidences of TCZ IV and SC formulation with the importance of IL-6 inhibition.

LS29-1

Importance of small joints evaluation in the diagnosis and therapy of early RA- including image modalities-

Isao Matsumoto
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Conflict of interest: Yes

Joint destruction in RA occurs very early. Around 70 % of patients with RA suffer joint erosion by X-ray within 3 years after diagnosis. Several definition of "early RA" exists, this definition is very important, because early intervention of RA results in remission, possibly prevents joint destruction in the future. To catch up "window of opportunity " in RA treatment, classification criteria of early RA was published in 2010 by ACR/EULAR. To classify RA, minimum one joint swelling is needed, and we should rule out other possible diseases possessing arthritis. After that, we need to evaluate 4 domains, and if the patients reach to 6 points as definite RA, otherwise we need to follow up consecutively. In 2012, ACR recommendation for treating early RA was published, and they defined early RA as within 6 months after arthritic symptoms. Disease duration, activity, and 4 factors of poor prognosis was evaluated, we must make individual therapeutic strategy. The goal of the treatment is remission or low disease activity. Thus, therapeutic strategy is different by individual patients. For example, if patients are in low disease activity and do not have poor prognosis factor, single DMARDs therapy is recommended. If they are in high disease activity and have poor prognosis factors, MTX or/plus TNF inhibitor should be considered. Moreover, in EULAR recommendation of 2013, if we classified RA, MTX should be considered first with/without the combination of DMARDs and/or steroid. If they are resistant to those therapies with poor prognosis factors, biologics should be considered. In this seminar, recent updates of pathogenesis and diagnosis/therapy of early RA will be discussed. Also, we will show our experience of imaging modality (including cMRI) for small joints involvements of early RA.

LS29-2

Imaging Evaluation in Rheumatoid Arthritis – Evaluation of Large Joints by ARASHI Scoring System and T2T Practice using Joint Ultrasonography –

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Conflict of interest: Yes

Larsen grade is widely used in radiographic evaluation of large joints with rheumatoid arthritis (RA). However, this grading system, composed of only 6 grades, has several limitations that small changes within a grade cannot be evaluated. We previously developed the ARASHI scoring system (Mod Rheumatol 2013), which resolves several problems of the Larsen grading system and enables easy and detailed evaluation of large joints. The ARASHI score is composed of "status score" to assess the baseline status and "change score" to assess the change during follow-up compared with baseline. Using this system, hip joints (n=96) and knee joints (n=86) in RA patients treated with TNF blockers were evaluated. We assessed the correlation between the ARASHI status score and the ARASHI change score at 2 years after treatment. We found that, in all joints with ARASHI status score ≥ 3 (n=12), the change score increased more than 1 point during 2 years. In contrast, among joints with status score ≤ 2, change score of more than 1 point were observed only in 6.5% of these joints. Furthermore, among status scores, the joint space narrow-

ing score was strongly correlated with the progression of joint destruction. EULAR recommendations for imaging of the joints indicated that joint inflammation (synovitis) detected by ultrasound (US) can be considered for the prediction of the further joint damage progression, and that US can detect synovitis which predicts further joint damage even in clinical remission. In order to prevent joint damage progression completely, RA should be managed stringently, and US findings may help this. In particular, RA patients with clinical remission, imaging evaluation with US is helpful for tight control aiming at no joint damage progression. In this seminar, we would like to discuss the importance of radiographic evaluation in large joints and the T2T practice with US.

LS30-1

Reconsideration of the tight control in rheumatoid arthritis therapy

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Conflict of interest: Yes

Rheumatoid arthritis is characterized by an imbalance in the activities of inflammatory cytokines, such as tumor necrosis factor and interleukin 6, within the synovial tissue of affected joints. Biological disease modifying anti-rheumatic drugs, such as inhibitors of tumor necrosis factor, have greatly improved the treatment of patients with rheumatoid arthritis. Timely initiation of biological therapy, with rapid attainment of a clinical target (e.g., remission or low disease activity), minimizes joint damage and preserves physical function. Achievement of the concept "Treat-to-Target (T2T) was attained by the appearance of several biologic agents. In Japan, seven biologic agents are approved as curative medicine for RA treatment in 2013. In the case of golimumab, a human anti-TNF monoclonal antibody generated by transgenic method, 100mg is available in addition to 50mg of the global standard in Japan. Therefore, it might be easier by using this two dosage properly to practice T2T. Nevertheless, information about the most effective use of golimumab, notably the best possible dose to initiate and potential consequences of later exchange of dosage, is unavailable. To reconsider the meaning of tight control, I would like to express an idea based on previous reports and a real clinical experience as to unaddressed questions: whether results might be affected by the target selected, specifically low disease activity versus stringent remission; whether radiographic no progression can be captured in remission; whether the concept of sonographic remission can be acceptable; whether golimumab 100mg might be powerful biologic agent; whether disease control can be maintained by golimumab 50mg in patients who achieved low disease activity by golimumab 100mg; and whether golimumab can be withdrawn in patients attaining stable low disease activity or remission.

LS30-2

Safety management of biologic use in rheumatoid arthritis

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Conflict of interest: Yes

Over the past 10 years, treatment algorism of rheumatoid arthritis (RA) has made remarkable progress. Updated recommendations for achieving optimal therapeutic outcomes in RA include a state of clinical remission as the primary target for treatment, and frequent adjustment of drug therapy is required until completion of the desired treatment target. Introduction of biologics, including abatacept, adalimumab, certolizumab pegol, etanercept, golimumab, infliximab, and tocilizumab, have significantly contributed to this evolution. In these circumstances, the most important safety concern with the biologic therapies remains the increased risk of infection. Physicians should exercise caution when considering the use of biologic therapies in patients with RA. Tips on how to minimize serious infection include (i) screening programs of latent infection of potential pathogenic microorganisms, including Mycobacterium tuberculosis, hepatitis B virus, and Pneumocystis jirovecii, prior to biologic treatment; (ii) treatment decision based on favorable risk-benefit balance; (iii) preventive use of anti-tuberculosis, anti-hepatitis B virus, anti-pneumocystis drugs when applicable and inoculation of vaccines; (iv) monitoring of new infection and reactivation of latent infection during the treatment; and (v) prompt introduction of treatment at onset of acute lung injury. It is also necessary to be cautious about rare events potentially induced by use of anti-TNF agents, such as psoriasis, demyelinating disease, and sarcoidosis. Finally, longer follow-up may be necessary to determine the association between biologic therapy and malignancy. In summary, appropriate safety management is crucial to maximize the benefits of biologic treatment in patients with RA.

LS31

Role of tacrolimus in the treatment of connective tissue diseases

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Conflict of interest: None

Connective tissue diseases have diverse clinical manifestations, such as symptoms of the joints or surrounding tissues in rheumatic diseases or symptoms caused by immunity to autoantigens in other autoimmune diseases. For rheumatoid arthritis (RA), availability of various oral DMARDs, high-dose MTX, and biological products has increased the treatment options. In contrast, management of other autoimmune diseases is still based on steroids and immunosuppressants, but it is important to treat each patient appropriately by considering both the short-term and long-term outcome and the QOL. Tacrolimus (TAC) is an immunosuppressant, a macrolide metabolite of *Streptomyces tsukubaensis*, which targets T cells. TAC was approved for RA in 2005, for lupus nephritis (LN) in 2007, and for polymyositis/dermatomyositis (PM/DM) patients with interstitial pneumonitis (IP) in 2013. The role of TAC in various connective tissue diseases will be discussed using overseas and Japanese evidence. For RA, combined therapy with oral DMARDs is prominent in the EULAR Recommendation 2013. In Japan, efficacy and safety of TAC plus oral DMARDs such as MTX have been reported, and this combination is useful for patients with a poor response or in whom the MTX dose cannot be increased. LN influences the prognosis of SLE. Combining a steroid with cyclophosphamide is useful remission-induction therapy, but there are problems with infection, myelotoxicity, and the long-term risk of malignancy. We will discuss the treatment of LN based on the results of remission-induction therapy using TAC and mizoribine at our hospital. IP is a complication that influences the prognosis of PM/DM. In particular, IP associated with amyopathic dermatomyositis (ADM) can sometimes progress rapidly and responds poorly to steroids alone. TAC was approved for PM/DM associated with IP last year, but there is little evidence about its use. We will also present the recent advances of diagnosis and treatment of PM/DM.

LS32

Osteoporosis treatment using anabolic agents

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Conflict of interest: Yes

Japan is one of the most aging countries in the world, and the proportion of people aged over 65 years old in the total population is highest in the world. By 2030, one in every three people will be over 65 years old and one in five people over 75. The aging of the society results in the increase in the number of osteoporosis patients, and more than 12 million osteoporosis patients exist in Japan. For aged people, to maintain mobility is critical for keeping independence, and osteoporotic fractures such as vertebral fractures and hip fractures are major causes of disability, morbidity and mortality in older people. The treatment of osteoporosis by anti-resorptive agents such as second and third generation bisphosphonates and selective estrogen receptor modulators (SERM) successfully reduces the osteoporotic fractures. However, the fracture prevention using these agents is not sufficient and several adverse events have been recognized. Teriparatide is an anabolic reagent which efficiently increases bone mass by stimulating novel bone formation, and prevents osteoporotic fractures. In this seminar, I would like to introduce the mechanisms of action of

teriparatide and the state of the art of the osteoporosis treatment in Japan.

LS33-1

Clinical features and prognostic risk factors in elderly patients with rheumatoid arthritis

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Conflict of interest: Yes

Rheumatoid arthritis (RA) is a chronic inflammatory disease causing joint destruction and functional disability. Although the disease is commonly diagnosed between the ages of 30 and 50, the mean age at diagnosis has increased recently in an aging society. Persons aged 65 years or older account for the fastest growing population in industrialized countries, especially in Japan, where the proportion increased from 12% of the total population in 1990 to 23% in 2010. These observations suggest the number of elderly patients with RA will increase over the next decade. Various studies have reported clinical feature, radiological outcome and physical function of patients with elderly-onset rheumatoid arthritis (EORA) diagnosed after the age of 60. However, it has not been clearly established whether there are important clinical differences between EORA and younger-onset rheumatoid arthritis (YORA). Two large prospective cohort studies assessed the effectiveness of TNF inhibitors in elderly patients with established long-standing RA in daily clinical practice and suggested that it was more challenging to control disease activity and normalize physical function in the elderly RA population compared to in younger RA population. Treat-to-target is the consensus treatment strategy for patients with RA. The management of RA should shift towards earlier more intensive treatment strategies, and EULAR Task Force emphasizes that risk stratification is an important aspect in the therapeutic approach to RA. Biologics should be considered when poor prognostic factors are present. This may be same as elderly patients. This seminar reviews the clinical features and prognostic risk factors in elderly patients with RA. I also present my data about structural damage and physical disability of MTX-naïve elderly patients who were treated aiming at low disease activity (LDA) by non-biologic and biologic DMARDs.

LS33-2

The Therapeutic Strategy for Elderly Rheumatoid Arthritis (ERA): What is the optimal "Treat-to-Target" in the ERA patients ?

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Conflict of interest: Yes

Recent progress in the treatment of rheumatoid arthritis (RA), including the early use of disease-modifying antirheumatic drugs (DMARDs) and the arrival of the 'biologic agents' era, has provided remarkable benefits to RA patients, resulting in a paradigm shift from "relief of clinical symptoms" to "remission." To prevent structural damage and functional disability, the importance of early aggressive intervention using DMARDs is emphasized in the most recent "RA treatment guidelines." Population-growth in the elderly and a better outcome for RA patients contribute to a significant increased number of elderly RA (ERA) patients who develop RA after the 65 years of age. It has also been shown that age of onset of RA is increasing and tighter control to improve quality of life is required in ERA patients. However, there are no specific recommendations regarding patient age for the use of these agents in the elderly population, and a small dose of corticosteroid and conventional DMARDs such as salazosulfapyridine, bucillamine, and mizoribine, are frequently used, taking into consideration patient co-morbidities and drug toxicity profiles. There are a number of obstacle factors for optimal treatments in ERA patients; 1) patient age, drug pharmacokinetics, decreased renal function and drug metabolism, 2) co-morbidities and other risk factors including heart disease, chronic lung disease, diabetes, infections, osteoporosis, malignancies, 3) interaction with concomitant medication and polypharmacy, 4) limitations in the number of clinical studies addressing the efficacy and safety of these medications in elderly patients. In this seminar, I will provide updated information regarding these issues and propose a suitable therapeutic strategy according to disease activity, with the aim of achieving disease remission as well as adjusting for individual characteristics in ERA patients.

LS34

Current management of systemic sclerosis and related autoimmune syndromes

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Conflict of interest: Yes

Systemic sclerosis (SSc) belongs to the family of autoimmune connective tissue diseases, which involve the human organism as a whole, and is still a challenge to every practising physician. SSc as prototype for these syndromes is characterized by progressing fibrosis of the skin and internal organs, an abnormal activation of the immune system and distinct changes in microcirculation. The increased morbidity and mortality depends predominantly on the extent of involvement of the affected organs in all disease subsets. Therefore, it is essential to diagnose SSc early and to identify and monitor closely all complications. Along this line, especially the pulmonary and gastrointestinal involvement is frequently neglected by the patients and physicians owing to its primarily not life-threatening appearing character, which results in a substantially delayed therapy and contributes significantly to morbidity and mortality in the affected patients. However, several approaches towards earlier diagnosis such as the EUSTAR-based VEDOSS program or the development of easier algorithms to detect pulmonary hypertension very early in the course of disease have improved the management of the patients significantly. These developments are being supported by novel advances in the therapeutic armamentarium in combination with up-to-date clinical trials such as the deSScipher initiative to facilitate a better long-term management of patients with this debilitating disease and its related syndromes

LS35

Iguratimod as a new member of conventional DMARD

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Conflict of interest: Yes

Iguratimod is a new member of conventional DMARD available in Japan. Conventional disease modifying anti-rheumatic drugs still play a major role in treatment of rheumatoid arthritis. However drug survival of disease modifying anti-rheumatic drugs is not very high, even that of methotrexate. To maintain stable remission, it is beneficial to have more choices for initial treatment and also to switch from one disease modifying anti-rheumatic drug to another disease modifying anti-rheumatic drug. Iguratimod has an anti-inflammatory property for the treatment of rheumatoid arthritis. It is approved as a treatment of rheumatoid arthritis in China and Japan. Its mechanism of action is mainly explained by the suppression of nuclear factor kB (NF-κB). In the past several years combination therapy, particularly triple disease modifying anti-rheumatic drugs, are becoming more common as the equivalent effectiveness to biologics has been reported. However, there is no clear consensus which combination of disease modifying anti-rheumatic drugs are superior. In the non-erosive era, it is imperative to treat rheumatoid arthritis to target, and timely adjustment of medical treatment is critical. We would like to discuss how iguratimod can be incorporated into the modern treatment of rheumatoid arthritis based on our clinical experience.

LS36

Current strategy for the treatment of connective tissue disease-related pulmonary hypertension

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Conflict of interest: Yes

Connective tissue disease is one of autoimmune diseases of unknown

etiology. The complication of pulmonary hypertension (PH) is seen in approximately 10% of patients with systemic sclerosis (SSc), mixed connective tissue disease (MCTD), and systemic lupus erythematosus (SLE). In 2013, the 5th World Symposium of pulmonary hypertension was held in Nice. PH was defined as resting mean pulmonary artery pressure > 25 mmHg under right catheterization. We speculate that the pathophysiology of PH in SLE and MCTD might be different from that in patients with SSc. Immunosuppressant is efficient for the treatment of PH with SLE and MCTD, but it is not for the treatment of PH with SSc. The distinction of the response to the immunosuppressive therapy may be explained by the difference of pathophysiology between two diseases. In patients with SSc, pulmonary arterial hypertension (PAH) is associated with the poor prognosis. We recommend PAH with SSc should be treated by PDE5 inhibitor as soon as possible after resting mean pulmonary artery goes up 20 mmHg.

LS37

Clinical characteristics of hyperuricemia and the condition of the patient with gouty arthritis for applying joint ultrasonography

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Conflict of interest: Yes

Gouty arthritis is one and only clinical symptom of hyperuricemia (HU) because of phagocytosis of deposit of uric acid (UA) crystals in joints. This leads to a sudden intense pain, but interval is distinctively long at the early stage. Thus, most of patients didn't have continuous UA-lowering therapy and then, gouty arthritis were repeated. After a while, an acute attack was advanced to chronic arthritis. Clinical conditions of each stage were quite difference in joint ultrasonography. On the other hand, UA crystals were also accumulated in kidney and lead renal dysfunction when most patients started UA-lowering therapy at last. eGFR of our patients were already lower by over 10 than those of healthy subjects at 40 years old. UA-lowering therapy can improve renal function in patients without uneven renal surface by abdominal ultrasound. Usual UA-lowering drugs, allopurinol and benzbromarone, couldn't sufficiently lower UA in the patients with low renal function. Febuxostat, which was approved in 2011, has strong UA-lowering effects and safety even in patients with low renal function. HU is significantly concerned with genetic factors and lifestyle. Visceral obesity was observed in lots of patients and visceral fat was thought to lead insulin resistance. Insulin resistance is well known as an inducer of diabetes as well as risk factors for dyslipidemia, hypertension and HU in obese patients. Patients with fatty liver were frequently observed and progression from fatty hepatitis to liver cirrhosis and cancer must be taken care. Intervention for lifestyle-related disease by lifestyle guidance and drug therapy is required for patients with HU. In this seminar, we will report (1) clinical characteristics of patients with gout/HU in our clinic, (2) efficacy of febuxostat in patients with low renal function, (3) evaluation of fatty liver and renal dysfunction by abdominal ultrasound, (4) evaluation of condition of gouty arthritis by joint ultrasonography.

LS38-1

Treatment of Rheumatism in the "Inflammation-Free" Age
-What make the RA patient "painfull"?-

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Conflict of interest: Yes

The recent emergence of biological drugs, however, made it possible to eliminate inflammation all together, creating an "inflammation-free" condition. Since most of disease activity assessment methods incorporate the patient's subjective assessment of pain, efforts for pain relief has a critical importance. If a patient evaluates his or her pain as bad in spite of better results by objective assessment using, for example, the degree of articular swelling and CRP, the disease activity index would show a higher mark, and low levels of disease activity and clinical remission, which are the target of most treatments, would be difficult to attain. We administered a formula containing tramadol hydrochloride and acetaminophen (Tramcet) to patients with the self-assessed pain level of 30 mm or greater on a 100 mm visual analogue scale (VAS) in spite of being given a standard treatment. As a result, their disease activity levels, evaluated by DAS28-CRP (4) or SDAI, decreased by a significant margin, despite that Tramcet is not an anti-inflammatory drug. This demonstrates that sufficient pain treatment is extremely important even when inflammation is under control, especially in the context of the current RA treatment that aims to achieve lower disease activity levels. Furthermore, pain disorders such as fibromyalgia syndrome, are becoming the target of aggressive pain treatment. Organic pains are commonly grouped into nociceptive pain and neuropathic pain, and when the organic cause of pain is not clear, it tends to be classified as a psychogenic pain. It is thought, however, that one of the factors that cause non-organic pain is functional pain syndromes or central nervous system dysfunction. The introduction of the concept of central nervous system dysfunction being a cause of pain would promote aggressive therapeutic intervention for relieving non-organic pain by preventing it to be immediately labeled as psychogenic one, and benefit both medical practitioners and patents.

LS38-2

Remission of Rheumatoid arthritis has been achieved, but the patients still complain of joint pain!: the mechanisms of the pain and its pharmacotherapy

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Conflict of interest: Yes

Rheumatoid arthritis (RA) is one of autoimmune diseases. RA induces inflammation in mainly joints and thereby patients with RA usually complain of joint pain. The underlying mechanism of such joint pain is called as nociceptive pain. Nociceptors on the peripheral nerve endings, which innervate into every tissue, are stimulated by the inflammatory 'soup' and nociceptive information is recognized as pain in the brain. Nociceptive pain is really physiological because nociceptive pain works as an alert of noxious stimulus to protect our body. However, either excessive noxious stimulus or successive nociceptive inputs, for example persistent inflammation, can lead to the hyper-activated state of the nociceptive neurons in the central nervous system. Such hyper-activation of the neurons are substantially comparable in function and capabilities of that in neuropathic pain, which is derived from lesion or diseases of the somatosensory nervous system. Further, RA can destroy peripheral tissues including nerve fibers. And thereby, RA has a potential to directly cause neuropathic pain. Moreover, in the CNS, in adition to the ascending nociceptive pain pathway from nociceptors to the brain, there is the descending pain modulation pathway, in which neurons mainly in the brain stem facilitate or inhibit activity of the spinal dorsal horn neurons according to peripheral nociceptive inputs. Persistent nociceptive pain enhances the descending 'facilitatory' pathway, and on the other hand, neuropathic pain attenuates the descending 'inhibitory' pathway. As the result, both nociceptive and neuropathic pain can cause dysfunction of the descending pain inhibition and hyper-activation of the spinal nociceptive neurons. Here, I present a practical approach of several lines of pharmacological treatment strategy for RA pain on the basis of underlying mechanisms. Among variety of analgesics, I focus clinical usefulness of pregabalin for neuropathic pain and tramadol for nociceptive pain.

Evening Seminar

ES1-1

The significance of IL-6 signal blockade for the treatment of RA

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Conflict of interest: Yes

The treatment strategy of Rheumatoid Arthritis (RA) has dramatically improved over the last decade due to the introduction of biologic agents. The new ACR/EULAR classification of RA and the "treat to target" concept enabled us to aim for a higher remission standard and allowed the patients (pts) to obtain better outcomes. Since each biologic agent differs in terms of efficacy, the function of the inflammatory cytokine network should be considered when selecting a drug for treating RA. In the RISING Study, TNFα and IL-6 concentration levels were examined for pts who received Infliximab (IFX) for 54 weeks. Remission rates were lower in pts who could not decrease the IL-6 level. This implies the importance of suppressing IL-6. In the Keio 1st-Bio Cohort, serum biological markers using ultra-sensitive ELISA and clinical responses were measured for 127 pts. 70 pts received Tocilizumab (TCZ) and 57 pts received IFX for 6 months. Baseline characteristics such as disease duration and disease activity were similar between the two groups. The concomitant use of MTX was 32.8% and 100% for TCZ and IFX group respectively. CDAI remission rates after 6 months were 38.6% for TCZ and 37.1% for IFX. Clinical response was comparable even though 67% of IFX pts had increased their dosage or shortened the infusion interval. 7% of IFX pts still had high disease activity levels, but there were none in the TCZ group. IL-6 concentration levels decreased in the IFX group and increased in the TCZ group. TNFα levels did not change in the TCZ group. Both TCZ and IFX reduced bone resorption markers, but only TCZ significantly increased osteocalcin - a bone formation marker. Our analysis suggests that TNFα and IL-6 play an important role in the cytokine cascade and their functional overlap. We consider that IL-6 inhibition widely covers the pathogenesis of RA by more than 10-15% compared to TNFα inhibition. Both TNFα and IL-6 should be further investigated to better understand their roles in RA.

ES1-2

Tocilizumab use in the United States and new IL6 inhibitors in development

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Conflict of interest: None

Inhibition of IL6 signaling has proven to be effective in the treatment ofrheumatoid arthritis as monotherapy or in combination with MTX in patients with active RA. Tocilizumab 4 or 8 mg/kg IV q 4 weeks or 162 mg SQ qow is approved in the US after failure of MTX, either as monotherapy or in combination with MTX. Many multinational clinical trials have been conducted over the years which the confirm the clinical, functional and radiographic efficacy of tocilizumab as monotherapy or in combination with DMARDs in both early and late disease as well as monotherapy in patients who had not failed MTX, although they may have not been naïve to MTX, (AMBITION) and TNF failures in combination with MTX (RADIATE) – the key studies are Charisma (phase 2 as mono or combination therapy in MTX-IR), OPTION (combination with MTX in MTX-IR), TOWARD (combination with a DMARD in DMARD-IR), LITHE (combination with MTX with radiographic outcomes). In some of these studies only 8 mg/kg IV q 4 weeks of tocilizumab was evaluated while in others both 4 and 8 mg/kg IV q 4 weeks were evaluated. Additional phase 4 studies have evaluated the effectiveness of tocilizumab monotherapy compared to adalimumab monotherapy (ADACTA), whether a patient with an incomplete response to MTX should be switched to, or, should tocilizumab be added (ACT-RAY) and the effectiveness of tocilizumab 4 and 8 mg/kg plus MTX compared to tocilizumab 8 mg/kg or MTX 20 mg a week as monotherapy in early disease (FUNCTION). Several studies have evaluated the effectiveness of tocilizumab 162 mg q week or every other week sub-cutaneously plus MTX (Summacta and Brevacta). Because of the effectiveness of tocilizumab in these varied clinical situations, several other IL6 inhibitors are in development. This presentation will review the efficacy and safety of tocilizumab in these multinational studies and introduce the early results (phase 2) with several IL6 inhibitors in development

ES2-1

The latest update on Certolizumab pegol in Japan

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Conflict of interest: Yes

For the treatment of rheumatoid arthritis, methotrexate (MTX) has been used for a long time, and biological DMARDs have been used since 1990's in western countries. In Japan, MTX was indicated for rheumatoid arthritis in 1999, and biological DMARDs were introduced since 2003. Having Certolizumab pegol, we can use 5 anti-TNF agents, and 2 biological DMARDs with different mode of action. Regarding treatment strategy, T2T recommendations, eg setting clinical remission as treatment target, are almost accepted. Indeed, in IORRA cohort, MTX was used in 78%, and biologic DMARDs are used in 19% of patients. In these consequences, remission is maintained in 48% of patients, and this ratio of remission is increasing in recent years. Accordingly, it is important to maintain lower disease activity by use these drugs efficiently. CZP is the newest biological DMARDs, launched in Mar 2013 in Japan. CZP, a PEGylated Fab' fragment of humanized anti-human TNF alpha, is different from other conventional anti-TNFs in its structure and has several unique characteristics in pharmacokinetics and pharmacodynamics. In clinical point of view, CZP has distinguishing features, such as loading-dose regimen despite of subcutaneous injection, administration every 4 weeks or every 2 weeks can be selected after achieving of stable disease state, etc. In clinical studies conducted in Japan, rapid onset of action and sustainable efficacy were confirmed. In recent post-hoc analyses, advantage of loading-dose regimen for long-term efficacy as well as rapid onset of action, and predictability of long-term outcomes by short-term clinical response were suggested. No particular new safety concerns were reported in the clinical trials. Post-marketing surveillance is underway in Japan.

ES2-2

Update on treatment strategies in rheumatoid arthritis - focus on certolizumab pegol

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Conflict of interest: None

Treatment of rheumatoid arthritis (RA) is focused on attaining remission or at least low disease activity within 6 months of treatment start. The 2013 update of the EULAR recommendations for the management of RA suggests to start therapy with conventional synthetic (cs) DMARDs in combination with low dose glucocorticoids, whereby MTX is the preferred compound, alone or together with other csDMARDs; whether such combination is superior to MTX monotherapy is currently an issue of debate. When this first treatment strategy fails, the EULAR recommendations suggest to stratify patients by risk of bad outcome, and in those with a high risk a biological agent should be added; biological agents in this regard can be any of the TNF-inhibitors or any of the other approved biologics. Among the TNF-inhibitors, certolizumab-pegol is a more recent addition that has meanwhile been approved in Europe for use not only in RA but also psoriatic arthritis (PsA) and axial spondyloarthritis (SpA) including ankylosing spondylitis (AS). In PsA as well as in AS the agent was studied intensively, and it has also shown significant efficacy in nonradiographic axial SpA. In RA trials, patients with active disease despite methotrexate respond well and to a similar extent as observed for other TNF-blockers; also safety aspects are similar in general. Certolizumab pegol is characterized by a relatively rapid onset of action and long-term extension studies have confirmed its sustained efficacy and acceptable safety. Certolizumab has also been assessed in patients with high disease activity despite prior TNF-inhibitor therapy in a subset of one of the clinical trials and also shown efficacy in such situation. In the CERTAIN trial, patients with mostly moderate disease activity have been

studied against placebo and, while in placebo patients disease activity even increased despite continuation of MTX, certolizumab therapy led to attainment of remission or at least low disease activity in the majority of patients treated. However, even when remission was achieved, withdrawal of drug was followed by a flare in the vast majority of individuals; importantly, reinstitution allowed recapturing the good outcome. Thus, overall certolizumab-pegol is an effective and sufficiently safe TNF-inhibitor to be employed as a biological agent in line with the EULAR recommendations and has, indeed, been studied in all populations in which a biological option is recommended.

ES3

Immune thrombocytopenia - recent topics of mechanisms, diagnosis, and treatment

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Conflict of interest: Yes

Immune thrombocytopenia (ITP) is an acquired bleeding disorder with a low platelet count mediated by immune-mediated mechanisms. This condition is seen in patients with various associated diseases, such as systemic lupus erythematosus (SLE), and can also occur without an underlying condition. Production of IgG autoantibodies to platelet surface glycoproteins is the hallmark of the disease. It has been thought that anti-platelet antibodies promote platelet clearance in the reticuloendothelial system, but recent findings indicate that anti-platelet antibodies also suppress platelet production. The diagnosis of ITP is one of exclusion, but we have proposed preliminary diagnostic criteria based on a combination of ITP-associated laboratory findings, including anti-platelet antibody responses, percentage of reticulated platelets, and plasma thrombopoietin (TPO). Thrombocytopenia is a common manifestation in SLE. The mechanisms are heterogeneous, and include ITP, thrombotic microangiopathy mediated by anti-ADAMTS13 antibodies, amegakaryocytic thrombocytopenia mediated by anti-TPO receptor antibodies, and hemophagocytic syndrome. Recently developed algorism based on a series of laboratory tests is useful for discrimination of underlying mechanisms. Corticosteroids are often effective for SLE-ITP, but sustained thrombocytopenia requires addition of immunosuppressants. Splenectomy is the most effective option, but eradication of *Helicobacter pylori* is ineffective. Rituximab now attracts attention as an alternative second-line treatment in primary ITP, and a clinical trial is now in progress in Japan. TPO receptor agonists that stimulate platelet production are a new class of drugs. Several clinical trials in patients with primary ITP have demonstrated high efficacy and continuance rate, but experiences in SLE-ITP are currently scanty. These drugs should be carefully used in SLE-ITP because of lack of effects on autoimmune pathogenesis and a high risk for thrombosis.

ES4-1

Therapeutic strategy of tocilizumab utilizing serum MMP-3 in the treatment of rheumatoid arthritis (RA)

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Conflict of interest: Yes

Tocilizumab (TCZ) was designed as a therapeutic agent to inhibit specifically IL-6 signaling and currently only available in practice. In the 2013 EULAR recommendations, TCZ is recognized as one of biological DMARDs which should be commenced with MTX in patients responding insufficiently to MTX and/or other conventional synthetic (cs) DMARDs. TCZ has been demonstrated repeatedly to be superior as a monotherapy over MTX or other csDMARDs. TCZ monotherapy also shows efficacy almost similarly to that of combination therapy of TCZ plus MTX in ACT-RAY trial. Additionally, ADACT trial, a head-to-head trial in the established RA patients who stopped MTX therapy, revealed that TCZ was superior to adalimumab in most endpoints. Thus, TCZ is preferentially recommended if biological monotherapy must be initiated. Since TCZ directly inhibits the acute phase protein production such as CRP and fibrinogen from hepatocytes, their values as inflammatory markers are limited during TCZ treatment. On the other hand, normalization of CRP is a surrogate marker for TCZ concentration enough to block the IL-6 signaling. In this situation, there is an urgent need for markers which represent well the severity of arthritis. Metalloproteinase (MMP)-3 degrades most of the proteoglycans and collagens in cartilage and bone, and considered playing important roles in joint destruction of RA patients. MMP-3 is produced mainly by inflammatory synovial tissues stimulated synergistically by IL-6 and TNF, or IL-1. It has been shown to well correlate with synovial inflammation and progression of structural joint damage. Furthermore, in the DREAM study, low serum IL-6 and MMP-3 levels at TCZ discontinuation were independent predictive markers for the longer efficacy duration without DMARDs after discontinuing TCZ in RA patients who previously responded to the agent. In this seminar, IL-6 biology and personalized medicine of TCZ for RA patients utilizing various biomarkers including MMP-3 will be discussed.

ES4-2

What is/are the most optimal target(s) for RA

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Conflict of interest: None

"Treat to target" (T2T) in the treatment of rheumatoid arthritis (RA) is well known as a concept of great importance. However, despite the fact that they are a major factor in the degree of error in treatment prognosis, it is difficult to say that a sufficient amount of discussion has taken place regarding the selection of appropriate targets. An ideal target has credibility, good reproducibility, can be cheaply and easily evaluated and offers a high degree of accuracy in the prognostics prediction of RA. With these requirements in mind, EULAR/ACR recommend SDAI, CDAI and Boolean. Under this scheme, if we have been treating with DAS28ESR should we at some point change over to SDAI? We have been attempting to find just what the optimum target in the treatment of RA. During the process it has become clear that rather than relying singularly on a DAS-28ESR≤2.6, a combination of this and MMP-3 level normalization, a marker of joint destruction, can offer a much more reliable, prognostic basis (T-4 1 year study). In addition, it has also been observed that in early-onset RA, early introduction of T2T is critical (T-4 3 year study). During the analysis process it became clear that the early induction of remission (DAS28 < 2.6, Normal MMP3 Levels) was of great importance in bringing about all-encompassing remission (Data withheld). Essential for the induction of early remission is the cost, ease of use and prognostic predictability of the target. In the search for even more useful targets, we are carrying out an observationally study, with the hopes of finding what exactly is of importance to the remission of early RA (symptoms duration ≤6 months). The T2T we attempted to achieve in this study was: Boolean Remission and HAQ=0 and normal MMP3 levels. Currently, we have evaluated 158 patients who are part of a two year follow up study, and it is from those results we hope to open the discussion on what is/are the most optimal target (s) for RA.

ES5-1

The newest knowledge about the pathogenesis of RA - The Treatment for Tomorrow

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Conflict of interest: None

Over the last two decades major progress has been made in elucidating the molecular and cellular pathways operating in the pathogenesis of rheumatoid arthritis (RA). In this regard it was proven that from a large array of studied proinflammatory cytokines and evaluated chemokines present in the disease, the inhibition of TNFa or IL-6 is of major benefit for most treated patients. Also reducing B cells with antibodies against CD20 and interferring with the monocyte-T cell interactions has proven to be beneficial. On the other hand, it is well established that not all patients respond well, especially over long time uses, and most importantly the disease cannot be cured yet. It is thereby not surprising that world wide over 500 clinical trials are currently targeting over 30 targets on a 7

Bio US-$ market which will be discussed at least in part within this lecture. On the other hand it is very puzzling, that none of these trials include the targetting of synovial fibroblasts (SF), although numerous laboratories around the world have characterized the activated phenotype of RASF. To taget the epigenetic modifications of these cells (1), such as in targetting the hypomethylation of RASF, novel strategies have been proposed (2). Specific miRs have also been designed to inhibit the activation of both TNFa and IL-6 as well as the MMP-production of RASF. 1) Klein K and Gay S. Epigenetic modifications in rheumatoid arthritis, a review. Curr Opin Pharmacol 2013 Feb 2, (Epub ahead of print) 2) Karouzakis, E, Gay RE, Gay S, Neidhart M. Increased recycling of polyamines is associated with global DNA hypomethylation in RASF. Arthr Rheum 64:1809-17, 2012.

ES5-2

Importance of Combination Therapy with Oral Disease Modifying Anti-Rheumatic Drugs (DMARDs) in Clinical Practice

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Conflict of interest: Yes

It is a broad procedure that if the target (remission) cannot be achieved with methotrexate (MTX), introduction of biologics therapy will be considered in RA patients. However, biologics therapy has issues that all patients cannot necessarily receive benefits because of the reasons including requirement of high health care costs, problems of adverse drug reactions (especially infection), and unestablished safety of long-term administration. Focusing on overseas trends, comparisons between non-biologics and biologics in patients with early RA have been actively reported in recent years, and in the USA (TEAR Study/RACATStudy) and Sweden (Swefot trial), multi-center controlled clinical trials between triple drug therapy with MTX plus salazosulfapyridine (SASP) plus hydroxychloroquine and biologics were conducted and showed equivalent results of disease activity in both groups. Currently in Japan, the cases of those patients who were diagnosed with RA less than three years before and poorly responded to existing treatments have been collected, and comparison studies (Japanese Strategic Treatment of Aggressive RA (JaSTAR) Study) between three drugs of DMARDs (Bucillamine, SASP, and MTX) and TNFα inhibitors plus MTX have been conducted mainly by practicing physicians across the country; one-year results showed no significant differences in disease activity. In treatment of RA, therapeutic strategies of how to set the treatment target should be determined through a shared decisions between physicians and patients in consideration of the disease activity and the characteristics (presence or absence of complications) of each patient. I will present a clear exposition of signification to choose oral DMARDs in treatment of RA in the light of the trends in current treatment in Japan and overseas.

ES5-3

Future perspectives

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Conflict of interest: Yes

Today the following challenges remain to be overcome in the therapeutic management of rheumatoid arthritis (RA): 1) Management of patients with severe comorbidities and/or those with advanced RA 2) Insufficient costs and risks of therapeutic agents with high effectiveness 3) Presence of RA patients refractory to available therapies The first step for the optimal use of available drugs should be the acknowledgement of the limitation of methotrexate (MTX), an anchor disease-modifying antirheumatic drug (DMARD) in RA treatment. Then, we should consider the choice of agents to be added to MTX in patients showing an inadequate response to MTX, based on the understanding of the significance of combined use of MTX and anti-tumor necrosis factor (TNF) biological agents. High plasma TNF level may be a poor prognostic factor, suggesting an inadequate response to MTX. Thus, neutralization of TNF by biological agents improves the potency of MTX. The dosage of biological agents should be determined by the amount of molecule to be targeted. Accordingly, it is reasonable to reduce the dose of agents when the expression of the target molecule decreases, in the view of therapeutic costs, although the accompanying therapeutic risk is unlikely to be much reduced. In order to successfully discontinue biological agents, the achievement of remission with biological agents is mandatory. Recent BuSHIDO (Bucillamine Study of Holding Remission after Infliximab Dose-Off) trial has suggested the usefulness of conventional DMARDs combination in the reduction of RA flare after discontinuing biological agents. Future promising molecular targets may include cytokines and chemokines, as well as intracellular kinases. However, all agents targeting above molecules do not seem to be satisfactory as a monotherapy. Thus, a different combination therapy for RA each patient to optimize the risk-benefit-cost balance should be the subject of intensive investigation.

ES6-1

Lifestyle-related issues identified in reports on work productivity published in the EU and the United States and a survey in rheumatoid arthritis patients conducted in Japan

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Conflict of interest: Yes

The development of biologics has dramatically improved the therapeutic goal for rheumatoid arthritis (RA) patients. It has now the standard of care for early RA patients to achieve remission as their therapeutic goal. At present, the key issue we need to enhance is how to maintain the achieved long term remission. The therapeutic goal is discussing the possibility of biologic-free remission in terms of achieving the ultimate therapeutic goal for last several years. The work productivity loss and daily activity impairment in RA patients have been reported in recent years in the EU and the USA. The improvement of the work productivity loss and the daily activity impairment in RA patients are the really importance to participate in social life, which is the therapeutic goal after achieving the remission maintenance defined by Treat to Target (T2T), as of achieving the ultimate therapeutic goal. In particular, the work impairment is converted into cost to show direct and indirect work productivity losses by the economic impacts. The degree of impairment and the amount of costs that have been reported are huge. A therapeutic goal for RA patients is to enable them to live a life as healthy people do. It is important for workers to recover their baseline work productivity, for those who had to change their job due to RA to get a job they like, and for those who had to quit their job due to RA to resume their social life. There are RA patients who have to take time off from work to receive treatment and those whose daily routine life is disturbed due to visit hospital for treatment. These are the issues that need to be addressed in order for them to live a life as healthy people do. In this article, I will discuss issues identified in reports on work productivity published in the EU and the USA, and daily living issues that need to be addressed, along with issues from a lifestyle perspective, based on results from a survey in rheumatoid arthritis patients conducted in Japan.

ES6-2

Therapeutic Goals and the Importance of Participation in Social Activities based on the ANOUVEAU Study Results

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Conflict of interest: Yes

As defined by the "Treat to Target" strategy (T2T), the primary therapeutic goal in rheumatoid arthritis (RA) is to achieve and maintain remission. The recent advances in medications, including biologics, have made it possible to achieve remission and maintain the achieved remission for a long period of time. Furthermore, T2T Overarching Principles include not only a goal of achieving remission but also a higher goal of "maximizing long-term quality of life (QOL) in patients through social participation." Participation of RA patients in social activities contributes to economic benefits to individual patients and also is expected to achieve favorable socioeconomic impacts. Some reports published in Europe and

the U.S. have shown that it is worth investing high costs in medications to reduce economic losses due to work impairment and daily-activity impairment. Assessments of work productivity in terms of its economic impact differ depending on different lifestyles, insurance systems and ways of thinking in different countries and regions. Therefore, overseas results do not necessarily apply to Japan. Results from a nationwide large-scale innovative study of work productivity, named ANOUVEAU Study have recently been presented in the EULAR and the ACR meeting in 2013. In this study RA patients treated with adalimumab were divided into two groups: home workers (HW) and paid workers (PW), and results on improvement in work productivity were reported for each group. The work productivity impairment of the HW was more progressive than that of the PW. In this article, I'd like to discuss desirable medications for RA in Japan based on the loss of social costs due to work impairment of RA patients and expenses of medications, considering the results of ANOUVEAU Study.

ES7-1

Basic research: a 'view from the benchside' about cytokines in RA

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Conflict of interest: None

There have been remarkable advances in the treatment of rheumatoid arthritis in the last decade. We have learned much especially from the advent of biologic therapeutics – specifically we have established that there are 'vulnerable nodes' in the inflammatory cascade that when inhibited lead to a 'collapse' of the inflammatory response such that clinical benefit can ensure. Particularly we have established that some cytokines offer pivotal points of traction for inhibition and from this we infer that they are pathophysiologically integral to disease pathogenesis. In this lecture I will discuss the basic patterns of cytokine expression in RA tissues and other lymphoid organs, and discuss how they change over time with disease progression. I shall highlight key moieties that are of current interest in terms of understanding pathogenesis. Finally I shall discuss the underlying cellular pathways that in turn regulate cytokine production particularly the microRNA networks that are increasingly emerging as key regulators of synovial cytokine biology. My focus will be particularly on cytokines of macrophage origin given the particular successes we have enjoyed in targeting the cytokines that derived from this cell lineage especially.

ES7-2

Concurring rheumatoid arthritis by cytokine suppressive therapy; from the bedside

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Conflict of interest: Yes

Although the etiology of rheumatoid arthritis (RA) remains unclear, the central role of cytokines in the pathogenesis is widely accepted. Detailed analyses have been conducted on background factors of the pathogenesis, and the effects of cytokine-suppressive therapy, particularly with regard to anti-cytokine therapy. In the latest treatment recommendation, anti-IL-6 agents as well as anti-TNFα agents are described as first-line biologics. Several studies have shown a relationship between RA treatment, cytokine and RA disease activity. For example, the data from the SAKURA cohort revealed that administration of MTX in early RA suppressed IL-6 and IL-1β, but not TNFα. Further, neither IFNγ nor TNFα were affected by administration of anti-IL-6R antibody tocilizumab (TCZ). Meanwhile, anti-TNFα antibody infliximab (IFX) reduced plasma concentration of IL-6, suggesting that TNFα is upstream of IL- 6, although no feedback from IL-6 to TNFα was noted. These findings clarify the cytokine network in RA pathogenesis where TNFα and IL-6 play central roles. With the advent of new agents such as anti-IL-17 and anti-GM-CSF antibodies, cytokine network will be further clarified in future studies. Concerning the relationship between the target molecule and corresponding drug dose in RA treatment, a higher dose of IFX are required in patients with relatively high plasma TNFα concentration, with clinical efficacy of TCZ reduced in patients with relatively high sIL-6R. As such, personalized RA treatment such as adjusting drug dosage by measuring the cytokine levels in advance, to maximize the therapeutic effects rapidly will be possible. A treatment flow involving the measurement of cytokines in each RA patients, determining the drug and dosage that should be used for that patient, and performing the treatment more effectively and efficiently may trend in the future. In this seminar, I will overview and give a prospect for the utility of cytokine-suppressive therapy in RA.

ES8-1

Renal failure in connective tissue diseases (CTD): focusing on current standard treatments

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Conflict of interest: None

Since CTD are inflammatory diseases, the renal failure caused by CTD is often responsive to immunosuppressive therapy. Above all, rapidly progressive glomerulonephritis (RPGN) is a serious condition that is associated with a poor prognosis and requires intensive immunosuppressive therapy. Microscopic polyangiitis (MPA) is the most common CTD associated with RPGN, followed by systemic lupus erythematosus (SLE) and Wegener's granulomatosis (GPA) in Japan. Treatment guidelines for ANCA-associated vasculitis, including MPA and GPA, have been developed in Japan based on the results of many clinical studies. The Western guidelines recommend early introduction of immunosuppressant in combination with glucocorticoid (GC) therapy. The Japanese guidelines recommend GC monotherapy as a treatment option especially for elderly patients or patients with less severe disease, considering the ethnic differences in specific disease types among the Japanese. In regard to the choice of immunosuppressant, cyclophosphamide (CY) is used as the primary agent for inducing disease remission. Recently, it was demonstrated that rituximab may be as effective as CY. The agents used for maintenance of remission include azathioprine (AZT), mycophenolate mofetil (MMF), and methotrexate (MTX), although the last agent should be used with caution in patients with renal dysfunction. For patients with SLE, lupus nephritis (LN) occurs at a frequency of 50% and is associated with a poor prognosis. Combined therapy with GC and CY therapy is the standard treatment for induction of remission. Western studies have shown MMF to be as effective as CY for inducing remission in patients with LN. ACR guidelines recommend the use of MMF for the management of LN. Recently, multi-target therapy using a combination of MMF and tacrolimus (TAC) has been shown to improve the remission induction rate. Agents used for the maintenance of remission in cases of lupus nephritis include AZT, MMF, TAC, and MZB.

ES8-2

Pulmonary complications in rheumatic diseases

Kazuki Takada
Department of Professional Development in Health Sciences, Graduate School of Medical and Dental Sciences, Tokyo Medical and Dental University

Conflict of interest: Yes

A variety of pleural and pulmonary conditions complicate rheumatic diseases and are causes of significant morbidity and mortality. These conditions may result from a direct pleural or pulmonary involvement of autoimmune, inflammatory, or fibrotic processes of rheumatic diseases, from direct effects of drugs used in treating rheumatic diseases, or from infection. These conditions may involve various tissues, ranging from the pleura, pulmonary parenchyma or interstitium, airway, to pulmonary vasculature, with predilections for certain tissues by many rheumatic diseases. Pleural conditions are more common in rheumatoid arthritis and systemic lupus erythematosus than other rheumatic diseases. Airway conditions are more common in rheumatoid arthritis and Sjogren syndrome. Pulmonary vascular conditions are more common in systemic sclerosis. Interstitial conditions are more common in rheumatoid arthritis, systemic sclerosis, polymyositis and dermatomyositis with an acute form with poor prognosis occasionally experienced in dermatomyositis and

systemic lupus erythematosus. Common pulmonary complications in rheumatic diseases will be reviewed, with a main focus in the treatment and prognosis of interstitial pneumonia.

ES8-3

Central nervous system involvement of systemic autoimmune diseases: neuropsychiatric systemic lupus erythematosus

Takao Fujii
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Conflict of interest: Yes

Central nervous system (CNS) involvement is one of the refractory disorders in patients with systemic autoimmune diseases such as systemic lupus erythematosus (SLE). The frequency of neuropsychiatric SLE (NPSLE) is reported to be various (12-75%), probably because NPSLE diagnosis is sometimes difficult. Although the pathological mechanisms of NPSLE is not well known, autoantibodies (auto Abs) (e.g., anti-ribosomal P and NR2 Abs), inflammatory mediators (e.g., IL-6 and IFN-α), and vasculopathy might be involved in the NPSLE pathogenesis. Cyclophosphamide in addition to high dose of CS is usually administrated in patients with severe NPSLE. In thrombotic microangiopathy-associated cases, plasma exchange is also considered. Besides immunosuppressive treatment, anti-psychotic agents and/or anticoagulation treatment are used for controlling clinical manifestations. When these combined treatments show insufficient response, rituximab, chimeric anti-CD20 monoclonal Ab, is a therapeutic option. We have shown that anti-U1RNP Abs in cerebrospinal fluid (CSF) has clinical significance in NPSLE and the presence of CSF-anti-U1RNP Abs is closely associated with the elevated levels of IFN-α and MCP-1. We experienced a severe NPSLE, who is 21 year-old women with CSF-anti-U1RNP Abs and resistant to high dose CS, cyclophosphamide, and plasma exchange. After obtaining an informed consent, rituximab treatment was initiated. She had multiple high intensity area in brain MRI and IFN-α level was elevated in CSF. Three weeks later of rituximab administration, her NP manifestations completely disappeared along with normalization of brain MRI and CSF findings. Rituximab treatment may act on both B and T cells by regulating their cognate interaction, resulting in the sufficient suppression of inflammatory mediators and/or vasculopathy. In this seminar, NPSLE will be focused and recent immunosuppressive treatment will be discussed.

ES9-1

Positioning of Golimumab in Tocilizumab resistant patients with rheumatoid arthritis

Hiroaki Matsuno[1,2]
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Conflict of interest: None

Currently, 7 biologic agents have been clinically used for rheumatoid arthritis (RA) treatment in Japan. The guidelines in western countries, however, do not show define criteria for identifying which of biologics as the 1st Bio is recommended for each cases. According to ACR recommendation, the first biologics (1st Bio) recommended for treatment of early rheumatoid arthritis with disease duration of less than 6 months is a TNF inhibitor. According to the NICE Guidance, TNF and IL-6 inhibitor are suitable as the first-line biologic agent. It has been reported an alternative TNF or a non-TNF inhibitor in patients who exhibit an inadequate response to a first TNF inhibitor may offer some benefit However, there is no clinical evidence for switching to IL-6 inhibitor from TNF inhibitor. This study evaluated efficacies on 31 RA patients with switch from TNF inhibitors or Tocilizumab (TCZ) to Golimumab (GLM). In TNF inhibitor treatment group, there were 13 patients who were treated with an adalimumab (5 patients) or a etanercept (8 patients) as TNF inhibitors. Eighteen patients were treated by a TCZ as first biologic agent. Clinical efficacies were evaluated by the percentage of CDAI and EULAR response, and treatment continuation ratio. There were no significant differences between characteristics of patients in both TNF inhibitor and TCZ treatment group. At the 52 weeks after GLM treatment, the percentage of low disease activity and remission, and a ratio of good response in EULAR criteria was as follows; 40%, 20% and 20% (TNF inhibitor treatment) and 50%, 25% and 50% (TCZ treatment). EULAR response ratio of TCZ treatment tended to be higher than TNF inhibitor treatment (P=0.052). Drug survival rate in TCZ treatment group was significantly higher than in TNF inhibitory group. (82.1% vs. 67.1 %, P=0.0149). Serum MMP-3 level was significantly reduced after treatment in both group. GLM can be an alternative as a switch biologic agent from TNF or IL-6 inhibitor.

ES9-2

Practicability of treatment holiday in Golimumab therapy

Eisuke Shono
Shono Rheumatology Clinic

Conflict of interest: None

Seven biological drug products are currently available for use in the management of RA in Japan as of the end of November 2013. No single RA specialist doubts about practicability of control of RA disease activity, inhibition of joint destruction progression, and maintenance of physical function have arrived thanks to the introduction of Bio drugs. In 2013, the EULAR recommendations were updated and therapeutic methods other than Bio drugs have also been being placed on review at major overseas academic societies. Thus, the day of advent of biosimilar agents will not be far distant. The cost effectiveness of Bio drugs considered to underlie. Evidence to support that introduction of anti-TNF monoclonal antibody treatment in an early stage enables bio holiday has been constructed. This has a great impact on the patient as well. In view of this, we explored the possibility of bio holiday in GLM. 19 patients (naïve 9 and switch 10) who had been begun on GLM post-marketing and thereby attained and maintained in clinical remission, hence becoming GLM-free. Concomitant MTX has been being continued after the introduction of a GLM-free state. Comparison between a group of maintained, stable GLM-free state and a group of a temporal relapse revealed the following patient background characteristics to account for the former group: shorter duration of disease, lower body weight, and low DAS28-CRP score and low Stage & Class at introduction of a GLM-free state. Cases in which a temporal relapse led to readministration of GLM were also encountered. In GLM therapy that has been evidenced to scarcely entail occurrence of anti-drug antibody, the results indicate that greater dosage of concomitant MTX does not be required than in treatment with other anti-TNF monoclonal antibody. We will discuss the results at this clinic as to how GLM is to be used in the clinical practice setting.

ES9-3

Sweet spots for golimumab

Satoshi Ito
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Conflict of interest: Yes

Golimumab (GLM) was approved as the 6th Bio in Japan. In domestic clinical trials, treatment with this drug yielded favorable outcome, when used with or without MTX. At our facility, we attempted to make full use of GLM's characteristics, avoiding the assumption that GLM is most powerful because it is the newest Bio. The drug was administered to 44 patients (8 males and 36 females) at our facility. In 3 of these patients, GLM was later switched to another drug because of lack of responses. In 4 of these patients, GLM was discontinued owing to adverse events. In the remaining 37 patients, the drug was effective and has been used to date. GLM is characterized by: 1. convenience in the frequency of administration (once in 4 weeks), 2. effective even without MTX and 3. undoubtedly less pain at the time of injection. With these features taken into account, GLM was used in the following cases: 1. patients unwilling to make self-injection and receive time-consuming drip infusion, 2. patients unable to receive MTX treatment at sufficiently high dose levels (a: switching from losing efficacy of etanercept or adalimumab without MTX; b: switching from MTX in patients receiving infliximab (IFX) + MTX when the MTX dose level needs to be reduced because of compromised renal function), 3. patients failing to show sufficient responses to dose increase or shortened dosing interval of IFX at the time of loss of efficacy, 4. patients having relapse of the disease despite IFX treatment aimed at "Bio-free condition" 5. patients having dementia and 6. patients

experienced injection-site reaction by other subcutaneous Bio injection. If the effectiveness of 4 is established, it seems possible to discontinue IFX therapy after reaching stable remission of the disease by switching IFX to GLM. In the near future, we plan to apply switching to GLM also to patients maintaining remission of the disease with IFX therapy and unwilling to discontinue IFX.

ES9-4

Regulation of Inflammatory Cytokine TNFα with an Appropriate Drug Dose Level – Should 50 mg be increased to 100 mg? Should 100 mg be adopted at the beginning?

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Conflict of interest: None

Golimumab (GLM; Simponi) approved as of September 2011 is a fully human anti-TNFa monoclonal antibody preparation produced using transgenic mice. This drug medication is characterized by once-in-every-4-weeks administration under the supervision of a healthcare professional, infrequent/modest emergence of anti-drug antibody, and rarity of injection site reactions after subcutaneous administration, which are markedly attractive features as compared to conventional drugs. Another characteristic feature of GLM lies in that dosage of 100 mg/4 weeks is approved solely in Japan in the world, enabling choice of a 100-mg dose level for a disease state uncontrollable with 50-mg doses. What about post-marketing clinical use results pertaining to GLM dosage increase? According to database TBCR at the Department of Orthopedic Surgery, Nagoya University, with which the present speaker is affiliated, data on post-marketing clinical use results covering 87 patients treated with GLM (percentage of patients continuously treated for 52 weeks: 87.4%) have been secured as of fall of 2013. Particularly, in 21 out of 54 patients who had been begun on GLM therapy at a dose level of 50 mg/4 weeks, the dosage of GLM was raised to 100 mg/4 weeks, with a consequent improvement of mean SDAI from 17.0 before dosage increase to 6.6 at Week 40 after dosage increase and of mean DAS28ESR4 from 4.4 before dosage increase to 3.2 at Week 40 after dosage increase. Thus, not a few patients who should have been rated as non-responsive and discontinued at the fixed dose level were relieved as a result of the dosage increase. At this symposium, we would like to pursue analysis and provide an overview of relevant data to explore what types of cases are to be subjected to such dosage increase and whether such patients should have been started on this drug at a dose level of 100 mg/4 weeks from the outset of this therapy.

ES10-1

Surgical treatment for Rheumatic wrist disorders

Yasunori Kobata, Ryota Hara, Yasuhito Tanaka
The Center for Rheumatic Diseases, Nara Medical University Hospital

Conflict of interest: None

Wrist disorders are most common symptoms in rheumatoid arthritis patients, but remarkable improvement of these symptoms are obtained due to the introduction of biological DMARDs. In this presentation, we will show the video of the rheumatoid arthritis patient treated with Sauvé-Kapandji procedure and discuss about the indication of surgical treatment for rheumatoid wrist problems.

ES10-2

Surgery of the thumb in patients with rheumatoid arthritis

Kensuke Ochi
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Conflict of interest: None

The thumb is the most important digit of the hand, which is necessary for grasp and pinch. Almost 70% of the patients has diseased thumb caused by rheumatoid arthritis. Most of the mild impairment could be treated conservatively, however, surgery can help patients with severe functional impairment. The surgery for the affected thumb is usually combination of synovectomy, soft tissue re-alignment, tendon reconstruction, arthroplasty, stabilization, and bone graft. In this talk, I would like to show what a rheumatologist should know in order to make a good consultation to a hand surgeon.

ES10-3

Reconstruction of Digital Deformities in Rheumatoid Arthritis

Shosuke Akita
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Conflict of interest: None

Rheumatoid arthritis (RA) is a disease of the synovial membrane and the resultant inflammatory synovitis is directly or indirectly responsible for the deformities seen in the digits. The two classic digital deformities seen in RA are swan-neck deformity and boutonniere deformity. An untreated rheumatoid digital deformity moves from a passively correctable flexible deformity to a deformity with limited motion, and finally a fixed deformity. Although many options are available for the treatment of flexible deformities, these options become progressively limited with increasing joint stiffness, and joint fusion is the only reliable option for a fixed interphalangeal joint deformity in RA. When evaluating digital deformities, the physician needs to classify them into flexible or a fixed deformities. If the patients have complains about the digital deformities, it is easier to treat the flexible deformities than fixed deformities. Treatment recommendations for this digital deformity of rheumatoid patients are discussed.

ES10-4

Recent trends in rheumatoid hand surgery from global perspective

Daniel Herren
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Conflict of interest: None

There is a significant decrease of handsurgical procedures in most first world countries in the world. This can be attributed primarily to the innovations in medical treatment. However there is a trend for recurrence under the biologicals after 4 to 5 years of treatment. In addition there are a significant number of patients in the world which are undertreated and which have no access to modern medication. Due to the decreasing numbers of surgical procedures and the fact, that musculoskeletal diseases are treated more often as an organ specific problem, the art of surgical procedures in rheumatoid patients is vanishing. It is therefore the duty of the more privileged societies to ensure the education of future rheuma-surgeons, especially in the underprivileged countries. Subsequently the surgical treatment of rheumatoid hand problems should further develop. There is a trend to either patients with good control of their inflammatory part of the disease but ongoing bone destruction or patients with only minor reaction to the medication. Often the x-ray findings resemble more to patients with a degenerative osteoarthritis than those of classic rheumatoid pattern. This offers a different spectrum of interventions including more arthroplasty procedures and the trend to partial fusion. However, the art of RA surgery in the hand remains the combination of determine the patients needs and expectations, the surgical possibilities and the technical skills.

Annual Course Lecture

ACL1

Rheumatic Diseases and Pregnancy

Atsuko Murashima
National Center for Child Health and Development

Conflict of interest: Yes

About one-third of rheumatoid arthritis (RA) develops in childbearing age women in their 20s and 30s. Recently, the high frequency of remission using biologics and MTX etc. and advances in reproductive medicine allow female patients with RA to consider becoming pregnant. However, there are still many people who feel anxious about the outcome of RA in the future. Regardless, the solution remains the same, the key point is the use of smart anti-rheumatic drugs (DMARDs). In general, RA patients experience a reduction of disease symptoms during pregnancy. Unfortunately, fewer than half of patients with moderate disease at conception experience a moderate to good response leaving the remaining women with intermediate to severe disease activity during pregnancy. The pregnancy in patients with systemic lupus erythematosus (SLE) needs very careful planning because the possibility of pregnancy itself has risks to mother and fetus. The level of disease activity is most important when considering the becoming pregnant. We should suppress SLE using steroids and a combination of immunosuppressive agents in some cases. The presence or absence of serious organ involvement such as lupus nephritis and pulmonary hypertention must be considered. It is also necessary to take into account the anti-phospholipid antibody and anti-SS-A antibodies in SLE, but the effects on pregnancy outcomes are unknown. Currently there are not a lot of published evidence supporting the safe administration of medication during pregnancy, but recent research is very supportive. Still we must proceed with caution. Allow me to explain how to treat patients with rheumatic diseases who desire childbearing focusing the medication during pregnancy and breastfeeding.

ACL2

Pulmonary involvement in connective tissue disease: importance of differential diagnosis

Masataka Kuwana
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Conflict of interest: Yes

Pulmonary involvement is a common complication in patients with connective tissue disease (CTD) and is the leading cause of morbidity and mortality. CTD affects respiratory tract, pulmonary interstitium, pulmonary vasculature, and pleura, leading to development of a variety of pulmonary complications, including bronchiolitis, interstitial lung disease (ILD), pulmonary hypertension, alveolar hemorrhage, and pleuritis. The lung is also the preferential target of infectious microorganisms and drug hypersensitivity. Thus, we should understand heterogeneity and complexity of pulmonary involvement observed in CTD patients during the course of the disease. For example, ILD in patients with rheumatoid arthritis is usually chronic and does not require intensive treatment, but a rare complication of acute interstitial pneumonia/diffuse alveolar damage is often fatal. Patients with systemic sclerosis and mixed connective tissue disease have chronic ILD without acute exacerbation. ILD in patients with polymyositis/dermatomyositis ranges from recurrent form to rapidly progressive form with poor prognosis. In contrast, ILD is infrequent in patients with systemic lupus erythematosus, but alveolar hemorrhage often leads to fatal outcomes. Interstitial pneumonitis is also caused by hypersensitivity to certain drugs, such as methotrexate, and by infection with pneumocystis jirovecii, which may further trigger onset of acute interstitial pneumonia. Therefore, it is imperative to make differential diagnosis and prediction of prognosis based on underlying disease, autoantibody status, and imaging and pathologic findings in CTD patients with ILD. Especially, prompt treatment decision is critical in patients with rapidly progressive ILD. In this lecture, typical case scenarios will be presented to learn how to evaluate and manage CTD patients with respiratory symptoms such as exertional dyspnea.

ACL3

Toward Successful Management of a Private Rheumatic Clinic: From the case of Oribe Clinic in Oita prefecture, Japan

Motohiro Oribe
Oribe Clinic of Rheumatism and Medicine, Oita, Japan

Conflict of interest: None

Introduction Taking the advantage of 21 years of my working experience in the Oita Red Cross Hospital, I established my own Rheumachi Clinic in February 2006. From the beginning, almost 800 rheumatoid patients visited my clinic during the opening month in 2006 that was a successful sign of opening a new clinic. I also realized that it is essential for someone who wants to establish a clinic to start and continue manage it with confidence. There are several prerequisites for opening a rheumatic clinic including basic and standard knowledge as a rheumatoid specialist doctor and the basic medical clinical abilities. Rheumatoid department is a lifetime treatment, therefor it is necessary to treat accurately and speed up the treatment and therapy. Working for Rheumatoid patience is not limited to the disease itself. You should expect and be ready for various demand and consultation service and have to build a special capacity as “everything OK pocket of Doraemon” as one of my patients described me. Other consultation demands form my patience numerous, either physical maters such as constipation, headache, hand numbness, cold feet or social and family matters such as argues with son or doubter’s family. You are like everything OK pocket of Doraemon, one of my patient told me when I treated her intractable stomatitis. The symptom was cured with my special prescription. I also introduce my own prescription for her face stain. That was the words that the patient said as a result of resolving of all patients complaints. It is important not to neglect other complaints by patients that are not related to rheumatoid and try to search for the solution politely. Having a strategy for problem solution according to clinical research can lead a clinic to a success. Conclusion There is no secret with success of a Clinic. The director’s humanity, clinical power and everyday efforts will lead a Clinic to success.

ACL4

The role of musculuskeletal ultrasound in rheumatology clinical practice

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Center for Rheumatic Diseases, Yokohama City University Medical Center, Yokohama, Japan

Conflict of interest: Yes

Most of the rheumatologists today already understand the usefulness of musculoskeletal ultrasound (MSUS) in patients with rheumatoid arthritis (RA) both in clinical practice and research. With MSUS, we can evaluate the presence of subclinical synovitis and subradiographic bone erosion. It is true that RA cannot be diagnosed solely with MSUS without other clinical information, but there is no doubt that the information shown by MSUS helps us to make the early diagnosis of RA, monitor disease activity and evaluate the state of clinical remission. In this lecture, I would like to discuss how to best integrate MSUS into daily clinical practice with the aim to improve the diagnostic algorithms, the daily patient care and the disease’s outcome.

ACL5

Clinical features and management of glucocorticoid-induced osteoporosis

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Conflict of interest: Yes

Oral glucocorticoids are prescribed for a wide variety of medical disorders. Reduced bone formation is the key process in glucocorticoid-induced osteoporosis. The risk of vertebral fractures increases more than hip fractures, substantially in oral glucocorticoid users. In a General Practice Research Database study, the daily glucocorticoid dosage correlated with the fracture risk. There was no threshold daily dose for the oc-

currence of vertebral fractures. The data from two randomized controlled trials of risedronate were used to identify factors predicting vertebral fractures within 1 year in the control patients, who received oral glucocorticoid therapy. Baseline lumbar-spine BMD was among the predictive factors, with each 1 SD decrease in the T score having a relative risk for vertebral fractures of 1.85 (95% confidence interval: 1.06-3.21). However, comparatively to the non-glucocorticoid-treated women, the glucocorticoid-treated women were higher risk for fractures despite a lower mean age and higher baseline BMD values. Thus, glucocorticoid-induced osteoporosis is characterized by relative dissociation between the BMD values and the fracture risk, which is higher than expected based on the BMD values. Current Japanese guidelines indicated that the treatment objectives are patients that are using or planning to use oral glucocorticoids for 3 months or longer with a fragility fracture, with less than 80% BMD of young adult mean, and with 5mg predonisolone equivalent or higher doses per day. We are now working on the revision of Japanese guidelines. Assessment of fracture probability in glucocorticoid treated patients using FRAX or similar algorithms may underestimate risk, and the role of primary prevention of glucocorticoid-induced osteoporosis is often insufficiently emphasized in current guidelines. Oral bisphosphonates provide the front-line treatment option in the majority of patients with glucocorticoid-induced osteoporosis.

ACL6

Rheumatoid arthritis treatment seen from a viewpoint of medical safety - what is the point?

Yuho Kadono
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Conflict of interest: Yes

Treatment of rheumatoid arthritis (RA) accomplished remarkable progress by the appearance of medicines, such as methotrexate (MTX) and biologics. When the medicine with high validity is not appropriately used, an iatrogenesis adverse event may be caused. If a patient took MTX every day, accumulation of MTX might stop all the cell division in the body. If biologics were accidentally used every day, a patient might suffer infection easily. On the other hand, when cortical steroid administration was stopped suddenly, an adrenal crisis might be caused. In fact, the RA patient who took MTX every day died in 2004. The occurrence of such a medical accident is usually based on the system defect. The chain of the error of people actualizes it and leads to the accident in many cases. Although it is possible for what is called a human error to reduce the risk by education, it is difficult to make an accident into zero. It is effective to detect an error at an early stage. To build the system which can stop the influence of subsequent at worst by early detection is also desired. Although the preventive measures which eliminate the cause of a human error by automation, and also carrying out automatic detection of an error and an impact mitigation measure are also effective means, it is most important on medical safety measures to carry out a collation check by the last executor. It is important to aim at making the organization which shares a risk exceeding an occupational description, or experience and a position, and is easy to take with communication among all the staff including a patient, families. While outlining the check of the basic point, and the type of a human error and the basic pattern of a measure concerning a medical safety control, I would like to propose actual measures including the communicating method by this training, assuming the concrete example of the medical accident relevant to RA treatment.

ACL7

ABC in the drug management of rheumatoid arthritis

Hisashi Yamanaka
Institute of Rheumatology, Tokyo Women's Medical University

Conflict of interest: Yes

Drug management of rheumatoid arthritis (RA) has been dramatically improved over the last 15 years. Newly developed drugs has been introduced into the daily practice, and disease activity of RA patients has become fairly well controlled. However, not all issues of RA have been solved, and new issues have been emerged. Abundant information has been provided in certain drugs, however, the basic knowledge to manage patients has not been well delivered. This lecture intends to provide an opportunity to consider how the drug management of RA should be in daily practice. (1) Rheumatologists should recognize the chronic nature of RA and should manage patients in a long time span. Not only the education of patient but also the understanding of the patient's circumstances is important. (2) Rheumatologists should aware that #1 of Overarching Principles of T2T is that the treatment of RA must be based on a shared decision between patient and rheumatologist. (2) There are two classes of drugs; for improving short-term QOL including NSAIDs or corticosteroids, and for improving the long-term outcome including DMARD and biologics. Rheumatologists should prescribe these with apparent purpose to use. (3) Disease activity of patients should be kept as low as possible, and the achievement and the sustainment of remission is necessary by monitoring the composite measures including DAS28. This, joint assessment in each visit is necessary. (4) Rheumatologists should recognize the comorbidity of patient, especially, occult infections and osteoporosis, and should treat them if necessary. (5) It is necessary to prevent the weakness of muscle strength and limitation of range of motion. Rheumatologists should introduce the muscle exercise to patients from early stage. Rheumatologist should not be the doctor who just prescribe medicines, but should aim to improve the long-term outcome of RA patients by using multiple services.

ACL-LS

Efficacy and safety of methotrexate (MTX) therapy with a higher dose for rheumatoid arthritis (RA)- From the results of post marketing surveillance -

Yasuo Suzuki
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Conflict of interest: Yes

DMARDs have a central position in the recent strategy of RA treatment aiming for remission. Among the DMARDs, MTX is a highly effective drug both as monotherapy and in combination with other DMARDs or biologics. MTX has greater long-term effectiveness, tolerability and safety than any other non-biologic DMARDs. Thus, MTX has served as not only a 1st-line drug but also an anchor drug in the treatment of RA. According to RA international database, MTX is taken by 83% of patients with RA compared to 23% for biologics. In Japan, an increase in dose of MTX up to 16mg/week was approved in February 23, 2011. At Tokai University Hospital, about 82% of RA patients receive MTX by monotherapy or combination therapy The efficacy of MTX increases dose-dependently between doses of 5mg and 20mg/week, although the effects tend to reach a plateau at around 15 mg/week. If MTX is used up to 10 to 12mg/week, higher efficacy and remission rate can be obtained. In addition, higher remission rate was observed when MTX was used as the 1st or 2nd-line DMARDs compared to the 3rd-line DMARD. MTX is usually well tolerated in most of RA patients with appropriate folic acid supplementation. However, 511 patients who died during MTX therapy by adverse events have been accumulated until November 30, 2012. Myelosuppression, pneumonitis, infections, and lymphoproliferative disorders are major fatal side effects. In addition, a certain number of cases of fulminant hepatitis by the reactivation of HBV and tuberculosis during MTX therapy were reported. The analysis of a post marketing surveillance (PMS) of MTX with higher doses in Japanese RA patients to assess effectiveness and safety is now under way. In this lecture, I discuss the practical points for the use of higher-dose MTX on the basis of the JCR recommendation and review the latest information regarding efficacy and safety including the results of the PMS.

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PL ..... **Presidential Lecture**

RS ..... **Representative Session**

S ..... **Symposium**

IS ..... **International Symposium**

SL ..... **Special Lecture**

EL ..... **Educational Lecture**

MTE ..... **Meet the Expert**

W ..... **Workshop**

ICW ..... **International Concurrent Workshop**

P ..... **Poster Session**

LS ..... **Luncheon Seminar**

ES ..... **Evening Seminar**

ACL ..... **Annual Course Lecture**

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