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ABSTRACT SUPPLEMENT

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JAPAN COLLEGE OF RHEUMATOLOGY ABSTRACT SUPPLEMENT

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ABSTRACTS

President's Address

PA

Rheumatic Diseases and Total Joint Arthroplasty

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In the basic research into rheumatic diseases in my department, we have investigated the mechanism by which hyaluronic acid affects cartilage or synovial cells via the CD44 and CD54 receptors, the functions of oxidized low-density lipoprotein and LOX-1, its receptor, in joints, and the effects of prostaglandin E2 on cartilage via the EP4 receptor, and have analyzed the expression and functions of SOX9, the master gene of cartilage formation. Clinically, we have mainly investigated and developed joint surgery using total arthroplasty and spinal surgery for rheumatoid patients. In this lecture, I will speak about my main work with total arthroplasty, and review its current status and its future in the treatment of rheumatic diseases. Total arthroplasty was initially developed for hip joints. It was well known that total arthroplasty has generally been used for the treatment of destructive hip joints since the end of the 1960s, when John Charnley developed a new total hip arthroplasty (THA) technique based on a polyethylene acetabular socket, a metal femoral head with a diameter of 22 mm, and bone cement fixation. There were two problems with this technique-the fixation of the implant to the bone and the wear on the artificial joint-and their resolution was the most important issue for successful joint replacement. We studied the interface between the biomaterial and the bone and found that bone could bind to biomaterials that had formed an apatite layer on their surfaces in the body. Therefore, we developed a new method of altering titanium surfaces to allow the formation of apatite layers on them. This method was used to make a new prosthesis for total hip replacements. The clinical results more than 10 years after surgery showed no loosening between the bone and the implant. Cross-linked polyethylene and ceramic-on-ceramic or metal-on-metal joints have now been developed to solve the problem of polyethylene wear. THA is now expected to permit excellent function for more than 20-30 years after surgery. Both the design of the prosthesis and the biomaterials used are very important for the success of total knee arthroplasty (TKA). Initially, the hinged knee prosthesis was developed but showed early loosening because the knee joint rotates with flexion and extension movements that the hinge does not allow. The stability of the total knee prosthesis was increased by developed mechanical properties of structures that separate the tibial and femoral surfaces. TKA has been highly successful since the 1970s when the total condylar knee was developed. The long-term results of TKA offered stable pain relief and the ability to walk, but the range of motion (ROM) of the replaced joint was unsatisfactory. This problem is particularly important for Japanese patients because of the Japanese lifestyle. To improve the ROM after the operation, we developed a new prosthesis that has an additional ball and socket joint on the posterior half of the conventional joint surface. This prosthesis markedly improved the ROM of the joint and I will demonstrate a motion analysis of this prosthesis in vivo in the human body. Joint replacement has been evaluated in numerous institutes with comparisons of numbers of different prostheses, respectively. Fifty thousand total hip arthroplasties and 75,000 total knee arthroplasties were recently performed in Japan in a single year. However, only a limited number of comparative studies have been undertaken to evaluate these at merely one or more institutes, and a nationwide registry is required. In 1973, a national registry was established in Sweden and most TKAs and THAs have since been recorded there. Internationally, many countries have established national registries, including several in northern Europe, Great Britain, Australia, Canada, and New Zealand. In Japan, the Japanese Society of Replacement Arthroplasty has tried to establish a joint registry, and to date, about 10% of hip and knee replacements have been registered and 55,000 TKAs and THAs have been documented. With these cross-sectional data, I will analyze and report the current status of knee and hip joint replacements in patients with rheumatoid arthritis.

Invited Lecture

IL

Induction of Pluripotency by Defined Factors

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Induced pluripotent stem (iPS) cells were originally generated from mouse and human fibroblasts by retroviral introduction of *Oct3/4, Sox2, c-Myc,* and *Klf4*. iPS cells are similar to embryonic stem (ES) cells in morphology, proliferation, gene expression, and most importantly, pluripotency. Compared to ES cells, iPS cells have less ethical controversy and can be generated from various genetically identified individuals including disease patients or those having specific human leukocyte antigen (HLA) types. Patient-specific iPS cells provide unprecedented opportunities in disease research, drug screening, and toxicology. A stock of iPS cells constructed from HLA-homozygous donors would provide significant resources for stem cell therapy. However, recent reports of tumor formation following transplantation, and the large diversity between iPS cell clones highlight potential problems. Furthermore, the mechanism of reprogramming remains unclear. In addition to fibroblasts, iPS cells can be generated from various somatic cells, such as hepatic cells, gastric epithelial cells, neural cells, dental pulp cells, peripheral blood cells, and cord blood cells. As alternatives to retroviral transduction, iPS cells can be generated by lentiviruses, adenoviruses, plasmids, transposons, recombinant proteins, or synthesized mRNA. Recently, we reported an integration-free induction method using episomal vectors. This method can induce human iPS cells efficiently and reproducibly. Regarding iPS cell induction factors, we discovered that L-Myc and the transcription factor Glis1, which is strongly expressed in the unfertilized egg, can establish iPS cells with a high efficiency and quality, replacing the oncogene c-Myc. Other reports suggest that chemicals can further enhance induction efficiency. Each induction experiment can result in up to 100 or more independent iPS cell clones. These iPS cell clones may vary qualitatively, considering responses to in vitro directed differentiation protocols and their propensity to produce tumors. In fact, we have previously shown that the origins of mouse iPS cells have profound effects on tumorigenicity. It is therefore essential to determine the best origins, the best induction protocols, and the best methods to evaluate iPS cell clones and subclones for future clinical applications. From this point of view, the need for genetic and epigenetic analyses, such as DNA methylation, histone modification, and genomic imprinting becomes more significant. It is also important to note that iPS cell within a clone can be heterogeneous, despite their common derivation from a single progenitor cell. This is likely because the process requires multiple cell division and cannot be completed by the four exogenous factors alone. Additional endogenous factors are required to achieve full reprogramming. Better understanding of the reprogramming mechanism will facilitate more uniform and complete reprogramming during iPS cell generation.

Symposium

S1-1

Intracellular cytokine signaling

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Conflict of interest: None

Cytokines such as TNF-a and IL-6 are known to activate numbers of intracellular signaling pathways after binding to its original receptor and plays a major role in the inflammatory milieu. Activation of the intracellular signaling pathway results in activation of the cell causing up-regulation of cytokine production, building up a pathological condition. Biologics targeting these cytokines or cell surface molecules existing extracellularly interrupt this malignant cycle and resolves the inflammatory condition. Within this context, compounds targeting the intracellular molecules activated by the extracellular molecules targeted by biologics possess the possibility to show similar anti-inflammatory effect with biologics. Numbers of compounds have been developed targeting the pathways activated in rheumatoid arthritis such as JAK-Stat, MAP kinase, Syk and NFkB. Among those, tofacitinib targeting JAKs have shown clinical efficacy on RA resembling the effect of biologics. It has been approved by FDA on Nov. 2012 and is expected to be approved in Japan in the near future. We have previously reported the phenotype of JAK3 deficient mouse, in vitro/in vivo studies with tofacitinib and more recently investigated the leukokinetics and its function in RA patients participating the tofacitinib clinical trial. Our investigation indicated that the anti-inflammatory effect of tofacitinib is based on the direct effect on the acquired immunity (lymphocytes). However, we and others have revealed the additive effect on mesenchymal cells (fibroblasts) and also on the innate immunity (monocytic cells) indirectly affecting the acquired immunity. Lymphokinetcs correlated with infectious adverse events while suppressed lymphocyte function correlated with clinical efficacy indicating its chemistry as a double edge sword resembling biologics. Based on the results from our study and clinical trails, indication for treatment of RA with tofacitinib will be discussed.

S1-2

Syk inhibitors

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Conflict of interest: None

Non-receptor type of protein-tyrosine kinase Syk (spleen tyrosine kinase) was isolated by a cDNA cloning in the University of Fukui in 1991. Syk is known to be essential for the various physiological functions, especially in blood and immune systems, such as IgE-mediated histamine release and production of cytokines from mast cells, Fc receptor-mediated phagocytosis of macrophages, activation of osteoclasts, integrin-mediated platelet aggregation, and B-cell antigen receptor-mediated B cell proliferation and differentiation. In addition, Syk is required for the immune response against fungus and virus infection, breast cancer, melanoma, and acute myeloid leukemia. Recently, novel Syk inhibitors were developed and its usefulness has been evaluated in the treatment of allergic rhinitis, rheumatoid arthritis, and idiopathic thrombocytopenic purpura. In this session, I will introduce the history, structure and function of Syk, and then review the novel Syk inhibitors and their current status. Furthermore, I will introduce our research of the adaptor protein 3BP2 (c-Abl SH3 domain-binding protein-2), as a novel target of Syk.

S1-3

Iguratimod

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Conflict of interest: Yes

Iguratimod (T-614, IGU) is a novel DMARD with a chromone ring. In pre-clinical studies, IGU inhibited production of inflammatory cytokines such as TNFα, IL-1β and IL-6 by monocytes/macrophages and synovial cells, and suppressed production of immunoglobulins (IgG, IgM) without an effect on B cell proliferation. Regarding the molecular mechanism of IGU, it is suggested that IGU suppresses NFκB activation without interfering with IκB α degradation. In the late Phase II clinical study in RA patients, a dose-escalation was recommended to dose 25 mg once a day (25 mg/day) for 4 weeks, and then increase to twice a day (50 mg/day). In a Phase III study, the improvement rate on ACR 20% (ACR20) of IGU was superior to placebo [53.8% (71/132) *vs* 17.2% (11/64)] and was not inferior to SASP [63.1% (65/103) *vs* 57.7% (60/104)] after 28 weeks. In particular, ACR20 by monotherapy was 56.3% (9/16) in patients with an inadequate to MTX. Moreover, in the comparison study (24 weeks) in patients with insufficient response to MTX, ACR20 was 69.5% (114/164) in IGU + MTX group (IM), and 30.7% (27/88) in placebo + MTX group (PM), by which a superiority was confirmed. ACR 50 and ACR 70 were 38.4% and 17.1% in IM, while 15.9% and 5.7% in PM, respectively, so IM is significantly better than PM. There was no significant difference on the incidence rate of AEs, which were 80.5% in IM and 75.0% in PM. There were five SAEs in IM and three in PM. The patients in IM received study drugs up to 52 weeks, and ACR 20, ACR50 and ACR70 were finally 71.3%, 49.4% and 23.8%, respectively. In the combination study, there was no increase of clinically problematic adverse events, and the tolerability was good in a long-term treatment. IGU, launched in Japan in September 2012, could provide useful and affordable new therapeutic option not only for mild to severe RA patients as monotherapy, but also for patients with an inadequate to MTX, in its combination with MTX.

S1-4

p38 inhibitor

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Conflict of interest: None

p38, one of mitogen-activated protein kinases (MAPKs) transducing a variety of extracellular signals to the transcriptional machinery was identified as either a kinase activated in response to endotoxin and osmolarity shock or a target for a group of cytokine-suppressive anti-inflammatory drugs. Through a kinase cascade composed of three hierarchial modules of MAPKKK/MAPKK/MAPK, p38 is activated like other MAPKs are done. Then, p38 phosphorylates other kainases and transcriptional factors in the downstream of signaling loop and consequently regulates various cellular output. In addition to the canonical kinase cascade, it was recently reported that the phosphorylation on Tyr-323 in p38 by Zap70 induces aoutophosphorylation-associated activation of p38. This pathway is thought to be crucial for differentiation of Th cell and is of interest as a stress-free activation pathway for p38. There are four mammalian isoforms of p38 (α, β, γ and δ). Those physiological and pathophysiological functions have been revealed by virtues of mice with genetic modifications. p38α ubiquitously expressed in adult tissues can be involved in erythropoiesis, placental organogenesis, apoptosis of lung stem/progenitor cells, cardiac hypertrophy, production of IL-6, IFN-γ production from Th1 cell, and progression of sepsis and inflammatory bowel disease. p38γ and δ are involved in muscle regeneration and skin tumorgenesis, respectively. In parallel with functional analyses of p38, clinical trials for p38 inhibitors are currently active to produce a specific medicine against inflammatory disease like rheumatoid arthritis (RA). In this 3-year trend, several drugs are discontinued, whereas several new drugs appear for the clinical trial every year, indicating that p38 inhibitors could be promising drugs for inflammatory diseases. I will summarize p38 inhibitors and show a topic, "critical role of p38 in IL-17 production from Th17" closely related to the pathogenesis of multiple sclerosis and RA.

S1-5

FTY720 (Fingolimod)

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Conflict of interest: None

Five high-affinity sphingosine 1-phosphate (S1P) receptors ($S1P_1$, ~$S1P_5$) have been identified and are expressed on lymphocytes, neural cells, and cardiovascular cells. Interactions of S1P with $S1P_1$ on lymphocytes facilitate lymphocytes egress from secondary lymphoid organs (SLO) to peripheral blood. Peripheral lymphocytes re-circulate to SLO by interactions with chemokines and hemokine receptors on lymphocytes. FTY720 (Fingolimod) is a immunosuppressive drug established by chemical modification of myriocin isolated from culture broth of Isaria sinclarii, a kind of vegetative wasp. After phosphorylation, FTY720-P induces internalization of $S1P_1$, rendering the cells unresponsive to S1P. Its immunomodulatory effects are primarily exerted by sequestration of lymphocytes within SLO. FTY 720 has been shown to be a useful agent for the prevention of transplant rejection and autoimmune diseases using animal models. Clinical trial of FTY720 was first studied for the prevention of acute rejection after renal transplantation. Although FTY720 provided adequate protection from acute rejection the effectiveness and safety profile was not satisfactory. However, FTY720 was highly effective in clinical trials with relapsing MS. Phase III TRANSFORMS study of FTY720 in relapsing remitting MS has showed a superior efficacy compared with a standard treatment of interferon-β. Another placebo-controlled Phase III FREEDOMS study to assess the impact of FTY720 in reducing the frequency of relapses has showed satisfactory results. Placebo-controlled phase II study has also showed satisfactory results in Japan. In addition to immunomodulatory actions FTY720 has direct protective effects against neural damages. We also observed that FTY720 has direct inhibitory effects to produce prostaglandin from synovial cells and enhancing effects to differentiate to osteoblasts. FTY720 may be applied new therapeutic tool for the treatment of RA.

S1-6

Future perspectives of small molecules in RA treatment

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Conflict of interest: Yes

Biological agents with great success in RA treatment are mainly targeting on the extra-cellular molecules such as cytokines and cell surface molecules. On the other hands, there are many targets within the cells. These targets inside the cells, particularly kinases,

have been extensively tested by small molecules to identify candidates for RA treatment. Several potential small molecules have been progressed to early and late clinical development. Given the establishment of pro-inflammatory cytokines by biological agents, signal transduction molecules in the cytokine receptors were potential targets. Among those molecules, JAK (Janus kinases) inhibitors have been tested in clinical trials. Tofacitinib, inhibiting chiefly JAK1/JAK3, was approved in RA in November 2012 in USA. Efficacy and safety of baricitinib, inhibiting mainly JAK1 and JAK2, and GLPG0634 on JAK1 are reviewed, based on the recent reports. In addition, profiles of the JAK inhibitor obtained in Japan will be introduced, and discussed the future perspectives of JAK inhibitors. Inhibitors of SYK (Spleen Tyrosine Kinaase), on the signal transduction through B cell antigen receptors and Fc receptors, have been developed. I will review the clinical trials data on fostamatinib and discuss the efficacy and safety of fostamatinib. Other targets including PI-3K patheay, NFkB pathway, and MAPK pathway are attracting lots of interests and studied extensively. Given overall knowledge at present, future perspectives and issues on small molecules in RA treatment are discussed.

S2-2

Advances in animal models for systemic vasculitis

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Conflict of interest: None

Since serum sickness models of periarteritis nodosa, animal models of systemic vasculitis have been key to clarifying the mechanisms underlying the development of vasculitis, and have been generated of the different pathological prototypes based on cellular, molecular and genetic events. Inductive (Baconian) and deductive trials have been performed to establish vasculitis models, in which the significant roles of immune complexes, the adaptive immunity against vascular components, anti-neutrophil cytoplasmic antibodies, cytokines and particular infections agents were clarified. Genome wide association studies have also shed some light on the complex clinicopathological manifestations of systemic vasculitis. In collagen disease model mice MRL/lpr, vasculitis developed as a cumulative effect with a particular combination of the susceptibility loci to collagen disease, each of which by itself did not have a significant effect to induce the related phenotype, thus indicating a polygenic system. The mice developed vasculitis in an additive manner of polygenes with a hierarchical effect, and some of them seemed to be common to those in other collagen diseases as well. Moreover, the polygene controlling tissue specificity of vasculitis was present. One of the polygenes for vasculitis showed an allelic polymorphism in the coding region, causing a qualitative difference in its function. Thus, a combination of polygenes with such an allelic polymorphism may thus play a critical role in developing vasculitis with a regular variation of pathological phenotypes in collagen disease. This system is designated as the polygene network in systemic vasculitis. This also indicates that systemic vasculitis can exist in collagen disease beyond the primary and secondary forms. Further hypothesis generation and testing using animal models will be required to elucidate the mechanisms underlying the development, and progression of vasculitis.

S2-3

International epidemiologic study of the vasculitis

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Conflict of interest: None

Geographical differences in the epidemiology of the vasculitis, such as Takayasu arteritis, giant cell arteritis, and Kawasaki arteritis, have been observed. As for small vessel vasculitis, the prevalence of microscopic polyangiitis (MPA) is more common in Japanese patients, but PR3-ANCA positive, granulomatosis with polyangiitis (GPA) in European and US patients. However, the existing schemes, such as ACR classification, CHCC definition and Japanese diagnostic criteria were made in the 1990s and either was used for each study. In this way, the absence of classification standard of the vasculitis has been considered as one of the problems of the international vasculitis study. After the 2000s began, the experts of EULAR and ACR started to discuss and review about the disease concept and classification criteria, et al. (DCVAS, in progress). Prior to this process, Watts et al. developed a stepwise algorithm for epidemiological studies of primary systemic vasculitis to permit comparison without confounding by classification (EMEA algorithm). To clarify the epidemiologic differences between Japanese and European patients with ANCA-associated vasculitis (AAV), 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, but this prospective study found MPA and MPO-ANCA to be more common in Japan, and GPA and PR3-ANCA in the UK. Recently, an international comparative study has been performed to investigate whether there were differences in phenotype and outcome in MPA between well-characterised patient cohorts in Europe and Japan. Phenotypes in MPA patients were different, but the survival and renal survival were similar between Europe and Japan. Under the same classification standard, it is hoped that the international comparative study of various vasculitides progresses in future.

S2-4

Clinical study for vasculitis in Japan

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Conflict of interest: None

Systemic vasculitis classified into two types, one is large vessel vasculitis such as Takayasu arteritis and Temporal arteritis, the other type is middle & small vessel vasculitis including polyarteritis nodosa, Kawasaki disease, anti-neutrophil cytoplasmic antibody (ANCA) associated vasculitis (AAV) and IgA vasculitis. In order to practice the clinical study of these diseases, nationwide studies by medical specialists are needed, because of these diseases are rare and intractable. The MHLW enforced the several clinical studies, such as the JMAAV study(severity-based treatment for Japanese patients with MPO-ANCA-associated vasculitis) and RemIT-JAV study (observational cohort study of remission induction therapy in Japanese patients with AAV). In 2011, the clinical practice guidelines of AAV was published by MHLW. Now, the MHLW participates in the ACR/EULAR diagnosis and classification of vasculitis study (DCVAS). In this symposium, We will discuss on the recent clinical study of vasculitis in Japan, especially ANCA associated vasculitis.

S2-5

Recent progress in the diagnosis of Takayasu arteritis

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tal University

Conflict of interest: Yes

Recent advances in diagnostic clinical tests especially imaging modalities and biomarkers improved the accuracy of diagnosis of TA and new immunosuppressive agents have been increasingly applied to TA. Although the clinical utility of these new technologies has not been settled yet, management of TA is changing. In this symposium my recent experiences in the management of more than 150 patients with TA in a single center are presented. Clinical utility of new biomarkers has been established. As compared to hsCRP and MMP-3, PTX3 could be a more sensitive biomarker to detect subtle TA activity even under steroid treatment. MMP-3 levels are affected by steroid treatment. HLA-B52 was confirmed to be a risk allele (OR3.31). We recently identified B67 as a new risk allele (OR4.85) for Japanese TA patients. Our experience in 39 patients showed sensitivity and specificity of diagnosing TA by ^{18}FDG-PET/CT were 91 and 89%, respectively. Although MRI is a useful for detecting arterial narrowing or dilatation, late gadolinium enhancement does not necessarily reflect active inflammation of TA. Prognosis of TA has been improved probably because of early diagnosis by new imaging modalities and progresses in immunosuppressive treatment. References 1. Ishihara T, et al: Sensitive assessment of activity of Takayasu's arteritis by PTX3, a new biomarker. J Am Coll Cardiol 57:1712-1713, 2011 2. Ohigashi H, et al: Improved Prognosis of Takayasu Arteritis in the Last Decade: Comprehensive Analysis of 106 Patients. Circ J 76: 1004-1011, 2012 3. Tezuka D, et al: Role of FDG-PET/CT and Utility of Max SUV in Takayasu Arteritis. J Am Coll Cardiol Imaging 5: 422-429, 2012 4. Takamura C, et al: A New HLA Risk Allele in Japanese Patients with Takayasu Arteritis. Circ J 76: 1697-1702, 2012 5. Ishihara T, et al: Diagnosis and assessment of Takayasu arteritis by multiple biomarkers. Circ J published on line.

S2-6

Recent progress in the treatment of vasculitis syndrome

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Conflict of interest: Yes

Vasculitis syndrome is the encompassing term for the inflammation of all-sized blood vessels excluding infectious vasculitis. In Chapel Hill Consensus Conference 2012, vasculitides are classified as large vessel vasculitis (e.g. Takayasu arteritis and Giant cell arteritis), medium vessel vasculitis (e.g. Kawasaki disease and polyarteritis nodosa), and small vessel vasculitis (e.g. 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 or methothorexate, or the additional therapy with plasma exchange in severe cases are recommended in the European League Against Rheumatism (EULAR) guideline for vasculitis. (2, 3). Although these standard protocols produce the initial remission in any forms of vasculitis, refractory cases are not rare. Recently the efficacy of tocilizumab for refractory Takayasu arteritis and rituximab for refractory ANCA associated vasculitis has been reported. In this session, the emerging new treatments for refractory vasculitis are presented based on worldwide clinical studies and better standard practices for vasculitis are discussed based on the clinical investigations in Japan. 1. Jennette J, Falk R, Bacon P, Basu N, Cid M, Ferrario F, et al. 2012 Revised International Chapel Hill Consensus Conference Nomenclature of Vasculitides. Arthritis Rheum. 2012. 2. Mukhtyar C, Guillevin L, Cid MC, Dasgupta B, de Groot K, Gross W, et al. EULAR recommendations for the management of primary small and medium vessel vasculitis. Ann Rheum Dis. 2009;68(3):310-7. 3. Mukhtyar C, Guillevin L, Cid MC, Dasgupta B, de Groot K, Gross W, et al. EULAR recommendations for the management of large vessel vasculitis. Ann Rheum Dis. 2009; 68(3):318-23.

S3-1

Bone and cartilage destruction from the standpoing of GWAS on rheumatoid arthritis

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Conflict of interest: None

Genome-wide association studies (GWAS) on the susceptibility of rheumatoid arthritis (RA) have been carried out in large-scale for multiple ethnic populations and many risk genes with risk variants have been identified. GWAS on RA is one of the most fruitful studies among many GWAS's on various diseases. Genetic studies on the susceptibility of RA have been always successful in all of three eras of pre-genome, genome, and post-genome. It seems because RA has relatively stronger genetic effect among complex genetic traits and because environmental contributions to RA are relatively weaker than lifestyle-related diseases. However genetic factors on subtypes or prognosis of RA, including destruction of bone and cartilage, have been far less identified. There seem multiple reasons. One reason is that subtypes and prognosis of RA are masked by introduction of effective therapeutic interventions, which has entangled subtypes and prognosis with responsiveness to treatments. The imperfectness in the measures of subtypes, stages and severity also seems to contribute the difficulty. The fact that the subtypes and prognosis are the heterogeneous mixtures of various autoimmune processes is one of the reasons. Although bone and cartilage destruction in RA is complicated and the genomic approach to the issue has multiple challenges, combination of genomic approach with other omics-science such as transcriptome analysis seems promising. The current status and future of genomic approach to bone and cartilage destruction are to be discussed.

S3-2

Imaging for diagnosis of cartilage destruction in rheumatoid arthritis

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Conflict of interest: Yes

Although software-based image analysis is important for studies of cartilage changes in rheumatoid arthritis (RA), quantitative software tool to evaluate these changes has not been established. To overcome the problems, we developed computer software named KOACAD which realized a full-automatic quantitative measurement of six parameters: medial & lateral minimum JSW (mJSW), medial & lateral joint space area (JSA), osteophyte area (OPA), and FTA, on plain knee radiographs; and a semi-automated software to quantify knee cartilage volume on high-resolution knee magnetic resonance (MR) images. Here, we investigated cartilage destruction using these two software tools in clinical studies. We first present a comparative study between RA (49 knees) and osteoarthritis (OA: 50 knees) patients on preoperative knee radiographs in total knee arthroplasty, using KOACAD software. Patient characteristics and KOACAD parameters were compared between RA and OA patients by logistic regression to test the association of knee radiographic features. This analysis after adjustment for age and confounding factors revealed that low lateral mJSW (OR=1.37,

95%CI=1.03-1.88) was positively associated with RA. The second study is an open-label study that investigate the effect of ETN+MTX treatment on cartilage deterioration on MR images (3.0-T Philips MR system with a knee coil, FFE sequence) as compared with MTX alone treatment using our developed semi-automated software for cartilage quantification (UMIN000005773). This study is now in progress, however, we obtained interesting cases that knee cartilage destruction of RA occurred on MR images, nevertheless radiographic joint space width was maintained. Namely- cartilage destruction occurred, except weight-bearing area. This knowledge is totally different from that of our OA cohort study (ROAD): cartilage destruction of OA occurred in weight-bearing area. Thus, there is a possibility of different etiology between RA and OA cartilage destruction.

S3-3

Dcir deficient mice as a novel disease model for ankylosing spondylitis

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Conflict of interest: None

Ankylosing spondylitis (AS) is an ankylotic joint disorder with chronic inflammation and heterotopic cartilage and bone formation. Enthesitis, inflammation at the attachment sites of ligaments, tendons and joint capsules to bone, is the first sign of the symptom, and gradually ankylotic changes develop nearby joints. These pathologies are clearly different from that of rheumatoid arthritis (RA), a typical autoimmune disease that causes bone erosion and synovial inflammation. However, the pathogenesis of the disease has not been well understood and effective therapies are still awaited. Because animal disease models for this disease are very limited, new animal models are awaited to understand the pathogenesis and to develop new therapeutics. Previously, we showed that deficient (KO) mice for the Dendritic cell immunoreceptor (*Dcir*), a C-type lectin receptor expressed in dendritic cells and macrophages, spontaneously develop enthesitis and joint ankylosis, accompanied with fibrocartilage proliferation and heterotopic ossification in multiple joints, including ankles, knees, and the spine. Because these pathologies resembled those of AS, we analyzed the mechanisms. Activated T cell population and T cell-derived inflammatory cytokine production were significantly increased in ankylotic *Dcir* KO mice. To examine the involvement of the immune system in the development of ankylotic joint abnormality, we generated *Dcir/Rag2* double KO mice, and found that these mice did not develop ankylosing change, suggesting a role for the immune system in the pathogenesis. Then, we next examined the roles of cytokines by generating *Dcir/Tnf*, *Dcir/Il17* and *Dcir/Ifng* double KO mice. Interestingly, the development of AS-like pathologies was completely suppressed in *Dcir/Tnf* KO and *Dcir/Ifng* KO mice, but not in *Dcir/Il17* KO mice. These results suggest TNF and IFN-γ as targets for the treatment of AS.

S3-4

Differential effects of biologics targeting TNF on the bone erosion and cartilage damage in patients with rheumatoid arthritis

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Conflict of interest: Yes

Recent progress in the treatment of rheumatoid arthritis (RA) with TNF-inhibitors has brought a paradigm shift, in which clinical and structural remission is now a target to be approached. However, joint damage already develops in a majority of patients before appropriate treatments are provided. Joint damage results from the destruction of bone and cartilage, which can be visualized via radiography as joint erosion (JE) and joint space narrowing (JSN), respectively. JSN is a surrogate marker for loss of cartilage and it also reflects damage to tissues causing joint dislocation, a phenomenon that is less prevalent among patients with early RA. JE has been perceived to be the most critical indicator of permanent disability in RA. However, recent studies have indicated that JSN is the more important to predict irreversible physical disability especially in the early disease process. It is well known that the combination of TNF-inhibitor and MTX reduces the risk of joint damage, measured by radiographic modified total Sharp score (mTSS). We assessed multiple baseline factors to predict changes of joint damage and serum levels of MMP-3 is a good marker to predict changes in mTSS and JSN, but not JE. Furthermore, yearly progression of mTSS and JSN, but not JE, after the treatment with TNF-inhibitors and MTX significantly correlated with MMP-3 levels at baseline and at 1 year after the treatment. Ultimately, MMP-3 in synovial fluid secreted from inflamed synovium might resorb the surface of cartilage, which resulted in changes of JSN. Recent reports indicate that JSN is associated with impairment in physical function greater than JE and the protection of JSN from the onset is prerequisite to manage patients with RA.

S3-5

Cartilage destruction and homeostasis via regulating mRNA stability and translation

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Conflict of interest: None

In rheumatoid arthritis (RA) pathogenesis, cartilage is damaged by inflammatory proliferating synovium, causing sever pain and disability of cartilage joint. microRNAs (miRNAs) are non-coding RNAs that disrupt translation or posttranscriptionally degrade target mRNAs in a sequence-specific manner. We and others recently identified miR-140 regulating cartilage homeostasis against inflammatory responses. In addition, using microarray and high throughput sequencing technology, other miRNAs have been identified as cartilage specific miRNAs. To identify the functional significance of these miRNAs, the level of the miRNAs in human cartilage samples have been examined. To understand the molecular pathway regulated by the miRNAs, we developed a luciferase reporter library, which allows us to screen potential miRNA targets in cell base way and non-bias way. Using this strategy, we try to reveal molecular networks in cartilage homeostasis and against rheumatoid arthritis.

S3-6

Molecular biology of chondrogenesis and articular cartilage regeneration

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Conflict of interest: None

Since discovery of *SOX9* mutations in the severe human skeletal malformation syndrome Campomelic Dysplasia in 1994, Sox9 was shown to be both required and sufficient for chondrocyte specification and differentiation. Both loss-of-function and gain-of-function analyses using mutant mice demonstrate that Sox9 is required for the commitment of osteochondroprogenitors,

chondrogenic mesenchymal condensation and proper chondrocyte proliferation, differentiation, maturation and hypertrophic conversion, suggesting that Sox9-Sox5, Sox6 form the master regulatory axis of chondrogenesis. Overexpression of Sox9, Sox5, and Sox6 in cultured cells and ectopic expression of Sox9 in mice induce the expression of type II collagen. Moreover, ectopic expression of Sox9 with retrovirus in chick limb bud induces alcian blue-stainable cartilage. Transgenic mice in which Sox9 was ectopically expressed in limb bud mesenchyme using the Prx1 promoter exhibited ectopic cartilage formation in association with the induction of ectopic Sox5 and Sox6 expression without any patterning defects in limb bud development. These lines of evidence clearly indicate that Sox9-Sox5, Sox6 are the master regulators of chondrogenesis. Sox9 transactivates several genes directly that encode cartilage matrix proteins, including type II, IX, XI collagen and Aggrecan. Static compressive force promotes type II collagen and aggrecan expression mediated by an increase in Sox9 expression. Furthermore, Sox9 induces the chondrogenic phenotype in another cell lineages. These findings suggest that Sox9 has potential clinical value. In this symposium, I introduce the current strategy of cartilage regeneration.

S4-1

Steroid psychosis: rheumatologist

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Conflict of interest: None

A variety of neuropsychiatric manifestations are seen in patients with systemic lupus erythematosus (SLE). American College of Rheumatology (ACR) developed a nomenclature for neuropsychiatric SLE in 1999, in which central nervous system manifestations are grouped into neurologic syndromes and diffuse psychiatric/neuropsychological syndromes. In the latter, 5 different psychiatric manifestations are included, so called lupus psychosis (LP). Since there are factors causing psychiatric manifestations other than SLE, the diagnosis of LP is often difficult and its treatment is challenging. Especially, steroid has been found to cause psychiatric manifestations by itself, so called steroid psychosis. It should be noted that even patients with LP often present psychiatric manifestations after the initiation of steroid therapy. Accordingly, 13 of the 25 patients who were diagnosed as LP between 2000 and 2012 in our institution had presented psychiatric symptoms after the initiation or increase of steroid. Eight of the 13 patients showed acute confusional state. On the other hand, in the multicenter retrospective study performed in 2001, 20 patients who showed psychiatric manifestations between 1993 and 2000 were judged as steroid psychosis (male:female=2:18, age:34.5±8.7 [mean±SD], dose of steroid at the onset:49.5±10.5m/day [4 patients with pulse therapy]). Eighteen of the 20 patients showed mood disorder (8 with insomnia), but none presented acute confusional state. CSF IL-6 was within normal ranges (0.15-2.1pg/ml) in 8 patients who received examination. Major tranquilizers were given in 14 patients, while 2 patients received no special medication for psychosis. These results have disclosed the clinical characteristics of steroid psychosis that it is a noninflammatory psychiatric disorder, resulting mainly in mood changes, in contrast to LP which cause severer manifestations, such as acute confusional state, through brain inflammation.

S4-2

Corticosteroid-induced psychiatric disorders

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Conflict of interest: None

Corticosteroid-induced psychiatric disorders (CIPDs) are not rare and negatively affect treatment of the underlying diseases and the patients' well-being. A meta-analysis reported severe reactions in 6% and mild to moderate reactions in 28% of the patients taking corticosteroids. CIPDs include delirium, psychotic disorders, and mood disorders (depression, hypomania, and mania). Recent studies have shown that short-term high-dose corticosteroid therapy usually leads to acute/subacute hypomanic/manic episodes, whereas long-term corticosteroid therapy tends to induce depressive episodes. Further, cognitive deficits, especially memory problems, have been often described after corticosteroid therapy, suggesting hippocampal dysfunction. High dose of corticosteroid (>40 mg/day of prednisone) is the most important risk factor for CIPDs. Age and history of CIPDs or psychiatric illness are not predictive factors for CIPDs. Cerebral spinal fluid/serum albumin ratio, a maker of blood-brain barrier damage, predicts CIPDs in patients with systemic lupus erythematosus (Nishimura et al., 2008). Little data is available on CIPD treatment. Management strategies for CIPDs include tapering corticosteroids with/without psychopharmacologic treatment. Adjunctive psychotropic medications are often required when the psychiatric symptoms are severe or the corticosteroid is indispensible. For cases with psychosis, mania, aggression, or agitation, second-generation antipsychotics, e.g., risperidone, olanzapine, and quetiapine, are the first-line drugs. Although lithium is used for preventing and treating CIPDs, it is contraindicated in patients with renal insufficiency, and some authors have suggested valproic acid or carbamazepine instead of lithium. When managing CIPDs, collaboration with psychiatrists is necessary, particularly in case of severe symptoms or suicidal risk. Further controlled studies are needed to completely understand CIPDs.

S4-3

Thrombosis and cardiovascular complication

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Conflict of interest: Yes

A number of epidemiological studies have shown high prevalence of cardiovascular events in American and European patients with systemic lupus erythematosus (SLE). In general Japanese population, the cardiovascular diseases are less common compared with Caucasoids, thus other complications would be more impressive rather than cardiovascular events in the management of Japanese patients with SLE. However, cardiovascular diseases could directly affect to the morbidity and mortality in lupus patients, therefore physicians should recognise the importance for the prevention of cardiovascular syndromes. Here we studied the risk factors for thrombosis in newly diagnosed SLE patients. Ninety seven patients with SLE (female 87, median age 32) in the absence of past thrombotic events were enrolled from 2001 to 2012. The endpoint was defined as development of thrombosis. The risk factors to develop thrombosis were retrospectively analyzed. Within the observed period (median 46 months), 14 patients developed thrombosis with the follow-up periods of 3.5 months. Multivariate analysis with Cox's proportional hazards model showed that older age at SLE onset (OR 2.01 for every ten age, 95%C.I. 1.26-3.20), positive aCL-IgG (OR 8.37, 95%C.I. 2.15-32.6) and positive aCL-IgM (OR 6.14, 95%C.I. 1.68-22.5) were statistically significant risk factors for thrombosis. Statin use significantly reduced the events (OR 0.17, 95%C.I. 0.036-0.764). Those data suggests that those risk factors should be considered in the management of Japanese lupus patients and appropriate prophylaxis would be desirable.

S4-4

Current Understanding and Future Perspective of Dyslipidemia and Atherosclerosis - a view from lipidology specialist -

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Conflict of interest: None

Dyslipidemia has been considered to be a major risk factor for atherosclerotic diseases, thus the goal of dyslipidemia management is to prevent such diseases. It was 1994 when simvastatin, one of statins, demonstrated a clinical benefit in patients with coronary heart disease, followed by many randomized clinical trials showing similar benefit in both primary and secondary prevention settings. CTT 2010 clearly demonstrated that 40mg reduction of LDL-C translated into 23% reduction of cardiovascular disease as well as 12% reduction of total mortality without increasing cerebral hemorrhage or cancers. Further, several recent topics include ezetimibe, a selective inhibitor for cholesterol transporter at intestine, and inhibitors for PCSK9, a protein involved in LDL receptor degradation, both of which exert potent LDL-C lowering effects with statins. Japan Atherosclerotic Society proposed guideline for management of atherosclerotic disease and the latest guideline published in 2012 is consistent with the previous versions with regard to LDL-C as a primary target and classification based on risks other the LDL-C but newly employed absolute risk, integral risk management including dyslipidemia, and familial hypercholesterolemia as high risk status. Although randomized controlled trials using statins demonstrated about 30% reduction on cardiovascular disease morbidity, this evidence also showed that there remained 70% risk. Among lipoproteins other than LDL, TG-rich lipoproteins (remnants) and HDL are considered to account for the residual risk. In particular, HDL, anti-atherogenic lipoproteins, may play a pivotal role to further reduce the residual risk. Decades of Intensive research on HDL succeeded to establish several CETP inhibitors. However, first two clinical trials using CETP inhibitors were prematurely terminated. In this symposium, I will discuss dyslipidemia in relation to atherosclerosis and current and future treatment.

S4-5

How can we mitigate risk for infection in patients with rheumatic diseases given immunosuppressive therapy?

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Conflict of interest: Yes

Glucocorticoid and immunosuppressants are widely used for treatment with systemic autoimmune diseases such as systemic lupus erythematosus and vasculitis syndrome. Recently, treatment strategy aiming at induction and maintenance of remission, the proverbial strategy for rheumatoid arthritis, has also been adapted to these diseases and more aggressive immunosuppressive treatment has been proposed to garner more stringent control of disease activity. In addition, molecular-targeting drugs represented by biologics have been used for some intractable conditions. Risk for infection in patients given immunosuppressive therapy is determined by various conditions; type, dose and duration of drugs, demographic features, type, disease activity and severity of rheumatic diseases, state of cutaneous and mucosal barriers, number and function of peripheral blood neutrophils and lymphocytes, serum immunoglobulin concentration, comorbidities and their severity, physical function, and nutritional state. In organ-transplant recipients, types of infectious diseases that are more likely to develop change chronologically, and guidelines based on such evidence for preventing infectious complications has been published. In patients with systemic autoimmune diseases, however, pathophisiology and treatment are more complicated, and management of infectious diseases significantly varies across medical institutions or specialists of rheumatology. In this symposium, we would like to review existing evidence in this medical field and provide and discuss about the results from a multi-center, prospective cohort study to identify risk factors for development of pulmonary infection in patients receiving immunosuppressive treatment for rheumatic diseases (PREVENT study) and other related studies.

S4-6

Steroid-induced osteonecrosis of the femoral head

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Conflict of interest: None

Osteonecrosis of the femoral head is well known to occur in association with the corticosteroids treatment. We firstly developed an animal model of osteonecrosis in rabbits, in which we confirmed that high-dose methylprednisolone (20 mg/kg) can induce multifocal osteonecrosis (ON) in conjunction with thrombocytopenia, hypofibrinogenemia, and hyperlipidemia. Moreover, we investigated the effects of the combination treatment with an anticoagulant (warfarin) plus a lipid-lowering agent (probucol) on prevention of steroid-induced osteonecrosis (ON) in this animal model. The incidence of ON in warfarin plus probucol (5%) was significantly lower than that observed in the control group (70%) ($p < 0.0001$). Our results experimentally showed that the combined use of an anticoagulant and a lipid-lowering agent helps prevent steroid-induced ON in rabbits.

S5-1

Toll-like receptor logistics by Unc93B1 as a mechanism regulating autoimmunity

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Conflict of interest: None

A variety of microbial products including lipopolysaccharide (LPS) are known to stimulate the immune system. The Toll family of receptors has critical roles in microbial recognition and activation of defense responses. Cell surface TLR dimers consisting of TLR4/MD-2, TLR1/TLR2, or TLR2/TLR6 recognize microbial membrane components such as lipopolysaccharide (LPS) or lipopeptides, whereas nucleic acid sensing TLRs including TLR3, 7, 8, and 9 reside in intracellular organelle. The subcellular distribution of TLRs shows strong correlation with TLR responses. TLR4/MD-2 induces proinflammatory cytokines from the cell surface and type I interferons from the endolysosomes. TLR7 and 9 reside in the endoplasmic reticulum (ER) and traffic to the endolysosomes for nucleic acid-sensing. TLR-trafficking is controlled by ER-resident proteins such as PRAT4A (Protein associated with TLR4 A) and Unc93B1. PRAT4A is a TLR-specific cochaperone working together with gp96, whereas Unc93B1 is associated with and control trafficking of TLR3, 7, 8, and 9. Immune cells such as dendritic cells (DC) or macrophages express multiple TLRs, which are concomitantly activated in response to pathogens, since single microbes or viruses express a variety of TLR ligands. Although the ligand specificity and downstream signaling pathways of each TLR have been extensively studied, much less is known as to how overall TLR responses are regulated. “TLR logistics” is an emerging

concept where appropriate TLR distribution and trafficking warrant innate immune responses to pathogens without hazardous tissue damages due to excessive or autoimmune responses. We here show our recent results on a role for Unc93B1 in TLR logistics

S5-2

The Inflammasome: A Double-Edged Sword

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Conflict of interest: None

Autoinflammatory diseases are mediated by Inflammasome-mediated IL-1β production. Blockade of IL-1 signaling is remarkably effective for the treatment of autoinflammatory disease patients. However, IL-1 blockade also inhibits IL-1-mediated immune responses including host defense against pathogens, so strategies to block IL-1 may result in increased susceptibility to infection. Antibiotic treatment effectively removes specific pathogens, but careless use of antibiotics is associated with the emergence of antibiotic-resistant strains. Pseudomembranous colitis is caused by *Clostridium difficle* (Cd)-induced intestinal damage in antibiotic-treated individuals. We recently found that disease severity is dependent on translocation of intestinal commensals which is regulated by IL-1β-mediated responses in a mouse model of Cd disease. Elimination of particular commensals that translocate through the Cd toxin-damaged intestine is critical for survival of mice lacking IL-1β/inflammasome signaling. Notably, IL-1β secretion after Cd infection requires not only Cd toxins, but also the commensals, suggesting that the function of IL-1β during Cd infection is to eliminate commensals but not Cd. IL-1β secretion in the intestine induces local (intestinal) and systemic defense responses against the commensals. The major source of IL-1β is neutrophil, and IL-1β plays a critical role in the recruitment of neutrophils through a positive feedback loop. We also found that direct induction of particular immune responses which act downstream of IL-1β eliminated the commensals and rescued mice lacking IL-1β/inflammasome signaling from commensal-induced lethality. Thus, handling of translocated commensals by inflammasome-mediated responses is critical for Cd-related disease, and presumably also for other diseases which are associated with the loss of physical barriers against commensals.

S5-3

Autoinflammatory disease and inflammasome

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Conflict of interest: None

Autoinflammatory syndrome is characterized by attacks of inflammation without significant levels of autoantibodies and autoreactive T cells. In this context, autoinflammatory syndrome seems to be a counterpart of autoimmune disease. Alternatively, it is thought that autoinflammatory disease is caused by innate immune dysregulation and autoimmune disease is caused by acquired immune dysregulation. However, both autoinflmmatory and autoimmune diseases seem to be a closely related disease. Inflammasome is a multi-protein complex, which recognize intracellular pathogens and metabolites. The inflammasome is thought to act as an important role in pathogenesis of autoinflmmatory disease. Prototype of the inflammasome consists of Nod-like receptor, an adapter ASC, and caspase-1, which can process an inflammatory cytokine interleukin-1β. Cryopyrin (NLRP3) inflammasome is well-characterized inflammasome, which reported to recognize a lot of microbes, crystals, metabolites, cationic strength and so on. An autoinflammatory syndrome, cryopyrin-associated periodic syndrome (CAPS) is reported to be caused by constitutive active mutation of cryopyrin. Another autoinflammatory syndrome, familial Mediterranean fever (FMF) is known to be caused by pyrin, which thought to suppress activated inflammasome. In this symposium, how inflammasome is involved in autoinflammatory disease will be discussed.

S5-4

Primary Nationwide Survey for FMF in Japan

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Conflict of interest: None

Familial Mediterranean fever (FMF) is a hereditary autoinflammatory disease that is prevalent in Mediterranean populations. While it has been considered to be quite a rare disease in the rest of world, a significant number of FMF patients have been reported in East Asia, including Japan. The primary nationwide survey of FMF was conducted in 2009. High-grade fever was observed in 95.5%, chest pain (pleuritis symptoms) in 36.9%, abdominal pain (peritonitis symptoms) in 62.7%, and arthritis in 31.3%. 25.4% of patients experienced their first attacks before 10 years of age, 37.3% in their teens, and 37.3% after age 20 years. Colchicine was effective in 91.8% of patients at a relatively low dose (mean dose: 0.89±0.45 mg/day). AA amyloidosis was confirmed in 5 patients (3.7%). Of the 126 patients studied, 109 (86.5%) were positive either for one, or more mutations and 17 (13.5%) had no mutation detected. Common *MEFV* mutations were E148Q/M694I (19.8%) and M694I/normal (12.7%). The differences in the prevalence of peritonitis, pleuritis and the presence of family history were statistically significant between FMF patients with *MEFV* exon 10 mutations and those without exon 10 mutations. Our data showed a significant prevalence of FMF in Japanese patients with unexplained fever or undifferentiated arthritis, and we have to be more aware of the presence of variant type of FMF or the modification of rheumatic diseases by the polymorphisms of *MEFV* gene.

S5-5

Disase-associated iPS cells from patients with autoinflammatory syndromes

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Conflict of interest: None

Human Induced pluripotent stem cells (iPSCs) are potential cell sources for regenerative medicine and other clinical applications, such as cell therapies, drug screening, toxicology testing, and the investigation of disease mechanisms. Discovery of disease-associated iPSCs has led to the development of a new field of disease modeling, as they can provide somatic cells which cannot be directly obtained from each patient. For establishing an in vitro model of autoinflammatory diseases by using disease-associated iPS cells, we have established novel differentiation systems from human pluripotent cells into innate immune cells such as neutrophils, monocytes, macrophages and dendritic cells. We then generated iPS cells from patients who have been diagnosed as CINCA syndrome, an autoinflammatory disease caused by gain-of-function

mutations of NLRP3. These patients have mutations of NLRP3 as somatic mosaicism, and we compared biological characteristics of NLRP3-mutated cells with wild-type cells. Currently, by using patient-derived iPS cells and a high-throughput screening system, we are trying to find novel compounds that can inhibit NLRP3 inflammasome. In this presentation, I review the current state of disease-associated iPSC study and discuss future perspectives.

S5-6

New project for the comprehensive understanding of autoinflammatory diseases in Japan

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Conflict of interest: None

Autoinflammatory diseases are hereditary diseases usually characterized by recurrent flares of systemic inflammation presenting most of the time as sudden fever episodes associated with elevation of acute phase reactants and with a number of clinical manifestations such as rash, serositis, lymphoadenopathy and arthritis. They are comprehended by seemingly unprovoked pathological activation of the innate immune system in the absence of autoantibodies or activated T cells. However, the incidence of these diseases are extremely rare, therefore, our understanding of autoinflammatory disease pathogenesis and its treatment remains limited. To resolve these problems, we have recently established the study group for autoinflammatory diseases supported by Ministry of Health, Labour and Welfare in Japan. Seven goals are set up. 1) registry for autoinflammatory diseases, 2) screening system using next generation sequencing system, 3) clinical study for the development of treatment, 4) flow chart for medical care, 5) banking of patient-derived iPS cells, 6) study for pathophysiology and medical treatment, 7) study for unclassified inflammatory diseases. I would like to introduce this project comprehensively.

S6-2

Total Hip Arthroplasty Up-to-date

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Conflict of interest: Yes

The number of total hip arthroplasty is constantly increasing in Japan. Advances in implant technology as well as surgical techniques significantly improved the longevity of THA. In this symposium, we report recent advances in THA through our experiences of the cementless THA. Polyethylene wear, osteolysis, loosening: Polyethylene (PE) wear is a key factor for the implant survival. however, the cross-linked PE (XPE) changed the scene dramatically. In our series, 0.0001mm/y of XPE wear is significantly lower than conventional PE and reduced the rate of osteolysis and loosening. Thus XPE improved the long-term results of THA Dislocation: Postoperative dislocation is a kind of fate in the ball and socket joint and the most frequent complication in THA. But large head size and contemporary technique of the implant technique reduced the dislocation. For example, the rates of dislocation after primary THA with 22, 26 and 32mm heads were 4.64%, 2.07% and 0%, respectively. Infection: The implant infection is rare, but a serious burden for both patients and doctors. A series of THA with cement containing antibiotics showed the improved implant survival in the Norwegian register. Cementless implant with antibiotics coating is now being developed. Light and shadow: Innovation did not always result in the improvement. Metal on metal (MOM) articulation enabled the larger head size than PE, however, a kind of MOM showed serious complications due to high concentration of metal ions.

S6-3

Up-to-date of total knee design

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Conflict of interest: Yes

Design of total knee prosthesis is classified to PCL retaining (CR), PCL substituting (PS), and PCL sacrificing (CS). Each design has inherent merits and demerits. In the CR design, the joint line is kept in a physiologic level and the retained PCL could suppress lift-off of the femoro-tibial joint and PE damage. Because of these advantages, surgical instruments for the CR design are developing to realize enough function of the PCL. In the PS design, the knee kinematics is controlled by the post-cam mechanism that facilitates so-called rollback of the femur and deep flexion of the knee. Since early 21st, therefore, many implants for high flexion have appeared in the Japanese market. However, there are some concerns in this design, including wear debris from the post-cam, patellar clunk and crepitus, anterior impingement between the post and the anterior femoral notch, and post-fracture due to anterior notch formation and excessive bearing loads to the post. The newest PS knees address these concerns and have modified the post-cam design. Bi-surface knee, which has been developed in Japan, has a unique design for deep flexion. The knee has a ball between the posterior femoral flanges and a shallow socket in the posterior part of the tibia, which works as an inverted post-cam mechanism and facilitates the rollback. In type V series, adding to the CS type, the PS type has advent, which has a small post installed at just anterior to the socket to improve stability and centering. This PS knee is thought to resolve many concerns inherent in the PS knee mentioned above and promising for good long-term results. Regarding the CS type, new implants have appeared, which attach greater importance to physiological knee kinematics, stability and longevity rather than to deep flexion. Design of total knee prosthesis is now progressing for physiological knee kinematics, knee function, longevity and high patient's satisfaction.

S6-4

Total Elbow Arthroplasty - up-to-date -

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Conflict of interest: None

The current focus of total elbow replacement is restoration of normal kinematics without compromise of stability. It would appear that an appropriate design and positioning of the humeral and ulnar component are essential to reduce the risk of instability and aseptic loosening. Kudo unlinked total elbow replacement is technically demanding surgery. We would advise particular care when inserting both the trial and definitive components in order to be certain that there is no mal-rotation of ulnar component and accurate positioning of valgus /varus humeral component such that the anatomical axis of movement should more closely replicated to native anatomy of the elbow. Coonrad-Morrey linked type is most reliable total elbow implant in the world. A selection of the implant including gender, bone quality and defect, size matching is essential part. There are a couple of issues in the linked total elbow replacement. The cement technique, how to couple the two component, and eccentric motion of the ulnar component against the

humeral component, is still controversial. While instability has been observed with unlinked total elbow replacement, the loosening rate depends upon the prosthetic design. Use of reasonable design of implant and appropriate surgical technique would decrease loosening and eccentric motion, decrease stress on the ulno-humeral articulation and therefore possibly reduce polyethylene wear, osteolysis, and loosening.

S6-5

Total Ankle Arthroplasty in Patients with Rheumatoid Arthritis

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Conflict of interest: Yes

Total ankle arthroplasty (TAA) are implanted in patients with rheumatoid arthritis (RA) and osteoarthritis (OA). Patient with RA usually have arthritic joints in proximal lower limbs and in the feet. The resulting malaligned lower leg, midtarsus or/and hindfoot are often seen in rheumatoid patients with end-stage arthritis of the ankle. The ankle joint itself is also often in a valgus or varus deformity. Patients with RA also have osteopenic bones and a poor soft-tissue envelope around the ankle joints, with fragile skin. Patients also have other systemic problems or comorbidities associated with the drugs such as steroids and immunosuppressants. These unfavorable backgrounds in rheumatoid ankle joint could lead to a poor outcome comparing with TAA in OA patients. So, the meticulous strategy against all of these problems should be elaborated to yield long-term good outcome of TAA in patients with RA. We have tried to perform the well-aligned, well-balanced TAA with augmented bone strength TAA is performed in patients with RA using several elaborate techniques as follows. We have used the specially designed hydroxyapatite augmentation for bone atrophy against the subcidence of tibial component, performed talocalcaneal joint arthrodesis with packing of interconnected porous csalcium hydroxyapatite ceramic to diminish the risk of talar component loosening, corrected malalignment in ankle and subtalar joint using the radiological evaluation with Cobey's method and hip-to-calcaneus view (HC view), used malleolar lengthening osteotomy for soft tissue balancing of deformed ankle joint, and used the 3D custom-made template for accurate tibial cutting. Furthermore, we have to continue to improve the implant designs at the same time of these techniques. On the other hand, the recent advance in pharmacotherapy for RA might lead the chance to preserve the talocalcaneal joint function by TAA using talar body prosthesis.

S6-6

Surgical updates for forefoot deformity in rheumatoid arthritis

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Conflict of interest: Yes

In advanced cases of rheumatoid arthritis (RA), metatarsophalangeal joint (MTP) sometimes shows hallux valgus deformity, subluxation and dislocation of phalangeal bone, and dislocation of the os sesamoideum with hammer toe deformity in lessor toes. Resection arthroplasty has been performed from 1960s. Although it showed stable results, shortening, instability, and muscle weakness of the hallux were problem. In order to improve these problems, silicone-based joint implant was introduced by Swanson in the 1970s. After additional modification of implant and the introduction of the grommet, reported post-operative results has been sufficient. We use Swanson type implant from 2004. In our early series, we resected MTP bone of the hallux as implant size according to surgical manual with resection arthroplasty for lessor toes. But the results showed the recurrence of hallux valgus deformity in some cases because relatively long residual hallux. 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 the hallux valgus. Additionally, we recently perform partial resection of metatarsal bone for lessor toes. Our results show that there are fewer cases with recurrence of hallux valgus in partial resection group of metatarsal bone than in resection arthroplasty group. This result reflects that preservation of the 2nd toe head of metatarsal bone may prevent the progress of hallux valgus. Improvement of disease activity of RA, essentially due to introduction of methotrexate and biological agents, total number of RA surgery has been decreasing. In contrast, the number of toe arthroplasty is increasing. We need careful selection of the optimal surgical technique such as resection arthroplasty, artificial joint, or osteotomy for hallux deformity based on each patient's degree of joint pain, the level of joint destruction of MTP, and the control of systemic RA.

S6-7

The current status of the Japanese Arthroplasty Register

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Conflict of interest: None

National arthroplasty registers are valuable tools for reporting on an updated epidemiologic survey of arthroplasties and for evaluating the performance of implants and operative procedures through the early identification of risk factors of failures. More than 10 registers have been launched globally, but no national register has been reported in Asia. In February 2006, a pilot project of the JAR for total hip arthroplasty (THA) and total knee arthroplasty/unicompartmental knee arthroplasty (TKA/UKA) was launched by the Japanese Orthopaedic Association (JOA). The aim of this project was to identify the types of data that should be registered in the databases and to establish methods for submitting the data collection forms for encouraging surgeons' participation and accumulating the data in the Japan Arthroplasty Register (JAR) office. Up to October 2012, 120 hospitals participated in the JAR project. From 2006 to 2012, 54,554 data collection forms were submitted; 27,819 for THA and 26,735 for TKA/UKA. A brief summary of the annual report of the JAR is available from The Japanese Society for Replacement Arthroplasty website at http://jsra.info/. A national arthroplasty register is a useful tool for evaluating the outcomes of interventions and the materials used in arthroplasties, and to provide rapid feedback to practitioners and patients about any failure of THA and TKA/UKA. Although there are several problems of data collection, compliance, organization, and operating fund to be solved, as the first national arthroplasty register in Asia, the JAR will help guide the development of registers of arthroplasty characteristics specific to Asian populations.

S6-8

Changes in patient's characteristics with indication of surgical procedures in this Bio decade

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Conflict of interest: None

Treatment of rheumatoid arthritis is made remarkable progress in this decade with biologics and MTX. Until now, patients with surgical procedure including joint replacement have had poor func-

tional prognosis. We will show the changes in patient's characteristics with indication of surgical procedures based on study in Nagoya University Hospital and Tsurumai Biologics Communication Registry (TBCR). Important findings are as follows: 1) About 75 % of patients who were needed TKA during treatment with biologics had remarkable structural damage (Larsen III-IV) at the initiation of biologics. 2) 60 % of arthritis in knee joint with Larsen 0-II grade structural damage was disappeared after treatment with biologics while 15 % of those knees were needed TKA during five years treatment. 3) Disease activity of patients with remained arthritis after treatment with biologics was low (DAS28-CRP 2.8). 4) More than 1mm of remarkable joint space narrowing, measured by computer-assisted system (KOACAD), was detected in 60 % of arthritic knee joint while 20 % of not-inflamed joint after treatment with biologics also had More than 1mm of remarkable joint space narrowing.5) Based on TBCR, an important factor for needing joint replacement was no-concomitant use of MTX during biologics. According to these results, there could be three category needing joint replacement. 1) Patients with no efficacy of biologics, 2) Patients with partial treatment response(knee joint was inflamed but arthritis in most of other joints were under control), 3) Patients with complete control of arthritis and secondary OA process because of cartilage damage by arthritis. We have to do joint surgery carefully in patients category 1, who should have risk factor for infection and other adverse events. The patients in category 3, should request higher satisfaction as well as OA patients.We have to recognized these mid, long term clinical results of biologics to plan proper treatment including surgical procedures.

S7-1

Practical direction from diagnosis to drug therapy in patients with rheumatoid arthritis

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Conflict of interest: None

Introduction Treatment of rheumatoid arthritis (RA) is become complicated by the appearance of biological agents, and has increased the importance of specialist. Given this background, I will describe the practical direction of the point of diagnosis and treatment. The diagnosis of RA. Diagnosis of RA is made by classification criteria ACR/EULAR 2010. If a patient was visited complaining of joint symptoms, the physician must diagnose the patient with responsibility as RA in need of treatment by anti-rheumatic drugs. Even if there is no characteristic bone erosion, if there are two or three inflammatory joints, inflammatory positive blood tests and immune abnormalities such as anti-CCP antibody or rheumatoid factor, treatment for RA is required due to anti-rheumatic drugs. Therapeutic strategy of RA. In a case of agressive RA from early period, we should immediately start anti-rheumatic drugs. If inflammation is strong from the initial visit, add small amount of steroid. If the control is insufficient in the anti-rheumatic drugs, methotrexate is started without delay. Depending on the disease state, it is needed to increase MTX from 6mg once a week by 4mg a month. When see the progression of bone destruction in 3-6 months despite non-Biological DMARDs and MTX treatment, the start of BIO should be considered. Order to eliminate primary no effect (this phenomenon means no effect from the first time), the most appropriate BIO are screened. In the severe inflammation, set the dose of variable type BIO (Tocilizumab, Infliximab) according to the intensity of inflammation. In a case of erosion is noticeable and increasing number and increasing volume, anti-TNFα BIO therapy are considered. Finally. Even if the time of BIO era, the therapy of RA is often difficult to control. In the case of the administration of BIO, the rheumatologists must bear the burden of responsibility. I introduce these clinical diagnosis and treatment.

S7-2

Health economic evaluations for anti-rheumatoid biologics

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Conflict of interest: Yes

The paradigm shift of the pharmacotherapy against rheumatoid arthritis (RA) has been observed by the introduction of biologics. They have sufficient efficacy, but their cost are expensive compared to conventional DMARDs. Thus, pharmacoeconomic analyses, in which both costs and health outcomes of them are simultaneously assessed, would be important to justify their use and for rational allocation of limited resources from societal perspective. We quantitatively measured QOL of patients based on EuroQol (EQ-5D), and analyzed the major determinants of EQ-5D in RA patients using a large observational cohort of RA patients, IORRA in Tokyo Women's Medical University. We also measured direct and indirect costs of RA. Average QOL scores of RA patients were 0.757±0.178 (mean±SD) and age, disease duration and severities significantly affected them. Annual direct and indirect cost per one RA patient were JPY1.68mil and JPY0.76mil (overall: JPY2.44mil), respectively. These costs increased progressively with worsening RA disease activity, disability level, or QOL. These costs for those who with higher EQ-5D score (0.8<) were JPY 1.33mil and JPY0.48mil (overall: JPY1.81mil), respectively. Those for patients with lower EQ-5D score (0.5<) were 2.6 times as much as them, or JPY2.90mil and JPY1.91mil (overall: JPY4.80mil), respectively. Total costs for whole RA patients (n=700,000) was JPY1.71tril. (direct: JPY1.18tril, indirect: JPY0.53tril). We also conducted conjoint analysis to determine how people value various factors of diseases in decision-making process for co-payment reduction. Based on this estimation, when we consider characteristics of anti-rheumatoid biologics, more than 95% people think that out-of-pocket rate should be reduced. We are currently reviewing clinical trials of anti-RA biologics conducted in Japan, which can contribute to economic evaluation. Based on those data, we think that we can evaluate the efficiency of various anti-RA biologics.

S7-3

Rehabilitation in patients with RA

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Conflict of interest: Yes

Recent developments in biological drugs for the treatment of rheumatoid arthritis (RA) have revolutionized the field. Remission in RA can be now achieved with adequate treatment. The aim and process of rehabilitation in RA have improved along with these changes in the treatment of RA. Early intervention including education for the patients and introduction of self-help devices as well as exercises to improve muscle weakness or joint dysfunction are essential. Recent systematic reviews indicate that aerobic capacity training combined with muscle strength training is recommended as routine practice, and occupational therapy has a positive effect on functional ability in patients with RA. In this symposium we will discuss how we can prevent joint disintegration in its early period from the viewpoint of rehabilitation for patients with RA.

S7-4

The role of surgical intervention for the treatment of rheumatoid arthritis in biologic era

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Conflict of interest: Yes

Orthopaedic surgery for rheumatoid arthritis (RA) has been established as one of the principle treatments with medication, rehabilitation, and patients' education. Surgery could be avoided as long as medical treatments successfully prevent the bone and joint destruction and maintain the patients' functional activity without joint deformity. This treatment goal is now a realistic goal among some population of patients with the introduction of new biologic (bio) and non-biologic DMARDs for these 10 years. However, these 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. Even if they were able to introduce, some patients show continuous inflammation of a specific joint, or other patients might already have joint destructions with irreversible functional impairments. For these patients, Japanese original treatment strategy (J-T2T) that includes a surgical intervention is needed even in the biologic era. 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. Accumulation of patients' oriented evidences would be needed for make proper decision or assessment in the multidisciplinary treatment for RA.

S7-5

Social support and the utilization for patients with rheumatoid arthritis

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Conflict of interest: None

The Support System for patients with rheumatoid arthritis (RA) has had a wide variety of aspects, such as the health care, the medical economy, the environment, and mental activity. Among these measures, the law called the Social Security System has been defined. These systems consist of social insurance (medical insurance, long-term care insurance, pension insurance), social welfare (welfare for the disabled) and public health (measures for intractable diseases). As social support under total management of RA, patients can receive mitigation measures and subsidies (physically disabled person's certificate, high-cost medical care, etc.) for high medical expenses at use of biological products, hospitalization and surgery. Furthermore long-term care insurance and disability pension can be used as a further support of home care. There is a limit to reduce health care costs in the current system. For instance, patients with early stage of RA cannot get physically disabled person's certificate. The maximum limit high medical expense supply is as much as 80,200 yen in general income. Only malignant rheumatoid arthritis (MRA) in broad sense RA is allowed as intractable disease, which Ministry of Health, Labour and Welfare specifies. Ministry of Health, Labour and Welfare will launch a discussion on the reduction of the maximum limit high medical expense supply. The Japan Rheumatism Friendship Association (JRFA) has demanded that patients with RA are certified as Long-term expensive medical treatment patient such as hemophilia and dialysis. Although some inductions into rheumatism insurance or rheumatism fund are considered, a concrete scheme has not been agreed yet. On the other hand, it is essential to establish evidence of cost-effectiveness under early drug- use and drug-free in order to allow young and working patients with early stage of RA to receive high medical costs such as biological products.

S7-6

Activities of The Japan Rheumatism Friendship Association and establishment of basic law on medicine

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The Japan Rheumatism Friendship Association

Conflict of interest: None

The Japan Rheumatism Friendship Association was inaugurated in 1960 as a group representing 152 patients, and was accredited as an incorporated association in 1970. In recognition of the group's continued efforts to work for the public benefit of rheumatism patients under the objective of "engaging in projects that contribute to raise awareness of rheumatism, and the establishment and promotion of measures to combat rheumatism, thereby contributing to improvements in the welfare of individuals with rheumatic conditions", the group was authorized as public interest incorporated association in 2012. During those period, the treatment environment for rheumatism patients changed dramatically, particularly, in terms of developments in medical treatment, and the White Paper on Rheumatism, the results of a survey conducted by our group every five years shows these changes in numerical terms. However, medical policy in Japan continues to take place without the involvement of patients or the wider public and debates on medical policy continue to be governed by the inertia of existing budgets. Fundamentally, the unchanging, core purpose of medical treatment is to protect people's lives and it should always be the first priority for the country. That is why Japan's needs to establish a basic law on medicine which serves as a grand design for formulating medical policy that embodies the Right to live and Right to the pursuit of happiness enshrined under Articles 25 and 13 respectively of the Japanese Constitution in order to build medical treatment systems that provide a high level of public service and are based on a patient-first, mutual trust approach. As a result of our group observing the long-standing failure to reflect the views of patients and the wider public into medical policy, we have reached the conclusion that the enactment of a basic law on medicine is the best way to ensure that the opinions of patients are reflected into the process of determining medical policy.

S8-1

Life prognosis of rheumatoid arthritis patients with myelopathy caused by upper cervical lesions

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Conflict of interest: None

【Purpose】 Few studies have reported the survival prognosis of rheumatoid arthritis patients with myelopahy caused by upper cervical lesions. A matched controlled comparative study of patients with upper cervical lesions caused by rheumatoid arthritis was performed at two different hospitals to evaluate the survival prognosis. 【Subjects and Methods】 A total of 40 patients with rheumatoid arthritis and myelopathy caused by irreducible atlantoaxial subluxation with or without upward migration of the odontoid process were studied. Nineteen patients were treated by occipitocervical fusion using a rectangular rod associated with C1 laminectomy at one hospital, whereas 21 matched patients were treated conservatively at another hospital. The patients were observed by the same protocol to assess the radiologic and clinical results, including sur-

vival prognosis.【Results】The survival rate was 84% 5 years after surgery, and 37% in the first 10 years. In the patients who did not undergo surgical treatment, all the patients were bebridden within 3 years after the onset of myelopathy. The survival rate was 0% in the first 8 years.【Conclusion】The findings lead to the conclusion that occipitocervical fusion associated with C1 laminectomy for patients with rheumatoid arthritis is useful for improvement of survival rate after the onset of myelopathy. However, new operative methods for upper cervical lesions has been introduced. On the other hand, the life prognosis of patients with rheumatoid arthritis is improving by progress of medical treatments including use of biological drugs. The usefulness of the surgical treatment for rheumatoid arthritis patients with myelopathy caused by upper cervical lesions must be reexamined.

S8-2

Have biologics changed surgical treatments for cervical spinal lesions in rheumatoid arthritis?

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Conflict of interest: None

Purpose In 1996, Yonenobu reported that the type of rheumatoid arthritis (RA) (least erosive disease [LES], more erosive disease [MED], and mutilating disease [MUD]) facilitated deciding the treatment strategy and whether cervical spine surgery was required. We have performed a wide range of fixation procedures from the thoracic spine to the occipital bone for MUD-type RA cervical lesions. Biologics were approved in 2003 for the treatment of RA. In recent years, the prognosis of RA-mediated joint destruction has improved dramatically. What differences might revolutionary treatment changes make to treatment policies for RA cervical lesions? We studied RA patients in the Nagoya Spine Group (NSG) database who underwent cervical lesion surgery and analyzed the changes in treatment strategies after biologics approval. **Methods** Changes in the number of RA cervical lesion surgeries in the NSG from 2000 to 2011 were examined. We analyzed patients with respect to the examination method, operative procedure, preoperative history of RA treatment, RA class (modified Ranawat classification and Steinbrocker classification), and complications. We then compared outcomes before and after biologics approval. **Results** The number of patients undergoing RA cervical lesion surgery was 173 (atlantoaxial fusion [C1-2] 75 cases, occipitocervical fusion [OC] 40 cases, occipitothoracic fusion [OT] 58 cases). There were 23 cases in 2004, versus 9 cases in 2001, with an especially marked difference in OT cases. Among patients receiving RA treatment in our hospital, none were given biologics until 2008.From 2009, 7 of every 11 patients received biologics. As to complications, none of the cases developed deep wound infections but one OT fusion case developed a pressure sore at the occipital lesion site. **Discussion** A number of the RA cervical lesion surgeries, especially OT, decreased after biologics were approved. As RA treatment advances, lower cervical lesions that follow upper cervical lesions are anticipated to show significantly improved outcomes with the shortest fixation possible.

S8-3

Relationship between Large joints and cervical spine instability in rheumatoid arthritis

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Conflict of interest: None

Background. Improved rheumatic drugs have provided significant benefits, but activites of daily living are not improved if spinal symptoms are overlooked. Furthermore, the appropriate timing for examination of the cervical spine in follow up is unclear. **Methods.** To evaluate the relationships of cervical spine instabilities and an index for cervical spine lesion in rheumatoid arthritis (RA) based on extremity radiographs, we examined preoperative radiographs in 116 RA patients who underwent total knee and hip arthroplasty. In extremity radiographic results for 8 large joints (bilateral shoulders, elbows, hips and knee joints), a Larsen Grade ≥ 2 for each joint was scored as 1 point, which we refer to as the "large joint index" (LJI: 0-8 points). The associations of radiographic cervical lesions with LJI, Ranawat class, the disease period, RA drugs or blood analysis data were evaluated. **Results.** Atlantoaxial subluxation (AAS: ≥ 5 mm) was found in 49 patients, vertical subluxation (VS: ≤ 13 mm) in 51, a posterior atlantodental interval (PADI: < 14 mm) in 21 and subaxial subluxation (SAS: ≥ 3 mm) in 25. Most patients with a PADI < 14 mm (19/21: 90%) were complicated with both AAS and VS. LJI had a significant association with AAS ($p<0.0001$) and VS ($p<0.01$). The PADI was significantly lower ($p<0.0001$) and the LJI was significantly higher ($p<0.01$) in patients of Ranawat Class II compared to the patients of Ranawat Class I. The disease period, age at surgery and onset age were also significantly associated with cervical instabilities. **Conclusions.** PADI should be recognized as a predictor of paralysis with both anteroposterior and vertical and middle-low cervical spine instability. The LJI proposed in this study has possibility of a predictor of cervical lesions. Patients with RA onset at a young age and a long disease period also have a risk of progression of cervical spine instability.

S8-4

Significance of atlantoaxial fixation in rheumatoid patients

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Conflict of interest: None

Rheumatoid spondylitis, such as atlanto-axial subluxation, vertical subluxation, and subaxial subluxation, seems to be decreased since the introduction of biological anti-rheumatoid drugs. However, surgery of the rheumatoid cervical spine is still necessary because of some reasons, for example, existing the non-responders for the biological drugs, rheumatoid spondylitis is never end-stage of rheumatoid arthritis, but it occurs in relatively early period, etc. For severe subaxial subluxation and vertical subluxation, occipitocervical or occipito-cervico/thoracic reconstruction is required. These cases usually contains severe myelopathy and the patients have intractable pain. On the other hand, patients with atlantoaxial subluxation usually have no myelopathy because of their wide space available for the cord. Compared to the patients with severe subaxial lesion, clinical symptoms in those patients is relatively mild but they sometimes complain numbness and sensory disorders in occiput or posterior part of auricle. JOA score does not reflect these symptoms. Many rheumatologists sometimes recommend conservative therapy such as wearing collar orthosis, however, if surgical intervention brings better quality of life and activity of daily living in such patients, it is better to turn our attention to surgery even in mild symptom patients. Since 2004 we have introduced the technique of atlantal lateral mass screws for atlanto axial fusion. Surgical results of such atlanto axial fusion are satisfactory

especially in pain relief. Few patients aggravated subaxial subluxation and there was no development of vertical subluxation. Atlanto-axial fixation contributes for better quality of life and activity of daily living in rheumatoid patients with mild symptoms.

S8-5

Sleep-disordered breathing in patients with rheumatoid arthritis and upper cervical lesions

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Conflict of interest: None

Sleep-disordered breathing (SDB) is a rarely documented, but possibly lethal complication in patients with rheumatoid arthritis (RA). However, there is no large study which systematically studied the association between SDB and upper cervical involvement resulting from RA. In the present study, we analyzed 70 consecutive RA patients who underwent orthopaedic surgeries from September 2006 to March 2009 and evaluated morphological parameters measured on cervical radiographs that contribute to the development of SDB in RA patients with upper cervical lesions. Patients who had apnea-hypopnea index (AHI) values greater than 5 were diagnosed as SDB. Abnormal respiratory events were analyzed to determine the type of SDB: obstructive sleep apnea (OSA) caused by the upper airway narrowing, or central sleep apnea (CSA) resulting from the impairment of the respiratory center located in the brain stem. Our study findings demonstrate a high incidence (88.6%) of OSA in RA patients who underwent orthopaedic surgeries, and that flexion at craniovertebral junction (CVJ) contributes to the development of OSA in patients with RA and upper cervical lesions. We suggest that rheumatoid involvement of the upper cervical spine results in the increase of upper cervical flexure or kyphosis in CVJ, which might lead to the narrowing of the upper airway and cause OSA. Therefore, posterior occipitocervical fusion with correction of kyphosis may have a potential to improve OSA in patients with upper cervical spine involvement secondary to RA.

S8-6

Thoracic and lumbar spinal lesions in patients with rheumatoid arthritis

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Conflict of interest: None

Involvement of the cervical spine in rheumatoid arthritis (RA) has been well studied. We analyzed the radiological findings of the lumbar spine and the clinical symptoms in RA patients. One hundred-six RA patients were included. All of the patients were asked to fill out a questionnaire about the existence of low back pain, leg pain and leg numbness. Radiological features of the lumbar spine, including scoliosis, spondylolisthesis, disc space narrowing, endplate erosion, osteophytes and osteoporosis, were checked. The presence mutilating disease was assessed. Of 106 patients, 42 (40%) had symptoms of low back pain. Abnormal radiological findings in the lumbar spine were detected in 57%. The prevalence of clinical symptoms tended to be higher in patients with end-plate erosion. Among the 106 patients, 43 (42%) had both lumbar and cervical lesions. The prevalence of lumbar lesion was not high in the mutilating type of RA, except for facet erosion and severe osteoporosis. The patients with pulse steroid therapy revealed a higher prevalence of vertebral fracture. From these results, we concluded that lumbar lesions were frequently observed in RA patients. 【Pathology of vertebral lesions in RA】 Spinal lesions in RA are caused by synovitis in the apophyseal joints, inflammation of the disco-vertebral junction and granulomatous nodule formation in the marrow space of the vertebral bodies. Dural sac or nerve root compression occurs due to an epidural nodule. These pathological changes result in neurological disturbances. 【Surgery for the treatment of vertebral lesions in RA】 Most of the symptoms due to the vertebral lesions in the lumbar spine are low back pain and/or radicular pain. Spinal fusion and decompression of the spinal canal are considered for the surgical treatment. However, vertebral collapse and/or loosening of the spinal instrument are frequently seen. Therefore, it is important to determine specific surgical strategy for the treatment of patients with RA.

S9-1

Regulation of Osteoclastogenesis

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Conflict of interest: None

Osteoclasts are unique bone resorbing cells, and have a pivotal role in decreased bone mass and joint destruction in an inflammatory condition. Osteoclasts are derived from monocyte/macrophage lineage cells, and the most characteristic feature of osteoclasts is multi-nucleation promoted by a cell-cell fusion of mono-nuclear osteoclasts. Previously, we identified DC-STAMP, as an essential molecule for osteoclast cell-cell fusion, and recently, we further identified OC-STAMP, as another essential molecule for osteoclast cell-cell fusion. We found that multi-nucleation by cell-cell fusion increases efficiency of osteoclast bone resorption. Osteoclast differentiation was characterized by NFATc1 activation by various signals under RANKL stimulation. We found that reduction of Bcl6, a transcriptional repressor, is required for osteoclastogenesis by RANKL. Blimp1, another transcriptional repressor, is induced by RANKL, and is required for Bcl6 suppression. Bcl6 inhibits "osteoclastic genes", such as *DC-STAMP*, *Cathepsin K* and *NFATC1*, and that Blimp1-Bcl6-osteoclastic gene axis is required for osteoclastogenesis. In case of inflammation, we found that STAT3 is activated by pro-inflammatory cytokines such as TNF, IL-1 and IL-6, all of which are therapeutic targets of rheumatoid arthritis either indirectly or directly. STAT3 activation further promotes expression of IL-6 family cytokines and RANKL, and causes chronic inflammation and joint destruction. I will discuss about these findings.

S9-2

Bone diseases related to osteoblasts or osteocytes

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Conflict of interest: None

There are many diseases associated with the defect of osteoblasts or osteocytes function. First of all, the wnt signalling is recognized as a key regulator of bone mass because human diseases, osteoporosis-pseudoglioma syndrome and van Buchem disease, are caused by the abnormality of the wnt signaling. The *SOST* gene is expressed specifically in osteocytes and encodes sclerostine, which functions as a wnt signaling inhibitor. Parathyroid hormone

exerts its anabolic effect on bone mediated by decrease in SOST expression in osteocytes. Osteocytes play a central role in mineral metabolism as well. Osteocytes secrete FGF23 and reduce serum phosphate levels. Recently, it is reported that FAM20C is expressed in osteocytes and phosphorylates sibling proteins such as MEPE and DMP1, resulting in inhibition of mineralization in bone. Interestingly, fam20c-null mice show hypophosphatemic rickets. In human, its defect causes Raine syndrome, which is characterized by sclerotic bone phenotype. Hypophosphatsia is caused by deficient activity of the tissue-nonspecific ALP. Hypomineralization of skeleton is observed in most patients with hypophosphatasia. However, hypophosphatasia is highly variable in its clinical expression. Based on the age of manifestation and its severity, hypophosphatasia is divided into 6 subtypes. Recently, non-lethal benign form of perinatal hypophosphatasia has been recognized, which is associated with no apparent defects of mineralization. Osteogenesis imperfecta (OI) is characterized by bone fragility and decreased bone density. 85% patients with OI have abnormality in type I collagen. Sillence initially classified this disorder into four types; however, its number is increasing. New genes involved in OI include *LEPRE1, PPIB, FKBP10, SERPINH1, Sp7, PLOD2, SERPINF1* and *BMP1*. Recently, *IFITM5* encoding interferon-induced transmembrane protein 5 has been identified as a responsible gene for OI type V, which is characterized by hyperplastic callus formation.

S9-3

The Regulation of bone remodeling

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Conflict of interest: None

After maturation, bone quality as well as quantity is maintained through remodeling activities. Bone remodeling is under stringent control until middle age; however, its deregulation thereafter underlies the pathogenesis of osteoporosis and fragility fractures. Each remodeling cycle starts with the recruitment of bone-resorbing osteoclasts and ends with the filling of the resorption lacunae by osteoblasts with newly synthesized bone. The major regulatory features in the process include the mechanism by which the recruitment of osteoclasts is targeted to a new remodeling site, the conversion of the catabolic into the anabolic phase with the attraction of new osteoblasts, and how the amount of new bone added is balanced with the amount of bone removed. These are all important and unsolved questions at present. Above all, the mechanism underlying the coupling of bone formation to the previous resorption activity has long attracted interest, and recent years have witnessed the identification of factors that act in the coupling process, with novel mechanistic insights emerging. Despite these efforts, coupling activity-based drug development has not been realized yet, and a new strategy that enables maintenance of the remodeling activity and effective prevention of fracture in the post-reproductive, involutional period is eagerly awaited.

S9-4

Regulation of bone remodeling by hormones and vitamins

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Conflict of interest: None

Hormones play important roles for bone remodeling as evident from the fact that menopause and hyperparathyroidism are leading causes for osteoporosis. In addition to these "classical" bone remodeling hormones, appetite-regulating hormones, such as leptin and neuropeptide Y, and neuroactive hormones, such as catecholamine and serotonin, have been shown to be intimately involved in bone remodeling by many groups. Deficiency or excess of fat-soluble vitamins, such as vitamin D, develop abnormal calcium and bone metabolism. Indeed, vitamin D and vitamin K are common osteoporosis medications in Japan. However, role of vitamin E on bone remodeling is not known. Though the analysis of a-TTP knockout mice, a mouse model of vitamin E deficiency, we demonstrated that a-tocopherol stimulates osteoclast fusion, independent of its anti-oxidant action. Moreover, mice and rats fed a a-tocopherol-supplemented diet develop osteoporosis. Thus, vitamin E is a novel determinant of bone mass. In this symposium, I will summarize current understandings of the comtrol of bone remodeling by hormones and vitamins.

S9-5

Regulation of bone quality by drugs for osteoporosis

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Conflict of interest: Yes

According to the present definition of osteoporosis, bone mineral density, architecture, and tissue material properties are important factors in determining bone strength. Bone matrix consists of a two-phase composite material in which the mineral phase provides stiffness and collagen provide tensile strength and ductility. These are regulated by cellular activities, tissue turnover rate, and the levels of oxidative stress and glycation. In this symposium, we show how we know and improve bone quality.

S9-6

Elucidation of mechanisms for inflammatory bone destruction and advances in therapeutic strategies for RA

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Conflict of interest: None

Bone is essential not only for the locomotive activity and mineral metabolism but also for the maintenance and regulation of lymphocytes and hematopoietic stem cells. The immune and skeletal systems are closely related through a number of shared regulatory molecules including cytokines and signaling molecules. Studies on bone destruction associated with rheumatoid arthritis (RA) have highlighted the importance of the interplay between the two systems, and promoted the new interdisciplinary field of "osteoimmunology". In turn, osteoimmunology research has contributed not only to our understanding of the pathogenesis of RA but also to the development of therapeutic strategies for bone and joint disorders. RA is an autoimmune disease characterized by synovial inflammation and bone destruction as a result of autoantigen presentation and helper T cell activation. Th17 cells, a unique helper T cell subset, produce IL-17 which activates synovial macrophages to produce inflammatory cytokines such as TNF-a, IL-6 and IL-1. RANKL on synovial fibroblasts induced by inflammatory cytokines plays a prominent role in excessive osteoclast differentiation and bone destruction in RA. Accumulating evidence has indicated that not only TNF-a and IL-6, but also CD80/86 on dendritic cells, CD19/CD20/BAFF on B cells, IL-17/IL-23 on Th17 cells, RANKL and CathepsinK are now recognized as potential therapeutic targets for RA. Recent research has elucidated the molecular mechanisms by which bone cells, such as osteoclasts, osteoblasts and osteocytes, communicate each other to maintain bone homeo-

stasis. The osteoimmunological insight is of growing importance in clinical applications in terms of prevention of bone destruction and promotion of bone formation. I will introduce recent advances in osteoimmunology which represents the viewpoints indispensable for our understanding of the mechanism of inflammatory bone destruction as well as for the development of therapeutic strategies for RA

S10-1

The application of the new EULAR/ACR Remission criteria in the DREAM Registry

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Objectives. The provisional ACR/European League Against Rheumatism (EULAR) definition of remission in RA requires a score of ≤1 on the patient global assessment (PGA, 0-10 scale). We explored the relation between the PGA criterion and the patient's clinical disease state in an observational dataset. Methods. Data of 512 newly diagnosed RA patients of the Dutch Rheumatoid Arthritis Monitoring (DREAM) remission induction cohort were analysed. Both 28-joint counts and more comprehensive joint counts (tender joint count-53, swollen joint count-44) were used. Results. ACR/EULAR remission was present in 20.1% of the patients when using 28-joint counts and in 17.4% of the patients when applying more comprehensive joint counts. In 108 patients, the PGA score was >1 despite fulfilment of the remaining criteria (TJC28, SJC28 and CRP in mg/dl 41). Residual disease activity was observed in 31.5% (34/108) and median (interquartile range) scores on PGA, pain and fatigue were 2.4 (1.8-4.0), 2.0 (1.1-3.0) and 2.7 (1.3-5.0), respectively. Applying more comprehensive joint counts showed comparable results. In 19.5% (100/512) of patients, disease activity was absent (TJC53 = 0, SJC44 = 0, and CRP ≤1). In 41% (n = 41) of these patients, the PGA score was >1. Receiver operating characteristic analysis showed moderate accuracy of the PGA to discriminate between fulfilment and no fulfilment of all remaining criteria. Conclusion. Frequently, patients did not meet the PGA criterion despite a good clinical disease state. Apparently the PGA is not solely influenced by RA disease activity. In patients with marked divergence between the PGA and objective clinical measurements, caution should be taken when applying the provisional ACR/EULAR definition of remission. Key words: rheumatoid arthritis, remission, disease activity, patient global assessment, patient-reported outcomes

S10-2

IORRA cohort and ACR/EULAR new remission criteria for rheumatoid arthritis

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Conflict of interest: None

The progress of agents for treatment of rheumatoid arthritis (RA) has brought the stringent treatment strategy and need for strict disease control. The new remission criteria was proposed by EULAR/ACR in 2010 and this criteria must be validated for its reliability by prevention of physical dysfunction as a long term outcome. We reported the usefulness of the new remission criteria by evaluating prevention of physical dysfunction in patients with RA in IORRA cohort last year. The physical dysfunction was aggravated within 2.5 years among patients who fulfilled remission criteria less frequently irrespective of criteria, such as DAS28, CDAI, SDAI, Boolean practice or Boolean trial. Least aggravation was detected when patients fulfilled Boolean practice or Boolean trial all the time during the observational period. Thus, we concluded that the new remission criteria is acceptable as target marker of disease activity. At the same time, it was revealed there are many patients who had both swollen and tender joint count ≤1, CRP (mg/dl) ≤1, but patient general evaluation [Pt VAS (cm)] close 1 but over. Then, whether the range Pt VAS ≤1 is essential or not need to be evaluated. The patients who have TJC≤1, SJC≤1 and CRP≤1 but 1<Pt VAS ≤2 was set as in "close remission" and compared those to the patients in "true remission". A total of 1,272 patients who were in remission and 538 patients in "close remission" were analyzed by using April 2011 IORRA database. The risk for close remission was pain VAS [odds ratio (OR) 1.29, 95% CI 1.23-1.29], swollen joints not detected by 28-joint count system but detected by 45-joint count system (OR 1.44, 95%CI 1.03-2.02), and physical dysfunction (Japanese version of HAQ) (OR 1.89, 95%CI 1.40-2.55). Finally, the new remission criteria including Pt VAS≤1 was revealed to be an acceptable criteria for evaluating remission in IORRA cohort.

S10-3

Evaluation of the remission of RA by MRI

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Conflict of interest: Yes

Remission of RA can be evaluated by clinical status, functional status, structural status and imaging status. Although clinical remission is a most basic measure, there is subset of the patients who shows further radiographic progression even achieved clinical remission, indicating an importance of qualification of imaging remission. Imaging remission can be evaluated by MRI or US since the inflammatory changes of rheumatoid joint are assessed by these modalities. The definition of clinical remission such as DAS, SDAI, CDAI, that of functional remission such as HAQ and that of structural remission such asΔmTSS are proposed. MRI-revealed rheumatoid joint injury is generally evaluated through RA MRI Scoring (RAMRIS) system. These scores are consisted from synovitis score, osteitis score, bone erosion score and tenosynovitis score. Gd-enhanced MRI is recommended to assess synovitis and tenosynovitis whereas plain MRI is enough for osteitis and bone erosion. We have found that osteitis is most specific MRI feature for RA, and in addition, our small clinical study indicates that the decrement of RAMRIS osteitis score by plain MRI is also significant during tight DMARDs treatment. These data suggest the usefulness of RAMRIS osteitis score to estimate MRI remission criteria, however, there remains to be a clear MRI remission criteria toward patients with RA. In this regard, the reduction of RAMRIS osteitis score (plain MRI is enough) less than 33 % as compared with baseline appears to be indicative for the protection toward further radiographic progression, which is guided by our small clinical study. We have tentatively considered "the reduction of RAMRIS osteitis score less than 33 % as compared with baseline" as "MRI remission criteria" and tried to apply toward our Nagasaki University Early Arthritis Cohort, indicating that the rate of patients of no radiographic progression and SDAI remission are high in RA patients achieving "MRI remission criteria". We are going to

discuss the evaluation of the remission of RA by MRI in this session.

S10-4

Supplementary use of ultrasound to improve the accuracy of remission criteria with clinical measures

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Conflict of interest: Yes

A proportion of the patients in clinical remission experiences progression of joint damage, showing the limited positive predictive value of the clinical remission to predict the halt of structural progression. Although the positive predictive value of the newly published ACR/EULAR provisional remission criteria is improved, the negative predictive value is low due to their strict threshold, raising concern about overtreatment. These data indicate the limited accuracy of clinical evaluation in predicting structural remission. Assessment of synovial Doppler signals predicts joint damage more accurately than clinical examination at an individual joint level. However, it is infeasible to scan all the joints in all the patients and the efficient selection of patients and joints to be scanned is necessary. The benefit of performing ultrasound is small in patients with clinically either very high or completely absent disease activity, or in joints with either marked swelling or no signs of synovitis ever. Thus the patients/joints where the presence of residual inflammation is equivocal can be the good candidates for performing ultrasound with large benefit. In order to determine the necessity for ultrasound-based accurate remission, the patient's risk for structural progression should be taken into consideration. In addition to the risk factors stated in the recent guidelines, involvement of weight bearing joints and also the class of medication, especially the use of corticosteroid and TNF antagonists need to be considered. Detecting sub-clinical synovitis with ultrasound in a patient in clinical remission can be beneficial when the patient possesses multiple risk factors, has symptomatic weight bearing joints, and is receiving corticosteroid, while it is not necessary for a patient with residual low disease activity when the patient has no risk factors, exhibits signs and symptoms of only small joints, and is receiving therapy with methotrexate plus a TNF antagonist.

S10-5

Treating rheumatoid arthritis to target and ACR/EULAR new remission criteria for RA

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Conflict of interest: Yes

Treating rheumatoid arthritis to target (T2T) consists of 4 overarching principles and 10 recommendations and was published in 2010. T2T has rapidly spread throughout the world as a standard therapeutic strategy for RA. The 6th recommendation of T2T states that the use of validated composite measures of disease activity, which include joint assessments, is needed in routine clinical practice to guide treatment decisions. Choice of composite measures, however, was left in hands of individual rheumatologist. American College of Rheumatology and European League Against Rheumatism collaboratively launched a committee and published the provisional definition of remission in rheumatoid arthritis for clinical trials (ARD/Arthritis Rheum 2011). Several investigators validated the new remission criteria using cohorts of RA patients and many recent clinical trials employ remission rate by the new remission criteria as a primary endpoint. We have demonstrated that rate of maintaining clinical remission is not high enough in clinical practice settings. Clinical remission rate of the patients enrolled in the REAL database was 32.1% (n=1034) and the percentage of patients who maintained clinical remission 6 months later were around 50%. The committee for developing clinico-epidemiological database of RA patients was convened in 2011 in the study group of Ministry, Health, Labour and Welfare entitled 'multi-layered investigation to standardize treatment of rheumatoid arthritis in Japan'. The committee is now implementing a clinico-epidemiological study to evaluate T2T strategy in RA patients with moderate to high disease activity. In this symposium, we would like to provide these data and discuss significance of the new remission criteria in T2T strategy.

S11-1

Systemic autoimmunity and regulatory T cells

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Conflict of interest: Yes

We have recently identified a novel CD4+CD25-Foxp3- regulatory T cells (Treg) population that characteristically expresses both lymphocyte activation gene-3 (LAG3) and early growth response gene-2 (Egr2). IL-10 producing CD4+CD25-LAG3+ Treg exhibit suppressive activity in murine colitis. Furthermore, T cell-specific Egr2-deficient mice were reported to develop lupus-like autoimmune disease. Here, we examined whether CD4+CD25-LAG3+ Treg play a role in the regulation of antibody production and systemic autoimmunity. Adoptive transfer of CD4+CD25-LAG3+ Treg from MRL/+ mice significantly suppressed progression of nephritis and anti-dsDNA antibody production in lupus-prone MRL/lpr mice. Analysis of gene-targeted mice revealed that Fas, PD-L1 and Egr2 were required for the antibody suppression with CD4+CD25-LAG3+ Treg. Interestingly, although Fas-Ig or PD-L1 monostimulation did not suppress B cell prolifetation and antibody production, dual stimulation with Fas-Ig and PD-L1 suppressed B cell functions. We have also identified human CD4+CD25-LAG3+ T cells that express IL-10, Egr2, and PD-L1 in peripheral blood and tonsil. The frequency of human CD4+CD25-LAG3+ T cells showed a significant decrease in SLE and RA patients. Human CD4+CD25-LAG3+ T cells also suppressed antibody production in vitro and GVHD response in vivo. We are now addressing the molecular mechanisms of CD4+CD25-LAG3+ T cells-mediated B cell suppression and the effect of Fas-Ig and PD-L1-Ig dualstimulation in human B cells. These results indicated that CD4+CD25-LAG3+ Treg have the capacity to control humoral immunity and systemic autoimmune disease. By exploiting the capacity of CD4+CD25-LAG3+ Treg, they can be useful for the treatment of autoimmune diseases.

S11-2

T cell blockade therapy of polymyositis/dermatomyositis

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Conflict of interest: Yes

Immunohistological studies of the muscles affected by poly-

myositis (PM)/ dermatomyositis (DM) suggested that the muscle damage at least in PM is driven by cytotoxic CD8 T cells. We found that PM patients had expansion of CD8 T cell clones in the peripheral blood and that some of them shared the antigen receptor clonotypes with those infiltrated in the affected muscles. These results supported the notion that PM is mediated by cytotoxic CD8 T cells. In the clinical settings, the most potent therapeutic tool to block T cell activation in autoimmune diseases is CTLA4Ig, abatacept. However, it has been assumed that CTLA4Ig controls immune reactions of CD4 T cells but not those of CD8 T cells. We thus studied whether or not CTLA4Ig can suppress a murine model of PM, C protein-induced myositis (CIM), which is driven primarily by CD8 T cells. We found that histological changes in CIM were suppressed by CTLA4Ig administration both in preventive and therapeutic protocols. The same effect was observed when CIM mice were treated with a combination of anti-CD80 and anti-CD86 monoclonal blocking antibodies. These results argued that the therapeutic effects were attributable to blockade of CD28-CD80/86 interaction. In order to study if CTLA4Ig can suppress CD8 T cells independent of CD4 T cell suppression, CD4 T cell-independent experimental myositis was employed. This model, called pCIM, was induced by injection of dendritic cells loaded by C protein-derived CD8 T cell epitope peptides together with local injection of complete Freund adjuvant. CTLA4Ig was also effective in treating pCIM, demonstrating that CTLA4Ig can control CD8 T cell function directly. A few case reports on successful treatment of PM/ DM with abatacept and the results of the present preclinical studies suggested us that CTLA4Ig should be a new therapeutic tool in treating PM/DM.

S11-3

Aberrant expressions of Ras Guanyl Nucleotide-Releasing Proteins (RasGRPs) in Autoimmune diseases

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Conflict of interest: None

RasGRPs are intracellular signaling molecules that activate Ras. RasGRP family includes RasGRP1-4. RasGRP1 is mainly expressed in T cells and plays an important role in their development. RasGRP4 was found in mast cells and leukemia cells. Recently we found RasGRP4 expression in monocytes. Aberrant expression of RasGRP1 in lupus T cells: Low expression of CD3ζ-chain is a prominent feature in lupus T cells. Recently, SF2 was found to control splicing of CD3ζ-chain. We previously reported aberrant splicing of RasGRP1 transcripts and low levels of RasGRP1 protein in SLE. In lupus T cells, low levels of DNMT1 have been known in relation with hypomethylation of autoimmune-related genes. We aimed to find factors related to abnormalities in RasGRP1-MAPK-DNMT1 pathway. The expression levels of SF2 were significantly lower in T cells from SLE patients as compared with healthy subjects. The expression levels of SF2 were strongly correlated with full-length RasGRP1 and DNMT1. Lower levels of SF2 may play an important role in abnormal splicing in RasGRP1 as in the case of CD3ζ-chain in SLE patients. RasGRP4 expression in RA: Based on the important roles of mast cells and monocytes in RA, we aimed to clarify the role of RasGRP4 in patients with RA. First, we evaluated the expression of RasGRP4 transcripts/ proteins in the PBMCs/monocytes from RA patients. The frequency of individuals with exceeded RasGRP4 expression was higher in RA patients than in healthy controls. Splice variants were more frequent in RA patients. RasGRP4 protein expressions in monocytes were lower in the patient group. We also evaluated RasGRP4 expressions in synovial tissues from RA/OA patients. RasGRP4 was expressed in synovium and the expression levels were not different between RA and OA. RasGRP4 transcript levels were in correlation with synovial cell proliferation *in vitro*. Altered expression of RasGRP4 may affect the functions of monocytes and may also affect synovitis in RA patients.

S11-4

Role of helper T cells in the pathogenesis of rheumatoid arthritis

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Conflict of interest: None

Introduction. Dichotomy of helper T cells, Th1 and Th2, was reported by in 1986. Many diseases have been divided into the 2 types. Rheumatoid arthritis (RA) was characterized as a Th1 disease; however, it was difficult to detect IFNγ in the serum, synovial fluid (SF) or synovial tissue (ST). Thus, it was 'enigma' in the pathogenesis. 1. Th17. We have reported that a sufficient amount of IL-17 is detected in SF from patients with RA and that IL-17 induces osteoclastogenesis (1999). Many papers on the role of IL-17 in the pathogenesis have been published since 1999. In 2005, a novel helper T cells, Th17, was discovered. 2. The role of T cells in the destruction of bone and joints in RA. We have investigated the role of osteoclasts (Oc) in the bone and joint destruction in RA since 1990. Our findings are as follows: 1) IL-6 and sIL-6R in SF from RA patients are responsible for Oc formation. Authentic Oc are present in ST of RA patients (1996). 2) The role of IL-17 as described above (1999). 3) Human T cells induce osteoclastogenesis from human monocytes through their RANKL expression (2001). 4) CD4+ T cells in ST from RA patients express RANKL. The ratio of RANKL to OPG in SF is elevated (2001). 5) Human Th1 cells induce human osteoclastogenesis from monocytes via the production of RANKL. T cells expressing both IFNγ and RANKL are elevated in the peripheral blood of RA patients (2005). 6) A novel peptide from (TCTA protein inhibits human osteoclastogenesis and the function of mature Oc (2009). 7) IL-17 alone induces human osteoclastogenesis without osteoblasts (Yago et al. 2009). 3. IL-23. We have reported that IL-23 plays an important role in the osteoclastogenesis (Yago et al. 2007). 4. Plasticity in the differentiation of helper T cells. It has bee recently reported that plasticity plays an important role in the differentiation of helper T cells. Conclusions. Novel findings discovered in the human immunology will be developed into an effective therapy in the near future.

S11-5

FoxP3+ regulatory T cells in autoimmune diseases

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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 cell population with distinct surface phenotypes, cytokine production profiles, and mechanisms of immune suppression. Regulatory T cells characterized by CD4, CD25, and transcription factor forkhead box P3 (FoxP3) are a subpopulation of $CD4^+$ T cells specialized for immune suppression. Thus, impairment of Treg-mediated immune regulation is thought to play a role in development of various autoimmune diseases. In addition, reduced proportion of Tregs and defect in Treg function have been reported in patients with various organ-specific autoimmune diseases, including type 1 diabetes, multiple sclerosis, and immune thrombocytooenia (ITP). We have recently reported a critical role of FoxP3+ Tregs in preventing the anti-platelet autoimmune response in mice deficient in functional FoxP3+ Tregs. In contrast, results of Treg proportion and function in patients with

systemic lupus erythematosus (SLE) are inconsistent among studies. In our recent analysis in SLE patients, proportion of FoxP3+CD4+ T cells in circulation was increased in patients with active disease and was correlated positively with disease activity index and anti-double-stranded DNA antibody titer, and negatively with serum complement activity. These conflicting results are primarily explained by heterogeneity and plasticity of human FoxP3+ Tregs. Specifically, human FoxP3+ Tregs can be divided into naturally occurring Tregs, adaptive Tregs that acquire regulatory properties in periphery, and effector T cells that lack regulatory function but have pathogenic Th1/Th17 activity. In summary, FoxP3+ Tregs are apparently involved in pathogenesis of various autoimmune diseases, but further studies are necessary to elucidate how this cell subset is compromised in individual diseases.

S12-1

Inflammaosome-independent pathway plays role in the acute IL-1 beta-dependent inflammation to sterile particle

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Conflict of interest: None

The sterile inflammatory response to cell death and irritant crystals is medically important because it causes disease. Monosodium urate crystal or calcium pyrophosphate crystal in the joint cause gout and pseudogout, respectively. Although these stimuli are structurally distinct, they cause inflammation through a common pathway that requires the cytokine IL-1. *In vitro,* the inflammasome, and in particular its generation of active caspase-1, is absolutely required to produce bioactive IL-1β. However, here we report that caspase-1 is not required *in vivo* for much of the IL-1β-dependent sterile inflammatory response. Furthermore, we find that cathepsin C, which controls the activity of a number of leukocyte serine proteases capable of processing IL-1β, plays a major role in this caspase-1-independent pathway. Mice that are deficient in cathepsin C have reduced inflammatory responses to dying cells and silica crystals. In the absence of cathepsin C, caspase-1 becomes rate-limiting such that mice doubly-deficient in both of these proteases make little IL-1β *in vivo* and have markedly attenuated inflammatory responses to the sterile stimuli. In contrast, these mutant mice generate normal inflammation in response to exogenous IL-1β, indicating that cathepsin C and caspase-1 function upstream of IL-1β, and in their absence, all components of the pathway downstream of mature IL-1β are intact.

S12-2

The Role of TLR in Systemic Lupus Erythematosus

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Conflict of interest: None

In systemic lupus erythematosus (SLE), autoantibody to self-DNA or -RNA contributes to the pathogenic and clinical course. Toll-like receptors (TLRs) have a crucial role in the early detection of pathogen associated molecular patterns and the subsequent activation of the adaptive immune response. There are many studies concerning TLR7 and TLR8 [activated by single-stranded (ss) RNA], and TLR9 (activated by unmethylated CpG motifs within ssDNA) in autoimmune animal models. One of the SLE model, BXSB mice develops an autoimmune syndrome with *Yaa* (Y-linked autoimmune acceleration) mutation present on BXSB Y chromosome. The *Yaa* mutation was shown to be a consequence of a translocation from the telomeric end of the X chromosome onto the Y chromosome. FcγRIIB is a negative regulator of BCR-mediated activation signals. The FcγRIIB-deficient C57BL/6 (B6) congenic mouse strain (B6.FcγRIIB-/-) spontaneously developed RA (Sato-Hayashizaki et al. Arthritis Rheum 2011). We found that in the B6.FcγRIIB-/- strain introduced with *Yaa* mutation (B6.FcγRIIB-/-*Yaa*), the incidence and severity of RA were markedly reduced, but instead severe SLE developed early in life with 50% positive proteinuria at 6 months of age. Irrespective of this phenotype conversion, B6.FcγRIIB-/-*Yaa* showed the marked increase in serum levels of both lupus-related and RA-related autoantibodies, as compared with findings in B6.FcγRIIB-/- and B6.*Yaa* mice. In addition, IL-21 and IL-10 expression levels were significantly increased in the spleen of B6.FcγRIIB-/-*Yaa* mice compared with B6.FcγRIIB-/- mice. Our data show that the strong epistatic interaction of FcγRIIB-deficiency and *Yaa* mutation in B6 background. The effect of TLR may lead to the disease phenotype shift from RA to SLE in the B6.FcγRIIB-/-*Yaa* mice carrying genetic predisposition to both RA and SLE.

S12-3

The role of innate immunity for the initiation of rheumatoid arthritis

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Conflict of interest: Yes

It is not fully understood how innate immunity contributes to the initiation of rheumatoid arthritis (RA). SKG mouse is a murine model for RA that spontaneously develops autoimmune arthritis as a result of a point mutation in ZAP70, a main T cell receptor transduction molecule. SKG arthritis is dependent upon IL-17 secreting helper CD4 T (Th17) cells. Interestingly, although they spontaneously develop arthritis in conventional environment, they fail to develop it in specific pathogen free (SPF) condition. However, we have found that the arthritis can be induced even in SPF condition by administration of b-glucan or mannan, cell extracts of bacteria or fungus. b-glucan or mannan not only activates Toll like receptors (TLRs) or Dectin-1, but also activates serum complement system. Complement activation product, C5a, enhanced the differentiation of Th17 cells in synergy with TLR or GM-CSF signaling and triggered arthritis. These results suggest that innate immune activation precipitated arthritis in genetically susceptible SKG mice. Recent reports suggest the positive correlation between RA and periodontitis. Because periodontal bacteria, *Porphyromonas gingivalis (P.G.)*, is the only known bacteria that secretes citrullnating enzyme, it can contribute to RA by inducing anti-citrullinated protein antibody (ACPA). On the other hand, *P.G.* is known to activate TLR or complement and preferentially drive Th17 cell differentiation. Although the role of Th17 cell in RA is still controversial, it is possible that *P.G.* contributes to the initiation of RA also by activating innate immunity and inducing Th17 cells. In this symposium, I would like to discuss about the innate immunity and RA by showing our recent clinical research result on the relationship between periodontitis and early RA in the KURAMA (Kyoto University Rheumatoid Arthritis Management Alliance) cohort.

S12-4

Establishment of Nod1 ligands-induced coronary arteritis model

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Conflict of interest: None

Kawasaki disease (KD) is an acute febrile illness of childhood with systemic vasculitis characterized by the occurrence of coronary arteritis. The etiology has been unknown since 1967, when KD was first reported. There are reports indicating the pathophysiology of KD might be excessive immune response to some infectious agents. KD is characterized by hypercytokinemia, but it is not clear which cells or tissues produce cytokines. First, we analyzed the gene expression of peripheral blood mononuclear cells of KD patients at acute phase and found that the genes related to innate immunity showed high expression. Furthermore, when human coronary arterial endothelial cells were incubated with various innate immune stimulators, the cytokines in supernatants were elevated by Nod1 ligands etc. Based on these results, we administered Nod1 ligands to mice subcutaneously and found that Nod1 ligands induced KD-like coronary arteritis in mice. In addition, the KD-like coronary arteritis was also induced by oral administration of Nod1 ligands. The frequency and severity of Nod1 ligands-induced coronary arteritis were enhanced by microbial components including lipopolysaccaride. To assess the mechanism of site-specific vascular inflammation, we analyzed Nod1 expression by immunohistochemistry and quantitative PCR, but Nod1 expression was ubiquitous. The cytokine levels were highest in supernatants from aortic root among various murine tissues stimulated with Nod1 ligands. Thus, site-specific vascular inflammation was ascribed to intrinsic nature of vascular cells. In this session, we would discuss the mechanism of KD, based on the data obtained from this Nod1 ligands-induced coronary arteritis model.

S12-5

Influence on the immune response by lipid associated molecules

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Conflict of interest: None

TLR is not only indispensable sensor as an infection protective mechanism, but it is a regulator for disease development of symptoms. RP105 is a molecule which makes the mature B cell avoid from the radiation or steroid induced apoptosis, and induces a strong proliferative reaction. RP105 is also one of the important TLR molecules from follower reason.1) RP105 resembles TLR4 structurally. 2) As TLR4 associates with secretion protein called MD-2, RP105 associates with MD-1. 3) RP105/MD-1 reinforces the B cell activation and the antibody production through TLR4/MD-2. Recently the structural analysis of MD molecules is reported that MD-2 binds to LPS (Lipopolysaccharide), and MD-1 binds to Phosphatidyl choline (PC) or Phosphatidyl ethanolamine (PE). We recognized that MD-1 also binds to the negative-charged phospholipids by using purified MD-1 or immuno-precipitation technique. In order to examine a meaning in the living body about MD-1, we established MD-1-deficient SLE model mice. Compared with the control mice, splenomegaly and lymph nodes swelling was reinforced in MD-1 deficient SLE model mice. Furthermore, the serum antibody titer against phospholipids was higher in MD-1 deficient SLE model mice than control mice. It was possible that MD-1 is a molecule which regulates survival and the immune response against lipids of B cells.

S12-6

Functional analysis of mouse TREM-1 ligand and identification of human TREM-1 ligand

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Conflict of interest: Yes

Triggering receptor expressed on myeloid cells (TREM)-1 is expressed by macrophages. Its activation augments inflammatory cytokine production triggered by Toll-like receptor engagement. TREM-1 blockade is supposed to suppress pathological inflammation with maintaining minimal inflammatory cytokine production for anti-microbial defense. Our aim is to develop a new anti-rheumatic therapy that is not associated with a risk of serious infections. We reported previously that TREM-1 is expressed on synovial macrophages in the rheumatoid joints and that TREM-1 blockade with TREM-1 extracellular domain-Ig fusion protein (TREM-1-Ig) ameliorated mouse collagen (CII)-induced arthritis (CIA), which is an animal model of rheumatoid arthritis. Furthermore, we have identified mouse TREM-1 ligand molecule (TREM-1-L) on B cells. Administration of anti-TREM-1-L antibody (Ab) ameliorated CIA. However, it was not clear whether the anti-TREM-1-L Ab acted agonistically or antagonistically in the therapeutic effects. Furthermore, human TREM-1-L was unknown, as human TREM-1-Ig did not bind to putative human orthologue of mouse TREM-1-L. The purpose of this study was to analyze the mechanisms of the effect of anti-TREM-1-L Ab on CIA treatment and to identify human TREM-1-L. TNF-α was produced when macrophages and B cells were co-cultured. Addition of anti-TREM-1-L Ab reduced TNF-α production by macrophages. This Ab had no effect on anti-CII Ab production. Therefore, the therapeutic effect of anti-TREM-1-L Ab should have acted antagonistically.Human TREM-1-Ig bound to B cell population of human peripheral blood mononuclear cells (PBMC). We have identified the molecule that binds to human TREM-1-Ig by expression cloning using PBMC cDNA library. Antibody development against the human TREM-1-L will enable us to develop a new anti-rheumatic therapy that is less associated with a risk of infection than the current treatments.

S13-1

The use of IL-6 inhibitors in the treatment of Rheumatoid Arthritis

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The metamorphosis of the treatment of rheumatoid arthritis has been exponential over the past 25 years from treating patients symptomatically to efforts to control disease activity in order to induce remission, inhibit radiographic progression and maintain patient function so that patients can be productive both at work and at home. Prior to the late 1980's, treatment was symptomatic with the use of NSAIDS, steroids and DMARDs such as gold, sulfasalazine and hydroxychloroquine which, although helpful, did not lead to effective, safe, prolonged disease control. The introduction of MTX in the late 1980's did produce improved clinical and functional responses and inhibition of radiographic progression in many patients. In the late 1990's and early 2000's, the introduction of TNF inhibitors changed the treatment paradigm for patients with RA with more effective therapies to control clinical disease activity, improve function and inhibit radiographic progression, but, not all patients can tolerate these medications and they are not fully effective in all patients. The introduction of inhibitors of IL-6 in the mid 2000's again changed the treatment paradigm. Tocilizumab, a

monoclonal antibody to the IL-6 receptor, has been shown to be effective as monotherapy and in combination with MTX or other DMARDs, in patients who are naïve to MTX, in MTX or DMARD incomplete responders and in patients who have failed TNF inhibitors, Recently, a subcutaneous formulation has been tested and shown to be equivalent to the IV formulation, both in combination with DMARDs and as monotherapy. This presentation will discuss the seminal studies of tocilizumab as well as the available information of other IL-6 inhibitors in development and briefly discuss tofacitinib, an oral immunomodulator which has many of the properties of tocilizumab.

S13-2

The Safety of Biological Thearpies in Rheumatoid Arthritis

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Rheumatoid arthritis (RA) is a serious disease that causes disability and early demise. There is a known increase in cardiovascular disease and serious infections in RA patients. Early, aggressive control of the inflammatory process in RA is the best patient care. Disease Modifying Synthetic agents, such as Methotrexate, only result in 30% of patients attaining low disease activity. Therefore, the use of biologics to control disease inflammation is needed. The question is: "Is it unsafe to leave the inflammation of RA inadequately treated?" Data for biologics decreasing cardiovascular risk, such as, myocardial infarction and death will be reviewed. The safety of individual biologic agents, such as, anti-TNF agents, Abatacept (ABA) and Tocilizumab (TCZ) will be discussed. Their serious infections, opportunistic infections and serious adverse events will be shown. Mono therapy with biological agents may be preferred by patients and Rheumatologists because of its safety and tolerability. The safety and efficacy of Mono therapy of biologics will be explored. Head to Head research trials and meta-analysis may be the best way to compare the biological therapies we have available. Comparative studies and meta-analysis for safety and efficacy will be reviewed. This will include the ADACTA (TCZ head to head to Humira), ACQUIRE (IV ABA head to head to SC ABA), ATTEST (IV ABA versus Infliximab) and AMPLE (SC ABA head to head to Humira). The Cochrane meta-analysis comparing safety and efficacy of biologics will complete this presentation.

S13-3

Cost-friendly Biologics and cost-conscious strategy with biologics

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Conflict of interest: Yes

One of the issues surrounding biological agents (Biologics) is the high cost of biological treatment in RA. Particularly, a part of the biologics cost must be paid by the patients in Japan, posing a big burden on the patients. Several approaches have been take to overcome the issues. 1) Cost-down the biologics: In order to simplify the methods to produce the antibody molecule, Lama IgG2 and IgG3 has been focused, because these two immunoglobulin has only heavy chain. Utilizing the Lama IgG2, ozoralizumab has been developed. Similarly, Fab' fragment produced by E. Coli has pegilated to enhance half-life. The product called certorizumab-pegol has been approved in many countries. The efficacy and safety of these products, in comparison to the previous anti-TNF biologics have been reviewed. 2) Bio-similar: The clinical development not only in the global, but also in Japan including infliximab bio-similar CT-P13 has been reviewed and the issues in clinical development and on the market will be discussed. 3) Biologics with longer half-life and higher potency: Anti-RANKL monoclonal antibody, denosumab is given every six months in patients with post-menopousal osteoporosis, introducing a possibility to make biologics with longer half-life. This implies that biologics with such profile can reduce the injection and total amount of biologics in RA, providing less expensive biologics. In order to obtain monoclonal antibody molecules with longer half-life, amino-acids substitution of Fc receptor binding sites have been tested, in addition to potentiate the effector function such ADCC and CDC. I will summarize the clinical development toward cost-conscious biologics and discuss the future perspectives of biologics in RA treatment.

S13-4

Approach to biologic-free remission in rheumatoid arthritis

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Conflict of interest: Yes

Biological agents targeting TNF have changed the treatment of RA. Clinical remission has recently become an achievable goal by the combination therapy of TNF inhibitors and MTX in many patients, and appropriate induction and maintenance of remission is a prerequisite to halt joint damage and functional disabilities. However, because of the economic burden and the long-term safety by inhibiting a particular cytokine, the possibility of discontinuation of biologics after the maintenance of remission needs to be considered. However, there is no well-established firm evidence that remission can be sustained even if a biological agent is discontinued. European studies such as BeSt and OPTIMA in patients with early RA and Japanese studies such as RRR using infliximab and HONOR using adalimumab in patients with long-standing RA encountered during routine clinical practice have shown that, after a reduction in disease activity to clinical remission or low disease activity by infliximab or adalimumab in combination with MTX, patients can successfully remain in clinical remission without TNF inhibitors with no radiological and functional damage progression of articular destruction. It has to be realized that intensive treatment with a TNF inhibitor is required to bring about the TNF-inhibitor-free remission efficiently since deep remission was a major factor affecting the success of discontinuation of TNF inhibitors in two Japanese studies. Ultimately, TNF inhibitors may change the disease process of RA and bring about the potential of immunological remission, raising the possibility of a 'treatment holiday' of TNF inhibitors after intensive treatment.

S13-5

Stringent Disease Control by Means of Biologic Agents and Their Perspective in Rheumatoid Arthritis

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Pharmacological therapy is the cornerstone in the management of established rheumatoid arthritis (RA). Generally methotrexate is regarded as the DMARD of first choice. The introduction of biological agents has greatly expanded the treatment options. For optimal treatment result long-term treatment strategies are essential. In this presentation clinical observations will be discussed that support the following conclusions. The need for biologic therapy can be determined in the first year of therapy. In case of incomplete response with the first TNF antagonist switching to another is more effective than dose increase. In case of failure of two TNF antago-

nists switching to another biologic agent is the best choice. In case of good clinical responses step-back strategies are safe and effective. Effective responses on biologic agents may induce a long lasting drug-free remission. Observational studies as will be presented closely reflect the effect and outcome of therapy in patients with RA in daily clinical practice and are therefore a valuable addition to randomized controlled trials.

S14-1

Importance of foot synovitis for assessing disease activity

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Conflict of interest: Yes

The target of treatment of medical treatment has become achievement of clinical remission. DAS28, SDAI and CDAI are often used for clinical assessment, and these criteria dose not include assessment of joints in the feet. However, there is a report that the forefoot had been affected at the debut in 45% of RA patients. Residual synovitis of the MTP joints causes various deformities of the forefoot and lead to functional, cosmetic problems. Despite of improvement of medical therapy, a number of arthroplasties for the forefoot have increased. Recently, a study for the consequences of remission misclassification due to residual disease activity in the feet was done. The ability of remission definitions with 28- versus 38-joint count to predict long-term good radiological and functional outcome was similar. They concluded that inclusion of ankles and forefeet in the assessment of remission was not required. However, 26-40% of clinical remission using 28-joint count showed residual activity in the feet, and several reports showed similar results. Clinical evaluation using 28-joint count reflect forefoot involvement in patient global assessment. Therefore, if the symptom is not severe, the patients with residual foot synovitis could be at risk for long-term morbidity and was lead to joint collapse and deformity of the forefoot. Ultrasonography is very useful to detect synovitis which is difficult to detect in clinical examination. Power Doppler ultrasonography (PDUS) make it possible to evaluate correct disease activity in the feet. We investigated PDUS and disease activity of 42 patients in early onset. Total PD score of bilateral MTP joints did not correlate composite measure using 28-joint count. We need to detect subclinical synovitis of the forefoot actively and it is very useful for education of RA patients to visualize synovitis by using PDUS.

S14-2

Prognostic factors for radiographic progression of feet in rheumatoid arthritis patients

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Conflict of interest: None

The objective of this study is to identify prognostic factors for radiographic progression of RA feet, the factors associated with the disorders of the lower limbs in RA patients, and risk factors for forefoot surgery in RA patients. The study was part of an observational cohort project of the Institute of Rheumatology, Tokyo Women's Medical University (IORRA). To identify prognostic factors for radiographic progression, a within-case analysis using radiographs of feet of 453 patients at 5-year disease duration was performed using modified Total Sharp Score (mTSS). Multiple linear regression analysis showed younger age of onset (P=0.007) and anti-CCP positive (P=0.011) had impact on radiographic progression. And to find the factors associated with the disorders of the lower limbs, we enrolled 5,227 RA patients from whom the HAQ score was obtained at the baseline and five years later. The HAQ score change of the lower limbs (ΔHAQ) is calculated as the Year 5 value minus the baseline. Factors associated withΔHAQ were analyzed by multiple linear regression analysis. Phase of IORRA at the baseline (P<2e-16), female (P=3.37e-05), younger age (P<2e-16) and disease duration of RA (P<2e-16) were the factors associated with the disorders of the lower limbs. And to assess risk factors for forefoot surgery in rheumatoid arthritis, patients recruited and followed prospectively for 9 years. The data were analyzed using the multivariate Cox regression model. Of the 9,150 patients registered at baseline, 187 (2.04%) had surgery on one or both forefoot joints. On multivariate Cox regression, the variables with positive coefficients were gender (P=0.0007), long RA duration (P=0.001), HAQ (P=0.000007), RF positive (P=0.03) and past history of surgery (P=0.00001).

S14-3

Study for effectiveness of interventions in conservative treatment of ankle-foot lesions

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Conflict of interest: None

[Objectives] Object is to reveal effectiveness of conservative treatment of ankle-foot lesions by means of shoes, insole, ankle-foot-device and so on, especially focused on early RA under 2years. [Methods] 192 RA cases are divided into 2 groups. One is disease duration is under 2years. The other is disease duration is and more 2years. We compare the number of ankle foot lesions, among 2 groups. We report shoes, insole, ankle-foot-device, especially focus on comport of counter, shank and fitting of shoes. [Results] 48cases are duration under 2years. 8cases are suffering from ankle-foot lesions (5cases forefoot, one case ankle, 3cases posterior tibia tendon dysfunction). 7cases was suffering from A-F lesions, and are free, are tight controlled. 144cases are duration and-more 2years. 64cases are suffering from A-F lesions(44cases forefoot, 2cases mid-foot, 21cases Ankle and or subtalar joint, 3cases PTTD). 5cases was suffering from A-F lesions, and are free. Cases established RA lesions on ankle and foot, were mostly using customized shoes, insole, ankle-foot-device, individually. [Conclusion] Ankle-foot injury was happened 30% of RA patients, duration under 2years. A half of them are recovered with tight medication, can wear common shoes. Ankle-foot lesions were established on RA patients, duration and-more 2years, difficult to be controlled. They need customized shoes, insole, ankle-foot-device, individually. Tight control medication makes recovery on ankle-foot lesions on RA patient in some cases of early stage.

S14-4

Current surgical treatment for rheumatoid forefoot

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Conflict of interest: None

Various operations for the correction of deformity of the forefoot in patients with rheumatoid arthritis (RA) have been described. There is a consensus that the function of the MTP joint can be sacrificed in such patients. Recently, DMARDs and biologic agents have caused a paradigm shift in the treatment of RA. Con-

sequently, improved medical control of joint destruction has led us to reconsider the benefits of joint preservation. Previous studies on joint-preserving surgery for RA forefoot deformity have involved distal osteotomy of the lesser metatarsals. We initially used distal osteotomy, but these procedures are technically demanding, especially in patients with severe dislocation or contracture. I developed combination joint-preserving surgery involving three different proximal shortening metatarsal osteotomies for forefoot deformities in patients with RA. The combination joint preserving operation has three components as follows: a first tarsometatarsal fusion and distal re-alignment, a shortening oblique osteotomy of the bases of the second to fourth metatarsals and osteotomy of the fifth ray. I would like to introduce my technique and outcomes of my procedure. Any symptomatic plantar callosities seen pre-operatively disappeared in all patients. In patients who showed favorable repositioning during follow-up, the head of each metatarsal was repositioned to the level of the proximal part of each dislocated proximal phalanx on pre-operative radiographs. Most had highly satisfactory walking ability. With good perioperative medical management of RA, surgical repositioning of the MTP joints by metatarsal shortening and consequent relaxing of surrounding soft tissue is suspected to be successful. They provide longitudinal decompression of the ray without tendon lengthening. This is beneficial for the joint's range of motion and improving gait. It can be performed preferentially in the early-to-intermediate disease stages, instead of joint-sacrificing procedures.

S14-5

Current status and surgical treatment of hindfoot deformity in RA

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Conflict of interest: Yes

Rheumatoid arthritis (RA) is frequently accompanied with foot and ankle deformities and ailments. However, sufficient attention has not been paid in treatment strategy of RA, and patients would be in despair in that regard. Drastic shift in medication of RA and steady improvement of joint arthroplasty, especially in large joints, has brought about better QOL for tremendous number of patients, which leaves foot and ankle deformities a missing lesion/point in treatment strategy. Hindfoot deformity prevails in patients and is well reported to lead to walking disability. Hindfoot consists of the talocrural joint and the talocalcaneal joint, and the talonavicular joint is also associated with hindfoot motion and its deformity. Recent advancement of surgical treatment includes total ankle arthroplasty and intramedullary nailing for hindfoot joints and has shown promising results, but the surgical techniques are relatively difficult with the implants underdeveloped. This presentation will put emphasis on the current status of hindfoot deformity in RA with the influence of medical treatment on the natural history of the involvement. Especially pivotal points in the surgical techniques will be discussed. The presentation will hopefully show a future perspective on this crucial issue.

S15-1

Joint destruction in rheumatoid arthritis: The current state and future prospects of the research and therapy of rheumatoid arthritis

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Conflict of interest: Yes

Synovial joint is composed of articular cartilage, synovial membrane and joint cavity. Once joint receives injuries, synovial membrane can be completely repaired, whereas articular cartilage results in irreversible damage. In rheumatoid arthritis (RA), articular cartilage and bone are target tissues, and destroyed by induction of proliferative synovitis, stimulation of chondrocytes by cytokines, and enhanced osteoclastogenesis. Members of the MMP and the ADAMTS gene families are believed to play a central role in the cartilage destruction by degradation of aggrecan and collagens, major constituents of the cartilage extracellular matrix, through three pathways: synovial membrane-derived proteinases in synovial fluids, chondrocyte-produced proteinases and direct contact of proteolytic synovial membrane and pannus tissue to the cartilage. Cathepsin K and MMP-9 play an important role in osteoclastic bone resorption. Recent introduction of cytokine-directed therapies using humanized anti-TNF-α antibodies and anti-IL6R antibody in RA patients has demonstrated that they are effective to abrogate synovitis and even improve bone destruction, suggesting the chondroprotective effect of this therapy may be possible if they are applied to the patients at early stages. The effects on the patients, albeit not all patients, demonstrate that these cytokines have crucial roles in RA synovitis and joint destruction, and suggest that the research on diagnosis and therapy at early stages is essential and RA is now changing from a manageable into a curable disease entity. In addition to surgical interventions, development of new therapies to prevent from progressive joint destruction and reparative medicine for damaged articular cartilage are expected for the patients at advanced stages. In this symposium, I will review the current state of cartilage destruction by metalloproteinases and mention on future prospects of the research and therapies of joint destruction in RA.

S15-2

Cartilage damage and proteinase -the regulation of chondrocyte-matrix interaction-

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Conflict of interest: Yes

Degradation of the cartilage extracellular matrix is a central feature of the osteoarthritis and rheumatoid arthritis and thought to be mediated by proteinases that degrade structural components of the matrix, primarily aggrecan and collagen. The roles of Matrix Metalloproteinases (MMPs) in cartilage matirx degradation had been well recognized. Moreover, MMPs have another important roles in cartilage metabolism. The processing of cell adhesion molecules and receptors in chondrocyte has an important effect on cartilage metabolism. Stability of cell-matrix interactions promotes tissue homeostasis, and matrix receptors provide for the assembly and retention of matrix as well as the linkage to the signal transduction pathways activated by the changes in the extracellular matrix. The changes in chondrocyte-matrix interactions influence the responses to cytokines and survival and consequently promote the cartilage destruction. The hyaluronan (HA) receptor CD44 serves as the critical link for the retention of HA-proteoglycan aggregates to the chondrocyte cell surface. This molecule is believed to serves as the adhesion molecules of cells, the receptor of growth factors and binding proteins of MMPs in chondrocyte. Disruption of chondrocyte CD44: HA interaction will induce a cascade of events resulting in the activation of the catabolic gene products such as MMPs and ADAMTS4. Fragments of HA produced in inflammatory condition may have the potential to augment the activation of NFk B in a CD44-dependent mechanism. This finding may suggest that CD44-mediated signaling affects both chondrocyte survival pathways as well as apoptotic pathways. The function of chondro-

cyte CD44 is still under investigation in many aspects. The future studies concerning on protease in cartilage breakdown will need to include the interaction of matrix and chondrocyte. This presentation discusses recent advances in understanding of the mechanisms regulating CD44:HA interaction with the proteinases.

S15-3

Bone destruction in arthritis and therapeutics

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Conflict of interest: Yes

Rheumatoid arthritis (RA) is a chronic inflammatory disorder characterized by progressive joint destruction. Recent studies have revealed that osteoclasts, multinucleated giant cells primarily responsible for bone resorption, plays an essential role in the bone destruction in RA. Osteoclast differentiation is critically regulated by a membrane-bound cytokine, receptor activator of nuclear factor kappa B ligand (RANKL), and synovial cells in RA patients express high levels of RANKL. Blocking RANKL activity by a specific antagonist osteoprotegerin or by gene disruption completely abrogated arthritis-induced bone destruction in animal models. In addition, denosumab, a fully human monoclonal antibody against RANKL, not only increased bone mineral density in RA patients but also suppressed bone destruction in RA. These results clearly demonstrated that therapeutics against osteoclasts provide a useful tool to cope with joint destruction in RA.

S15-4

Preservation and Repair of Joint Structure with Biologics in Patients with Rheumatoid Arthritis

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Conflict of interest: Yes

Accumulating data on effect of biologics on joint damage have provided us with the understanding into the excellent but limited clinical efficacy of biologics and the new insight in pathogenesis of joint destruction in RA. Especially, data shown in the cumulative probability plot of radiographic progression showed us that conventional DMARDs or MTX also have good efficacy in preserving and repairing the joint structure, and that biologics improve more both of the ratio of patients without joint damage progression and the yearly progression ratio of joint destruction. Notwithstanding the excellent efficacy of biologics, 20-30 % of patients treated with biologics remain in the progression of joint destruction, even in cases with clinical remission or early intervention with biologics. Furthermore, the dissociation between radiographic deterioration and clinical remission has been recognized. Although there are the several possible explanations including the problem of remission criteria that lack predictive validity for structural deterioration, insufficient sensitivity of clinically used methods evaluating inflammation and carry-over effect of the inflammation before remission, we must be aware of the possible pathophysiologic mechanism of joint destruction independent from inflammatory signs. This dissociation also means that it is not appropriate to judge the joint preserving effect by anti-inflammatory effect evaluating with existing methods including US and MRI. So, we should again realize the significance of sequential radiographic evaluation that is most popular modality in the world. That is also driving background for task to develop the surrogate markers of judging the efficacy on preserving the joint structure from deterioration. Biomarkers associated with cartilage and bone metabolism including C2C/CPII and dkk-1 are possible candidates. We always have to translate clinical findings into new insight of pathophysiologic mechanism of joint destruction in RA.

S15-5

Articular cartilage regeneration with synovial mesenchymal stem cells

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Conflict of interest: None

Cell transplantation has shown to be a promising strategy to repair cartilage defects. Mesenchymal stem cells derived from synovium have been shown to be a superior cell source for cartilage regeneration to those from other mesenchymal tissues due to their higher rates of colony formation, proliferation potential with autologous serum, and in vitro/vivo chondrogenic potentials. We have found that approximately 60% of synovial mesenchymal stem cells placed on cartilage defects adhered to the defect within 10 min, and the addition of magnesium enhanced this percentage further, which resulted in better cartilage regeneration. Based upon several basic research studies performed in our lab, we have begun the transplantation of synovial stem cells arthroscopically in a clinical study for the treatment of cartilage defects. To date, no adverse events have been reported in the study. Regeneration of cartilage, reduction in defect size and an improvement of symptoms have been obtained in most patients over the last 4 years.

S16-1

Novel therapy for SLE: anti-BAFF antibody, Syk inhibitor etc.

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Conflict of interest: None

Treatment for systemic lupus erythematosus (SLE) has traditionally been restricted to broad-based immunosuppression, with glucocorticoids being central to care. Although the prognosis of SLE 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. Recent insights into lupus pathogenesis promise new, selective therapies with more favorable side effect profiles. Against the background of considerable progress in conventional therapies, belimumab recently became the first drug to meet the current approval standards of the US Food and Drug Administration for the treatment of SLE. Notably, it has not been studied in severe active lupus nephritis or severe active CNS lupus and it has not been studied in combination with other biologics or with IV cyclophosphamide. Atacicept is a fusion protein combining the extracellular domain of TACI with the Fc portion of human IgG. Epratuzumab, a humanized anti-CD22 monoclonal antibody, also has inhibitory effects on B cell signaling and is now undergoing phase III study for SLE treatment. Spleen tyrosine kinase (Syk) is a critical component for signal transduction through the B cell receptor. Fostamatinib, a Syk inhibitor, is currently being investigated to treat rheumatoid arthritis, lymphoma, bronchial asthma and ITP. Strategies targeting anti-DNA antibodies, Toll-like receptors, T cell surface molecules or other cytokines, such as interleukin 6 (IL-6) and interferon (IFN)-α, are also on the horizon. Despite the lack of evidence in randomized trials, anti-CD20 antibody treatment for SLE remains to consider the trial design and the difficulties to treat the heterogeneous disease. There is hope that more therapeutic options will be found in the near future to establish

personalized therapies for the highly heterogeneous population of patients with lupus.

S16-2

New therapeutic strategy for Sjögren's syndrome: Efficacy and safety of abatacept, messages from ROSE trial (Rheumatoid Arthritis with Orencia Trial Toward Sjögren's syndrome Endocrinopathy)

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Conflict of interest: Yes

<Background> Sjögren's syndrome (SS) is subcategorized into primary SS which is not associated with other CTDs, and secondary SS associated with other CTDs. Recently, efficacy of biologics such as TNF, IL-6 blockers, and inhibitor for T cell activation (abatacept) for RA has been confirmed. On the other hand, efficacy of TNF blockers for SS has not been established, only chimeric anti-CD20 antibody (rituximab) has been shown to be effective for SS. $CD4^+$T cells have crucial roles in the pathogenesis of SS, therefore we expect abatacept to be effective for SS. <Objective> To clarify the efficacy and safety of abatacept for secondary SS associated with RA. <Methods> 1) We designed open-labeled, prospective, observational, and multicenter study (ROSE trial) for secondary SS (diagnosed by 1999 Japanese criteria) associated with RA (by 1987 or 2010 ACR criteria), who were over 20 years old and consented to this study. 2) Primary endpoint was frequency of SDAI remission at 12 months after initiation of abatacept. Secondary endpoints were Saxson test, Schirmer test, and patients' VAS for dryness and pains of parotid glands. 3) Adverse events during observational periods were analyzed. <Results> 1) 23 patients (all females) have been enrolled in this study at Dec 2012. 2) Midterm analysis at 6 months of 9 patients showed that SDAI significantly decreased from 18.93±9.82 (0 month) to 9.77±10.21 (6 months) ($P<0.05$), and one patient achieved remission, 4 patients achieved LDA in SDAI. Both salivary volumes by Saxson test and tear volumes by Schirmer test significantly increased from 2096±1510 to 2971±1649 mg/2 min, and from 6.0±6.9 to 7.9±8.0 mm/5 min, respectively ($P<0.05$). Patients' VAS for dry eye significantly decreased from 43.56±25.11 to 24.56±12.70 mm ($P<0.05$). 3) One severe adverse event (urinary tracts infection) has occurred in one patient at Dec 2012. <Conclusion> The results indicated abatacept might be effective for both RA and SS involvements in secondary SS associated with RA.

S16-3

New treatments of polymyositis / dermatomayositis

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Conflict of interest: Yes

Recent etiological studies revealed that seventeen thousand patients suffer from polymyositis (PM) or dermatomyositis (DM) and that approximately two thousand patients are newly diagnosed with these diseases. The mainstay of the treatment has been administration of glucosteroids. Azathioprine and cyclophosphamide have been locally approved for concomitant use with steroids since their use was approved for treatment of rheumatic diseases. Intravenous infusion of immunoglobulins was approved recently and exerts acute but temporal effects. Intermittent methotrexate administration as in treatment of rheumatoid arthritis (RA) is also effective, but calls for special caution since almost a half of the patients have interstitial lung diseases (ILD). Calcineurin inhibitors are favored especially for the patients with acute progressive ILD. The current treatment depends heavily on glucocorticoids, which are non-specific immunosupressants with quite a few side effects. A paradigm shift, seen in RA treatments, is yet to come. This is partly due to absence of appropriate animal models for pre-clinical studies. We thus developed a new mouse PM model, called C protein-induced myositis (CIM). It resembles PM not only in its pathological processes but also in responses to therapeutic intervention, and should serve as a good model for development of new treatments. Studies of CIM led us to believe that activation of muscle antigen-specific T cells as well as that of innate immunity in the muscle tissues are both essential for development of the myositis. Based on this, we propose "the seed and soil model of autoimmunity", regarding T cells as seeds and target tissues, which accept T cells, as soil. They both should be therapeutic targets. While past clinical trials depended on the drugs that had been used successfully in RA, our model should offer good rationale for development of therapeutic strategies specific to PM/DM pathology. We will present some examples for discussion.

S16-4

Current and future therapeutic strategies for systemic sclerosis (SSc)

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Conflict of interest: None

SSc is an intractable disease characterized by excessive fibrosis of the dermis and internal organs, and widespread microvasculopathy. In the past, corticosteroids and D-penicillamine were used as potential disease-modifying treatments, but these drugs are hardly used anymore due to lack of evidence to improve survival. In 1990's, clinical trials of MTX, IFN-gamma, relaxin, and oral administration of type I collagen were conducted in patients with early diffuse cutaneous SSc, but all of them failed to show improvement of total skin score. In a placebo-controlled, double-blind, randomized trial in SSc patients with interstitial lung disease, one year of treatment with oral cyclophosphamide resulted in significant beneficial effects on lung function and total skin score, but treatment effects were very small and lost at one year of follow-up. Recently, autologous hematopoietic cell plantation was shown to reduce clinical worsening in comparison with patients treated with intravenous cyclophosphamide, but we still don't know who benefits by this aggressive treatment. In addition, anti-TGF-beta1 antibody metalimumab, rituximab, imatinib, and bosentan were shown to be ineffective for treating patients with early diffuse cutaneous SSc. These pessimistic results of clinical trials in SSc patients may be due to inappropriate trial design and difficulty of discriminating a physiologic would-healing process from mechanisms for pathogenic fibrosis. Nevertheless, recent basic researches involving molecular/cellular techniques and SSc-mimic mouse models lead to the discovery of novel therapeutic targets, such as pan TGF-beta family, IL-6, JAK-2, and lysyl oxidase-like 2. Clinical trials of these potential therapeutic strategies are currently ongoing.

S16-5

New therapeutic strategies for vasculitis, mainly biologics

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Conflict of interest: None

Pathogenesis of primary vasculitis includes the impairment of immune system. The impaired humoral immunity leads to the production of immune complexes, anti-neutrophil cytoplasmic antibodies (ANCA), anti-endothelial cell antibodies, or anti-phospholipid antibodies. The impaired cell-mediated immunity results in the granuloma formation by self-reactive T cells. Based on these observations, the therapeutic strategy for vasculitis aims the improvement of these abnormalities by combination of glucocorticoid (GC) and immunosuppressive agents such as cyclophosphamide (CYC). In Japan, the numbers of patients with microscopic polyangiitis (MPA) and those with granulomatosis with polyangiitis (GPA) have shown a rapid increase. The standard therapy for remission induction in MPA/GPA of systemic type is the combination of GC (prednisolone 1mg/kg/day) and CYC (1.5-2mg/kg/day). Instead of an oral CYC, an intravenous CYC (IVCY) may be employed at 0.5-1.0mg/m^2/month for 3-6 months. Remission induction rate is around 90% in randomized controlled trials (RCTs) with this standard regimen, 10-20% of cases being resistant to the treatment. The standard therapy for remission maintenance is the combination of low-dose GC and azathioprine (AZA). Several new treatment strategies for CYC-resistant MPA/GPA were shown in EULAR recommendations (2009). These included mycophenolate mofetil (MMF), 15-deoxyspergualin, intravenous immune globulins, anti-thymocyte globulin, infliximab and rituximab (RTX). Two RCTs of RTX were published in 2010 - RITUXIVAS and RAVE trials, in which it was shown that RTX seemed to be useful in patients with relapsed disease. Besides RTX, other novel therapies such as intravenous AZA, anti-T cell antibodies, radiation therapy, and stem cell transplantation have been reported. In this symposium, the latest findings of new therapies in vasculitis, mainly biologics, will be presented.

S16-6

New therapeutic strategy in adult-onset Still's disease: Tocilizumab and the other biologic agents

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Conflict of interest: Yes

Adult-onset Still's disease is an inflammatory disorder of unknown cause, characterized with a spiking fever, arthralgias/arthritis and an evanescent rash. Its prevalence in Japan was estimated to be 0.73 and 1.43 per 100 thousands population in male and female, respectively. It was classified into 3 categories of monocyclic systemic, polycyclic systemic and chronic articular type based on its clinical course. Proinflammatory cytokines, such as IL-1, IL-6, IL-18, IFN-γ and TNF-α are involved in the pathophysiology of adult-onset Still's disease. Non-steroidal anti-inflammatory drugs have only a limited effect for adult-onset Still's disease. Glucocorticoid is a mainstay of treatment of adult-onset Still's disease even at present. Addition of methotrexate and/or cyclosporine to glucocorticoid is challenged in steroid-resistant or steroid-dependent adult-onset Still's disease. Biologic agents including interleukin 1 inhibitors, TNF inhibitors, tocilizumab (anti-IL-6 receptor antibody) and abatacept (CTLA-4 immunoglobulin fusion protein) have been used in these intractable cases. The efficacy of anakinra, etanercept, tocilizumab and abatacept in the intractable cases had been reported by Godinho et al. in 2005, Kraetsch et al. in 2001, Iwamoto et al. in 2002, and Quartuccio et al. in 2010, respectively. A long-term efficacy and safety of tocilizumab in steroid-dependent adult-onset Still's disease treated in our institution will be presented here along with that of other biologics in the literature.

S17-1

Overview and Comprehensive Diagnostic Criteria for IgG4-related disease (IgG4-RD)

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Conflict of interest: None

IgG4-related disease (IgG4-RD) is a novel clinical disease entity characterized by elevated serum IgG4 concentration and tumefaction or tissue infiltration by IgG4-positive plasma cells. IgG4-RD may be present among a certain proportion of patients with a wide variety of diseases, including Mikulicz's disease, autoimmune pancreatitis, hypophysitis, Riedel thyroiditis, interstitial pneumonitis, interstitial nephritis, prostatitis, lymphadenopathy, retroperitoneal fibrosis, inflammatory aortic aneurysm and inflammatory pseudotumor. Although IgG4-RD forms a distinct, clinically independent disease category and is attracting strong attention as a new clinical entity, many questions and problems still remain to be elucidated. This has led to the organization of two study groups by the Ministry of Health, Labor and Welfare Japan to analyze this condition. One of these groups is Umehara team with 66 members, seeking to establish diagnostic criteria for IgG4-related multi-organ lymphoproliferative syndrome (IgG4-MOLPS), whereas the second group is Okazaki team with 56 members, seeking to understand the etiology and pathogenesis of IgG4-related systemic disease. Since IgG4-RD includes a wide variety of diseases, these groups consist of physicians and researchers in various disciplines, including rheumatology, hematology, gastroenterology, nephrology, pulmonology, ophthalmology, odontology, pathology, statistics, and basic and molecular immunology throughout Japan. Collaborations of the two study groups (All Japan IgG4-RD team) have involved the detailed analyses of the clinical symptoms, laboratory results and biopsy specimens of patients with IgG4-RD, resulting in the unification of term "IgG4-related disease" and the establishment of disease concept and coprehensive diagnostic criteria for IgG4-RD. Thus, All Japan IgG4 team clearly established the new clinical entity of IgG4-RD discovered in 21st century.

S17-2

IgG4-related autoimmune pancreatitis

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Conflict of interest: None

Recently, IgG4-related disease (IgG4-RD) has been recognized as a novel clinical entity with multiorgan involvement and unknown origin, associated with abundant infiltration of IgG4-positive cells. The Japanese research committee supported by the Ministry of Health, Labor and Welfare of Japan unified many synonyms for these conditions to the term "IgG4-RD" in 2009. Recent studies suggested two subtypes of autoimmune pancreatitis (AIP), type1 related with IgG4 and type 2 related with a granulocytic epithelial lesion. Apart from type 2 AIP, pathological features of type 1 AIP with increased serum IgG4/IgE levels, abundant infiltration of IgG4+plasmacytes and lymphocytes, fibrosis, and steroid responsiveness are suggestive of abnormal immunity such as allergy or autoimmunity. Moreover, the patients with type 1 AIP

often have extra-pancreatic lesions such as sclerosing cholangitis, sclerosing sialadenitis, or retroperitoneal fibrosis showing similar pathological features. Although significance of IgG4 in the development of IgG4-related disease still remains unclear, we have proposed a hypothesis for the development of type1 AIP, one of IgG4-related disease. In this symposium, I will discuss the current concept and diagnosis, and treatment of IgG4-related type1 AIP.

S17-3

IgG4-related dacryoadenitis and sialadenitis (Mikulicz's disease)

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Conflict of interest: None

Mikulicz's disease (MD) is a chronic inflammatory disorder presenting bilateral and symmetrical swelling of lacrimal and salivary glands. MD is considered to be IgG4-related dacryoadenitis and sialadenitis. The nationwide survey in 2009 showed MD patients were estimated to be 1,100-4,300 in Japan. We constructed the SMART database to clarify the clinical characteristics of MD and the related diseases (Küttner's tumor and IgG4-related dacryoadenitis) and spread the useful information at practice. The subjects were 99 patients with MD and the related diseases. They were registered to the SMART database and followed by us as of July 2012. We analyzed the sex ratio, age distribution, organ dysfunction except lacrimal and salivary gland, complication of malignancies, treatments, remission and relapse rate. The sex ratio was almost the same. The mean age was 64.3 years, and over sixties accounted for about 3/4 of the total. 65.7% of the patients presented with organ dysfunction except lacrimal gland salivary gland. They were retroperitoneal fibrosis (25.8%), autoimmune pancreatitis (22.6%), IgG4-related kidney diseases (16.1%), lung and airway diseases (15.1%). The rate of complication with malignancy was 7.1%. Glucocorticoid treatment was carried out in 81.8%. The average dose of prednisolone was 5.6 mg/day. The rate of concomitant use of immunosuppressants was 9.1%. The remission rate was 73.7% and the drug-free rate was 6.1%. On the other hand, the relapse rate was 16.2%. A half of them presented with the recurrence at the organs other than lacrimal and salivary glands. The SMART database tells us the following. In the diagnosis of MD, we have to consider the complication with various organ dysfunction and the malignancies. In the treatment, there are relapse cases during tapering steroid. We have to check the whole body because the relapse could occur in the other organs.

S17-4

IgG4-related kidney disease

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Conflict of interest: None

The main finding of IgG4-related kidney disease (IgG4-RKD) is tubulointerstitial nephritis (TIN) with dense IgG4+ plasma cell (PC) infiltration and fibrosis. It is characterized by decreased renal function (RF) with usually mild urinary abnormalities, but RF is normal in about half of the patients (pts). Diagnostic clues of IgG4-RKD include elevated serum IgG or IgE level, or hypocomplementemia. When IgG4-RKD is suspected, radiologic and histologic approaches are important. Multiple low-density lesions on enhanced CT are the most common radiologic finding, while diffuse renal swelling is another feature. Histologically, lymphoplasmacytic TIN is the main feature. In contrast, necrotizing vasculitis, granuloma or neutrophil infiltration is rarely seen, and the existence of these lesions point to other disease. Although dense IgG4+ PC is crucial to IgG4-RKD, several other diseases, in particular ANCA-associated vasculitides including Churg-Strauss syndrome, show dense IgG4+ PC infiltration. 40% of cases have associated glomerular lesions, with membranous nephropathy being the most frequent. Corticosteroid has a dramatic effect on RF. We analyzed 34 pts with an average follow-up of 34 months after starting therapy (Tx), and found that 20 with an eGFR of less than 60 ml/min before treatment showed a rise of eGFR from 34 to 45 one month after starting Tx. Radiologically, 46% of pts showed renal atrophy. While cases with decreased RF before Tx showed more frequent renal atrophy, about 20% of cases with normal RF before Tx also showed renal atrophy. This finding suggests that prompt initiation of Tx is mandatory in cases with IgG4-RKD even if RF is not impaired before Tx. In addition, about 20% of the pts experienced recurrence under steroid maintenance Tx. This suggests that establishment of more effective maintenance Tx and discovery of useful monitoring markers will be necessary for more successful treatment of IgG4-RKD in the future.

S17-5

IgG4-related lung disease

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Conflict of interest: None

'Immnoglobulin G4 (IgG4)-related disease (IgG4-RD)' is a new concept of multi-organ disease. IgG4-RD has also been found to involve thoracic organs, manifesting as interstitial pneumonia, inflammatory pseudotumor, mediastinal fibrosis, pleurisy, and bronchial inflammation. To clarify the clinic-radiological and pathological characteristics of lung involvement associated with IgG4-related disease, we retrospectively assessed the patients with IgG4-related disease. 1) Clinically, the lung/mediastinal disease occurred predominantly in middle aged to elderly men. They were usually asymptomatic, but some patients presented asthmatic symptoms. In laboratory data, the patients presented high serum concentrations of IgG and IgG4. 2) Common radiological findings included mediastinal lymphadenopathy and thickening of the perilymphatic interstitium, with or without subpleural and/or peribronchovascular consolidation. 3) Pathologically, abundant plasma cell infiltrates (IgG4/IgG positive plasma cells >40%) were seen with fibrosis in and around the lymphatic routes, with distribution well correlated with radiologic manifestations. IgG4-related lung disease should be differentiated from similar diseases, such as sarcoidosis, multicentric Castleman's disease, Sjögren's syndrome and malignant lymphoma. The correlation of clinicoradiological and pathological characteristics is crucial for the diagnosis of IgG4-related lung disease.

S17-6

Involvement of T cell subsets in the pathogenesis of IgG4-related disease

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Conflict of interest: None

【Objectives】 IgG4-related disease is a systemic disease characterised by the elevation of serum IgG4 and infiltration of IgG4-positive plasma cells in the target organs. IgG4-related dacryoadenitis and sialoadenitis (IgG4-DS), so-called Mikulicz's disease, is

included in IgG4-related disease and shows similarities to Sjögren's syndrome (SS). In this study, we therefore examined the association of Th subsets with germinal center (GC) formation and IgG4 production in salivary gland lesions of IgG4-DS, in comparison with those of SS, to elucidate an involvement of T cell subsets in the unique pathogenesis of IgG4-DS. 【Methods】 Fifteen patients with IgG4-DS, 18 with SS, and 18 healthy subjects were included in this study. Expression of Th1-, Th2-, Treg-, Th17-, and Tfh-related molecules in labial salivary glands (LSGs) was examined by immunohistochemical staining and real-time PCR. 【Results】 In LSG from SS patients, expression of Th1-, Th2-, Th17-, Tfh-related molecules was higher than those in controls. The Th1- and T17-related molecules were strongly detected in areas without GC, while the Th2- and Tfh-related molecules and IL-21 were in areas with GC. IgG4-positive cells were hardly observed. In LSG from IgG4-DS patients, expression of Th2-, Treg-, Tfh-related molecules was higher than those in controls and SS patients, and the Treg-related molecules and IgG4-positive cells were detected around GC. The Tfh-related molecules were detected in/around GC, while the Th2-related molecules and IL-21 were diffusely. Furthermore, the expression of IL-4, IL-10, and IL-21 was positively correlated with number of IgG4-positive cells and expression of IgG4. 【Conclusion】 In SS, Th1 and Th17 might be involved in the early stage, while Th2 and Tfh in the late stage in association with GC formation. In contrast, in IgG4-DS, Th2, Treg, and Tfh might play key roles in GC formation and IgG4 production and involved in the unique pathogenesis.

S17-7

Pathological features of IgG4-related disease

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Conflict of interest: None

IgG4-related disease (IgG4-RD) is characterized by abnormal findings, including serum IgG4 elevation and abundant tissue infiltration with IgG4-positive cells. However, lesions with such findings are not always diagnostic indicators of IgG4-RD. An increase of IgG4-positive cells is often seen in neoplastic diseases, granulomatosis with polyangiitis, and Castleman's disease, but etiologically these are fundamentally different to IgG4-RD. As a result, pathological findings play an essential role in the correct diagnosis of IgG4-RD. According to the recently published international consensus statement on the pathological diagnosis of IgG4-RD, the importance of specific histological features in diagnosis was stressed, especially storiform fibrosis and obliterative phlebitis. The report also strongly recommended that diagnosis should not be made with immunohistochemical staining alone. The basis for this can be seen in the period before IgG4 immunostaining and IgG4-RD, when type 1 autoimmune pancreatitis was recognized as histologically unique (lymphoplasmacytic sclerosing pancreatitis). The variance of IgG4-RD histological features among organs is also well known. In comparison with the abdominal organs, the head and neck feature marked lymphoproliferative lesions, little fibrosis, and storiform fibrosis and obliterative phlebitis are relatively uncommon. In the Japanese comprehensive diagnostic criteria for IgG4-RD 2011, histological criteria have been adopted with a stronger emphasis towards immunohistochemical findings compared with histological features (dense lymphoplasmacytic infiltration and fibrosis + IgG4/IgG positive cell ratio ≧40% + IgG4-postive cells >10/hpf). Histological criteria also differ for each specific organ, reflecting the variance of histological features for each organ. In this lecture, I will present the background of the histological criteria as well as problems which can occur in the histological diagnosis of IgG4-RD.

S18-1

Pathological changes in joint components due to biological medications

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Conflict of interest: None

Before the use of biologicals, cases in which surgery revealed dark red villiform outgrowths of synovial membrane within joints were common. However, with the use of biologicals in RA, it is now common to find fibrous synovial membrane within joints in which inflammation is subsiding, providing many opportunities to appreciate the treatment efficacy of biologicals. Pathological findings regarding RA in the synovium include characteristics of multistratified lining cells, infiltration in the sublining cells of inflammatory cells such as lymphocytes and plasma cells, neogenesis of blood vessels et al. However, with RA where disease activity responds well to biologicals, in frequent cases lining cells become monostratified and the number of inflammatory cells infiltrating sublining cells decreases. Reports have been made to the effect that the decreased expression of CD68 in sublining cells correlates with response to treatment, and that the expression of TNFα in sublining cells correlates with response to treatment with TNF inhibitors; however, many points regarding the influence of biologicals on rheumatoid arthritis in synovial tissue remain unclear. As well, at present the use of six varieties of biologicals has become possible, but the disparities among varieties in synovial pathological findings are still unclear. This report presents our comparative consideration of the pathological changes in the synovium in a single patient, for whom extraction of synovial membrane was possible both when biologicals had not been used and subsequent to their use.

S18-2

Effects and limitations of biologic therapies on weight-bearing joints in patients with rheumatoid arthritis

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Conflict of interest: None

Rheumatoid arthritis (RA) is a chronic inflammatory disease that causes joint pain, swelling and stiffness, leading to structural damage. Tumor necrosis factor (TNF) -blocking therapies have been shown to remarkably reduce the associated inflammation and inhibit the progression of joint damage. However, the assessment of joint damage is mainly restricted to small joints in hands and feet. Since radiographic damage of large weight-bearing joints, such as hips, knees and ankles, is strongly associated with walking disability in patients with RA, it is indispensable to assess the extent of radiographic damage in these joints after TNF-blocking therapies. We have evaluated the effect of TNF-blocking therapies on weight-bearing joints of patients with RA. TNF-blockers inhibited the progression of joint damage in most of hip and knee joints with baseline Larsen grade 0 and I. However, hip and knee joints with pre-existing Larsen grade II showed gradual progression. On the other hand, these joints with baseline Larsen grade III and IV resulted in rapid radiographic progression even after TNF-blocking therapies. The radiographic progression in ankle and subtalar joints was different from that observed in hip and knee joints. TNF-blocking therapies inhibited the progression of ankle and subtalar joint deterioration, regardless of the grade of baseline joint dam-

age. In addition, several patients showed improvement of erosion in ankle and subtalar joints. There was a relationship between the disease activity and the progression of joint damage in weight-bearing joints. Sustained high disease activity tended to show the progression of joint damage as compared to patients with low disease activity. These findings appear to support the importance of the early intervention and tight control of TNF-blocking therapy for patients with RA in order to prevent radiographic progression of weight-bearing joint damage.

S18-3

Orthopedic Interventions in the Rheumatoid Arthritis Patients with Biologics–A Repot from NinJa Cohort-

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Conflict of interest: None

As increasing the number of Biologics (i.e. BIO) administration, we found well-controlled disease activity of RA and prevention of joint destruction. Therefore we expected the decrease of orthopedic surgery and the increase of joint-preservation surgery and cosmetic small-joint surgery. Meanwhile, the risk of surgical site infection was being concerned. We examined the impact of BIO on surgeries of RA patients in clinical practice using NinJa Cohort 2003-2011. [Material and Method] The patients who underwent RA-related surgery were extracted. The frequency of surgery, the constitution of procedures, pre-operative conditions, and their chronological changes were evaluated. [Result] The frequency of surgery decreased from 5.9% to 3.8%. The ratio of Single-joint operated patients to the patients who underwent surgery increased from 25.3% to 56.8%. The frequency of surgical procedures through the period was : TKR>THR>Toe arthroplasty>Wrist>TER. TKR decreased and TER slightly increased. The surgery rate of BIO patients (4.6%) was higher than that of DMARDs patients (3.6%). Regarding Bio patients, the rate of Total Joint Replacement and Large Joint surgery were significantly higher than DMARDs patients (p=0.002). We were able to detect the expected results only partially, but pre-operative conditions of BIO patients revealed that indication for surgery changed. The patient with lesser pain underwent surgery, which may reflect the change of Disease Image. Patients who acquired remission after surgery without drug change were 58 cases (5.6%). This may suggest the usefulness of surgical procedure in remission induction. We also found that the number of late infection of operated joint slightly increased. We should care about late infections as well as acute surgical infections in BIO patients who underwent surgeries.

S18-4

Indication of surgical intervention for rheumatoid joints

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Conflict of interest: None

Biologic agents (Bio) have dramatically changed the treatment of rheumatoid arthritis (RA) over the past decade. Not only clinical remission but also structural remission has been recognized as a realistic goal. However, surgical interventions are necessary for some RA patients either who cannot use Bio due to primary, or secondary failure, patient's complication, or economic reason, or whose joint destruction has already extended before beginning to use Bio. Indication of surgical intervention has also changed in consideration for the effect of inhibition the joint destruction. As the structural remodeling of the joints has been frequently noted in patients with good clinical response, surgeons should ascertain the drug efficacy prior to the indication of the surgery. Indication of surgical intervention for damaged RA joint is comprehensively determined by patient's pain, range of motion, degree of disability, imaging findings, and general condition. Radiographic examination, computed tomography, magnetic resonance imaging, and ultrasonography are widely used before surgery to investigate damaged RA joint precisely, and help the surgeon to determine the surgical method. The operative methods that can preserve affected joint such as synovectomy, arthroplastic surgery of the wrist, and shortening oblique osteotomy of the metatarsal bone are considered as much as possible in the new era of modern medical treatment, unless there are severe joint destruction or dislocation. On the other hand, arthrodesis or artificial joint arthroplasty should be indicated for the advanced joint destruction as in the past. We have experienced 180 procedures (17.9%) under Bio control of total 1007 RA joint operations from 2004 to 2011.In this symposium, we would like to discuss about the indication of surgical intervention on the basis of our procedures under Bio control.

S18-5

Perioperative management for rheumatoid patients treated with biological DMARDs

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Conflict of interest: None

Introduction It was reported that the rate of operations for RA patients treated with biologics was increasing,and chance of having biological treatments with joint arthroplasty was more than twofold greater in patients with surgical-site infections (SSI) compared with those treated with non-biologics agents. Biological treatment was actually withheld for some weeks prior to surgery. Our planning about the duration of interruption before surgery is 4 weeks in Infliximab (IFX),Tocilizumab (TCZ),Abatacept (ABA) and 2 weeks in Etanercept (ETN) and Adalimumab (ADA). Then biological treatment restarted after reunion of the skin incision and confirmation of lack of SSIs. Patients and methods. Evaluation of the SSI in surgical interventions for 128 RA patients treated with biologics was performed. Mean age was 65.8±10.2 years. Twelve patients were treated with IFX, 78 patients were treated with ETN, 28 patients were treated with TCZ, 6 patients were treated with ADA, and 4 patients were treated with ABA. Joint replacement surgeries were performed in 57 patients; 33 were total knee arthroplasty (TKA), 13 were total hip arthroplasty (THA), 7 were total elbow arthroplasty, 4 were total shoulder arthroplasty. Operations for forefoot deformity were performed in 38 patients, and operations for hand or wrist were in 21 patients. About TKA and THA, same clinical pathway was used in patients with RA and osteoarthritis. The number of operations for fracture was four, enough interruption before surgery could not taken, each duration was 4,6,8,18 days. Results Two cases with postoperative SSIs were

identified among the 128 surgeries(1.6%), comprising one superficial incisional SSI requiring debridement in patient treated with ETN, and one organ/space SSI requiring reoperation for removal of the hip prosthesis in patient treated with TCZ. Conclusion The infection rate in patients treated with biologics are not high in our data, following the rest period before surgery described in the guidelines.

S18-6

Surgical treatment for rheumatoid arthritis in the era of biologics

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Conflict of interest: Yes

In recent years, methotrexate and biologic agents have brought about a paradigm shift in the treatment outcome of rheumatoid arthritis (RA), and remission has become the main target in the treatment of RA(1-5). As a result, a paradigm shift has also been made in surgical treatment for RA. The overall number of surgical procedures in RA appears to be decreasing, but the hand and foot surgeries have been increasing, according to a report from our institute(6). On the other hand, the use of biologic agents is reported to be associated with an increased incidence of surgical site infections among patients undergoing major joint surgery, though no significant increase in deep infection after joint replacement surgery was found(7). We may change the surgery policy flexibly to adapt it to recent changes in treatment strategy in the era of biologics. 1. Aletaha D, et al. Arthritis and rheumatism. 2010;62(9):2569-81. 2. Felson DT, et al. Arthritis and rheumatism. 2011;63(3):573-86. 3. Smolen JS, et al. Annals of the rheumatic diseases. 2010;69(4): 631-7. 4. Smolen JS, et al. Annals of the rheumatic diseases. 2010; 69(6):964-75. 5. Singh JA, et al. Arthritis care & research. 2012; 64(5):625-39. 6. Momohara S, et al. Annals of the rheumatic diseases. 2010;69(1):312-3. 7. Kawakami K, et al. Rheumatology (Oxford). 2010;49(2):341-7.

International Rheumatology Symposium

IS1-1

Overview of pathogenesis of rheumatoid arthritis

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Rheumatoid arthritis (RA) treatment has been transformed by the advent of biologic therapeutics and by the application of formal strategies to align and enhance the use of such therapeutics. Current unmet clinical needs include the predominance of partial responses to most monotherapies, and the relatively rare occurrence of remission in the context of general treatment. Much work is ongoing to elucidate mechanisms that underlie the emergence of autoimmunity in RA and factors that mediate transition to, and maintain chronicity of synovial inflammation thereafter, representing failure of homeostatic inflammation resolution. Complex interplay exists between 'professional' immune cells and stromal cellular pathways that together contrive to perpetuate, or resolve articular inflammation. In this presentation I shall reflect on recent clinical therapeutic advances and address the key elements of our understanding of disease pathogenesis built on such advances, and in this way address novel potential approaches to therapeutics and pathogenesis discovery.

IS1-2

Genes, environment and adaptive immunity in arthritis

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Rheumatoid arthritis (RA) is a heterogeneous disease, where the major subset is characterized by the presence of autoantibodies to post-translationally modified, i.e. citrullinated proteins, named ACPA:s. This RA subset offers great opportunities to study the initiation and regulation of specific autoimmune reactions that may contribute to a human prototype inflammatory disease. We have further characterized ACPA-positive RA concerning specificity of T and B cell immunity to citrullinated antigens as well as genetic and environmental determinants for the elicitation of the various autoimmune reactions; Specific HLA class II allelic variants that define different structures in the MHC class II binding grooves were associated with different specific B as well as T cell reactivities. Environmental exposures, in particular smoking, was found to induce expression of citrullinated antigens in lungs that may trigger citrulline immunity that subsequently may contribute to joint inflammation and joint destruction. Taken together we have at hand a situation where specific environmental triggers elicit specific MHC class II restricted T and B cell reactivities to post-translationally modified proteins and that such immunity may contribute to a disease phenotype. We have used this situation to initiate studies on presence, activation and differentiation of T cells reactive with specific citrullinated peptides. In vitro activation systems as well as class II tetramer technology was used to identify various subsets of peptide-specific T cells, including Il-17 and IFN-gamma producing T cells as well as cells with T-reg phenotypes. These results will be discussed in the context of disease mechanisms involved in arthritis, including local T-cell driven production of monoclonal human anti-citrulline antibodies that are derived from single synovial B cells.

IS1-3

From Genetics to Functional Insights into Rheumatoid Arthritis

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Conflict of interest: Yes

The etiology of rheumatoid arthritis (RA) is still unknown. Genome-wide association study (GWAS) has been contributed to identify RA associated genes. However, genetic study does not necessarily provide a final conclusion and information from GWAS should be used to understand the functional mechanisms of RA. HLA-DR4 has been reported as the strongest genetic factor in RA. However, the precise mechanism in RA pathogeneses has been unknown. We reported functional haplotypes of PADI4, encoding citrullinating enzyme peptidylargimine deiminase 4, are associated with RA. Our results imply that the RA susceptible PADI4 haplotype increases production of citrullinated peptides acting as auto-antigens. The function of PADI4 in inflammatory arthritis has been studied using knock-out mice. We have also identified a polymorphism in the chemokine receptor CCR6 gene is associated with RA. CCR6 is a surface marker for Th17 cells. The CCR6 susceptible genotype was correlated with the expression level of CCR6 and associated with the presence of IL-17 in the sera of RA patients. These results suggest that CCR6 is critically involved in IL-17-driven autoimmunity in RA. However, the roles of IL-17 producing Th17 have not been firmly established in RA. Auto-reactive $CD4^+$ T cells should play a key role in the break of self-tolerance in RA. We focused on immunoglobulin-binding protein (BiP) as an auto-antigen, and BiP-derived epitopes binding to RA-associated HLA-DR4 molecules. One of BiP peptides induced the strongest proliferation of PBMCs from HLA-DR4-positive RA patients. Strikingly, as much as 0.5% of peripheral $CD4^+$ T cells and 5% of synovial $CD4^+$ T cells were positive for BiP-HLA-DRB1*0405 tetramer in RA patients. These BiP-$tetramer^+$ $CD4^+$ T cells contained higher percentages of IL-17-producing cells and expressed Th17-signature genes. We believe that these findings are filling gaps between genetic studies and functional insights of RA.

IS1-4

T cells in Rheumatoid Arthritis

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The three dominant cell types in RA synovial tissue are T lymphocytes, type A synovial cells (of monocyte/macrophage lineage) and type B synovial cells (fibroblast-like synoviocytes or FLS). We have investigated direct interactions between FLS and T lymphocytes that could be important in the pathogenesis of RA. Immunohistologic studies show that FLS and T cells are indeed in contact within RA synovium. Using FLS lines, we have shown that FLS are potent antigen presenting cells for superantigen recognition by human T lymphocytes. FLS also present peptides from arthritogenic autoantigens (type II collagen and human cartilage glycoprotein 39) to cloned CD4+ hybridomas in antigen-specific and MHC-restricted fashion. Moreover, FLS lines can take up these from synovial fluid, and activate the T cell hybridomas. This suggests a role for FLS in the afferent as well as efferent stages of RA. Co-culture of resting T cells with FLS also activates a pro-inflammatory pattern of gene expression from the FLS. This is optimized when cytokine activated T cells (Tck) are used, which synergize with IL-17 to induce high grade IL-6 and IL-8 secretion by FLS. Tck use membrane anchored TNF expressed on their service to activate the FLS. FLS express B7-H3 that localizes to the contact point between T cells and FLS and delivers a co-activating signal to Tck's. In addition to Tck's, CD4+ subsets, particularly Th17 and Th1 cells, are likely important in the pathogenesis of RA. The analysis of respective contributions of these subsets is complicated by extensive overlap between Th1 and Th17 cells. We have recently shown that Th17 cells induce cytokine production by FLS predominantly through the action of IL-17 itself, while also inducing upregulation of cell interaction surface molecules on FLS through secretion of interferon gamma. The studies described above may be of value in assessing potential new therapeutic targets for the treatment of RA that would focus on FLS/T cell interactions.

IS1-5

Osteoimmunology in RA

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Conflict of interest: None

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. Rheumatoid arthritis (RA) is an autoimmune disease in which activated immune responses causes the severe bone destruction, the studies on which have been the driving force for the field of osteoimmunology. Th1 and Th2 cells inhibit osteoclastic bone resorption through IFN-g and IL-4, respectively. In contrast, Th17 cells which infiltrate into RA synovium produce IL-17 which induces RANKL in synovial fibroblasts and inflammatory cytokines such as TNF-a and IL-1. These cytokines increase RANKL further and stimulate the osteoclast precursor cells, synergistically contributing to the bone destruction. Here I review the history and recent advances of osteoimmunology, which provided molecular basis for understanding the pathogenesis and developing new strategies against RA.

IS2-1

Exploration of Cell Mechano-Sensing and Subsequent Suppression of Inflammation

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Cellular responses to mechanical stresses underlie a number of critical biological functions and phenomena from normal morphogenesis to carcinogenesis, cardiac hypertrophy, wound healing and bone homeostasis. Recent studies indicate that various signaling systems and pathways are involved in mechanotransduction, including tyrosine phosphorylation. However, molecular mechanisms of cell mechano-sensing by which cells sense mechanical stresses and initiate intracellular signaling cascades are poorly understood. To exclude any extraneous molecular interactions, we have developed an in vitro protein extension system that allows us to stretch single molecules and biochemically analyze the stretching effect. Using this, we previously showed that the Src family kinase substrate p130Cas acts as a direct mechano-sensor that converts physical stimulation into a biochemical signal (Sawada et al. *Cell* 2006). We then furthered exploring the roles of p130Cas in the context of mechanical behavior of the cells. We have observed that the rapid exchange of p130Cas molecules at cell-matrix contact sites is a critical element that dynamically links actomyosin contraction to cell migration (Machiyama et al. in submission). In addition, we have found that phosphorylation of p130Cas is essen-

tial for myogenic differentiation (Kawauchi et al. *Biochem J* 2012). We are currently focusing on the anti-inflammatory/aging function of p130Cas that we expect plays significant roles in the maintenance of tissue homeostasis. Our recent findings from this perspective will be presented and discussed with particular reference to sarcopenia, the age-related muscle atrophy. The long-term goal of our research on mechano-sensing is to provide a scientific foundation for 'optimal' exercise or physical therapy to combat age-related disorder/dysfunction of locomotive organs that has been recognized as 'locomotive syndrome'.

IS2-2

Osteocyte network and mechanical stress

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Conflict of interest: None

Osteocytes, which are embedded in the bone matrix, establish an extensive intracellular and extracellular communication system via gap junction-coupled cell processes and canaliculi, through which cell processes pass throughout bone, and the communication system is extended to osteoblasts on the bone surface. The lacunocanalicular network formed by osteocytes is thought to be an ideal mechanosensory system and suitable for mechanotransduction. However, the overall function of the osteocyte network remains to be clarified, since bone resorption is enhanced by osteocyte apoptosis, which is followed by a process of secondary necrosis due to the lack of scavengers. Therefore, we need a mouse model in which the osteocyte network is disrupted but no bone resorption is induced, to evaluate the functions of the osteocyte network. We found that overexpression of *BCL2* in osteoblasts eventually caused osteocyte apoptosis, and the frequency of TUNEL-positive lacunae reached 75% at 4 months of age. However, bone resorption was not enhanced in the transgenic mice, probably due to the reduced number of osteocyte processes and canaliculi. The cortical bone mass increased due to enhanced osteoblast function and suppressed osteoclastogenesis at 4 months of age. In the unloaded condition, the trabecular bone mass decreased due to impaired osteoblast function and enhanced osteoclastogenesis in wild-type mice but not in *BCL*2 transgenic mice at 4 months of age. *Rankl* expression in osteoblasts was increased in wild-type mice but not in *BCL*2 transgenic mice, and Sost was locally induced in wild-type mice but not in *BCL*2 transgenic mice in the unloaded condition. These findings suggest that the osteocyte network negatively regulate bone mass by inhibiting osteoblast function and activating osteoclastogenesis, and these functions are augmented in the unloaded condition at least partly through the upregulation of *Rankl* expression in osteoblasts and that of Sost in osteocytes.

IS2-3

Osteocyte RANKL: new insights into the control of bone remodeling

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Osteoclasts are large multinucleated cells that resorb bone and their differentiation and activity are controlled by other cell types. One of the factors supplied by these other cell types is RANKL, which is a cytokine that is essential for osteoclast differentiation, function, and survival. However, the identity of the cell types that supply RANKL under different physiological and pathophysiological conditions has been uncertain. A large body of evidence obtained from in vitro experiments suggests that cells of the osteoblast lineage are an important source of RANKL. To address this question in vivo, we generated mice harboring a conditional allele for RANKL, designated RANKL-flox mice. We then crossed RANKL-flox mice with mice expressing Cre recombinase under the control of osterix (Osx1-Cre), osteocalcin (OCN-Cre), or dentin matrix protein 1 (DMP1-Cre) gene regulatory elements. Deletion of RANKL using Osx1-Cre or OCN-Cre caused severe osteopetrosis associated with retention of mineralized cartilage in the long bones and spine in 5-week-old mice. Consistent with this, immunohistochemical analysis revealed that both Osx1-Cre and OCN-Cre deleted RANKL from hypertrophic chondrocytes. Deletion of RANKL with DMP1-Cre also increased bone mass at 5 weeks of age, but this was not associated with retention of calcified cartilage. Bone mass continued to increase with age in DMP1-Cre;RANKL-flox mice, relative to DMP1-Cre littermates, so that by 6 mo of age, there was a 30% difference in BMD in the spine, suggesting that osteocytes are an essential source of RANKL during bone remodeling. Consistent with this, RANKL mRNA levels and osteoclast numbers were lower in bones from DMP1-Cre;RANKL-flox mice. These results demonstrate that hypertrophic chondrocytes are an essential source of RANKL during endochondral bone growth and that osteocytes are an essential source of RANKL for bone turnover during adulthood.

IS2-4

Regulation of bone remodeling by osteocytes

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Conflict of interest: None

Bone homeostasis depends on the coordination of osteoclastic bone resorption and osteoblastic bone formation. RANKL induces osteoclastogenesis through activating a transcriptional program mediated by the master transcription factor, NFATc1. Although it is well accepted that the RANKL-NFATc1 pathway is crucially important for osteoclastogenesis, little is known about the major cellular source of RANKL in the bone microenvironment. RANKL has been postulated to be mainly expressed by osteoblasts, bone marrow stromal cells and T cells. However, here we show that osteocytes, the most abundant cell type in bone tissue embedded within the bone matrix, are the critical source of RANKL in bone remodeling. Based on the osteocyte location within the bone matrix and the cellular morphology, it is proposed that osteocytes potentially contribute to the regulation of bone remodeling in response to mechanical and endocrine stimuli. Although the potential importance of osteocytes has been recognized, there has been limited *in vivo* evidence for functional roles of osteocytes in bone metabolism. Using a newly established method for the isolation of high-purity Dmp1-positive osteocytes from bone, we have found that osteocytes express a much higher amount of RANKL and have a much greater capacity to support osteoclastogenesis than osteoblasts and bone marrow stromal cells. The crucial role of RANKL expressed by osteocytes was validated by the severe osteopetrotic phenotype observed in mice lacking RANKL specifically in osteocytes. We provide *in vivo* evidence for the key role of osteocyte-derived RANKL in bone homeostasis, establishing a molecular basis for osteocyte regulation of bone resorption. Recent advance in this field will be discussed.

IS2-5

Unloading-mediated signal transduction in skeletal muscle cells

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Conflict of interest: None

The Cbl-b gene is highly sensitive to mechanical stress (unloading). Therefore, we reasoned that some of the components of the signal transduction pathways which regulate the expression of Cbl-b are likely to be important sensors of mechanical stress. We investigated the transcription factors that regulate Cbl-b expression using rat L6 myoblasts and differentiated myotubes. The biological relevance of Cbl-b expression as a sensor of unloading is strengthened by the finding that both oxidative stress and 3D-clinorotation induced Cbl-b expression in L6 myoblasts and myotubes. These findings suggest that increased levels of ROS link mechanical stress to downstream signaling pathways. In the present study, we observed that H_2O_2 treatment promoted the binding of Egr to the 5'-franking region of Cbl-b gene. Moreover, 3D-clinorotation and H_2O_2 each induced the expression of Cbl-b, in a manner accompanied by the early expression of Egrs 1-3. Consistent with the findings of another laboratory using Egr-2 or Egr-3 knockout mice, our results obtained in Egr knockdown studies (siRNA) confirm that Egr transcription factors play a major role in 3D-clinorotation-mediated Cbl-b induction. Several lines of evidence in diverse cell types point to the involvement of Egr transcription factors in the response to mechanical stress. Egr expression induced by 3D-clinorotation occurs within 90 min of stimulation, indicating that the Egr genes are in close temporal proximity to the mechanical stress "receptor". Consistent with the role of oxidants as the second messengers of Egr activation and downstream unloading responses, the ERK1/2 pathway, a common target of oxidative signaling, was activated by 3D-clinorotation and H_2O_2. Together, these data uncover the molecular mechanism through which mechanical unloading is transduced into biochemical signaling in skeletal muscle.

IS3-1

ACR/EULAR 2010 classification criteria for RA - What has changed after all?

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Starting treatment of rheumatoid arthritis (RA) in most countries and settings requires a prior proper diagnosis. The process of establishing a diagnosis of RA is not trivial, as (like in most other rheumatic diseases) there are no diagnostic criteria available. The common classification criteria are not meant to work best in the individual, but rather on the group level, and have been developed for enrolling patients in studies. Nevertheless, the 2010 classification criteria have improved the early classification of RA, as has been shown in respective validation studies since their publication. They may be used to inform a diagnosis, but clinicians may need to consider overruling their results in the individual if there is a suspicion of false positive or false negative classification. Establishing the diagnosis, however, is only the last stretch of several possible delays of therapy. These delays are partly on the patient side with long lag time before individuals present to their doctors, usually their family doctor. Then again, patients may not be referred to the rheumatologist and might be treated only symptomatically (i.e. without disease modifying treatment) for prolonged periods of time. All these delays can be shortened, and examples for possible approaches are given in the lecture.

IS3-2

ACR/EULAR Definition of Remission in Rheumatoid Arthritis (RA): Significance for clinical trial and daily practice

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In the last 20 years the effectiveness of RA treatment has improved enormously making it possible for many patients to achieve remission. Also, persons with RA in remission have better functional and radiologic outcomes than those not in remission. However, there is no universally used remission definition. In 2009-2011, an ACR/EULAR committee met to define remission. Among the requirements laid out by the committee were that a definition of remission must be stringent, allowing for little if any residual active disease. The definition must predict later good outcome defined as a lack of x-ray damage and stable good function. First, the committee decided that joint counts must be <=1 for remission to be present. We evaluated a large number of candidate definitions of remission including DAS28 definitions. In analyses of trial data, we found that patient reported outcomes should be included in our definition because they discriminated statistically between active and placebo treatments. We also found that patients with DAS28 remission scores (<2.6, < 2.0) often had at least 2 tender or swollen joint counts, suggesting these thresholds were incompatible with remission. Further, DAS28 did not predict later good outcomes as well as our selected definitions of remission. We chose 2 definitions of remission: 1. SDAI $\leq$ 3.3 or 2. a tender and swollen joint count $\leq$ 1, CRP $\leq$ 1mg/dl and patient global assessment $\leq$ 1 (0-10 scale). While developed for trials, subsequent studies have validated the use of these definitions in clinical practice (the SDAI becomes a CDAI $\leq$ 2.8 and for the other definition, CRP is not used). There are unresolved concerns about how the patient global assessment is worded and whether the score is too stringent, Also, whether to include feet and ankle joints,not part of the 28 joint count, is unresolved. Lastly, studies are examining whether ultrasound would identify even better than clinical remission those with a favorable long term disease course.

IS3-3

Clinical and pathogenic significance of anti-citrullinated protein antibodies in RA

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Rheumatoid arthritis (RA) is a chronic, destructive autoimmune disease affecting primarily the joints. With more sophisticated and effective therapies becoming available, early intervention is crucial for preventing irreversible joint damage. Antibodies to citrullinated antigens (ACPA) provide an effective tool to diagnose erosive arthritis in a very early stage of the disease. All strategies in RA clearly show that a window of opportunity exists during which the disease contracts characteristics that make the disease process chronic. I will discuss some treatment strategies in the earliest phases of the disease process (i.e. undifferentiated arthritis), using analyses of the immune response against citrullinated antigens with respect to antigen specificity, isotype usage and affinity maturation. I will also discuss IgE antibodies directed to citrullinated antigens, putatively allowing for anti-IgE mediated therapies in patients harbouring such antibodies. Finally I will show that a new autoantibody system, autoantibodies against carbamylated antigens is relevant in anti-ACPA negative RA patients, possibly allowing a more detailed diagnosis in this subgroup of patients.

IS3-4

Novel multi-biomarkers for estimating disease activity in rheumatoid arthritis

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Conflict of interest: Yes

Disease activity measures have been instrumental in assessing disease activity of RA. Quantitative measurement of RA disease activity is recommended to improve patient outcomes, with greater rates of remission and improved radiographic results and it becomes more important to use disease activity measures that are consistent across patients and practices. We have developed an algorithm to combine the levels of 12 serum RA biomarkers, encompassing diverse biological pathways, to generate a multi-biomarker disease activity (MBDA) score between 1 and 100 assessed with 0.2 mL serum. We have estimated the MBDA score in RA patients treated with biologics. First, we studied the relationship between the MBDA score and disease activity measures including DAS28, SDAI, and CDAI in patients treated with TNF inhibitors including IFX, ETN and ADA in 147 RA patients. The MBDA score significantly and highly correlated with clinical disease activity measures at baseline and the MBDA score tracked response in clinical disease activity in patients treated with different TNF-inhibitors. The changes in the MBDA score significantly correlated with those in the conventional composite measures. Also, an IL-6 inhibitor TCZ efficiently improved the MBDA score and changes in MBDA were correlated with those in conventional measures. Furthermore, the MBDA score reflects disease activity and tracked therapeutic effects and MBDA-remission might be superior to DAS28-remission for predicting good outcome in both radiographic damage and physical function in RA patients treated with TCZ. Ultimately, these studies, along with others addressing the validity of the MBDA score in other RA populations, will be critical to the assessment of the MBDA as a clinically valuable index of RA disease activity. [This is part of a comprehensive program in collaboration with DJ Haney, R Bolce, N Defranoux, D Chernoff, Crescendo Bioscience Inc. CA, USA]

IS3-5

The optimization of the management of rheumatoid arthritis using musculoskeletal ultrasound

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Conflict of interest: Yes

Inflammation in the synovial tissue is the central pathology of rheumatoid arthritis (RA), and therefore, the assessment of synovitis comprises a large part of the evaluation of RA. However, the accuracy of the conventional measures to estimate synovitis is limited, potentially causing under- and over-diagnosis/treatment. Musculoskeletal ultrasound, on the other hand, directly visualizes the synovial tissues and provide information on the presence and the severity of synovial inflammation. Although the 2010 ACR/EULAR criteria refer to a possible use of imaging techniques such as ultrasound “for confirmation of the clinical findings”, validated methodology to translate ultrasound findings into a dichotomous variable for the presence of synovitis has not been reported. We investigated the impact of ultrasound on the 2010 ACR/EULAR RA classification criteria when the joint involvement was determined by using ultrasound. 109 patients with early arthritis underwent musculoskeletal ultrasound and the semi-quantitative scores for gray-scale synovitis and synovial power Doppler (PD) signals were recorded. When the presence of joint swelling and the number of involved joints were determined by ultrasound, the classification of RA was changed in approximately 20 % of the patients. Moreover, the accuracy of the classification to identify the patients who required methotrexate (MTX) treatment within a year improved by ultrasound. We also investigated the advantage of ultrasound over the conventional measures. In 48 RA patients who received either MTX or a biological agent, the change in X-ray score during 24 weeks significantly correlated with the time-integrated total PD score but not with the time-integrated DAS28-CRP. Interestingly, the correlation was more significant in MTX-treated group, while it was not in TNF antagonist-treated group due to minimal radiographic progression despite the presence of comparable synovial PD activity.

Educational Lecture

EL1

Radiographic evaluation and scoring of joint destruction in rheumatoid arthritis

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Conflict of interest: None

Development of therapeutic strategy for rheumatoid arthritis (RA) has changed its target from a pain control to an inhibition of joint destruction and functional disability, followed by improvement of life prognosis, through controlling disease activity. Many tools have been proposed to evaluate joint destruction, including X-ray, ultrasonography, and MRI, and X-ray is the gold standard as a convenient, economical, and repetitive tool. Moreover, X-ray is of increasing significance in association with inhibiting joint damage as current realistic target to treat in RA. Various procedures have been proposed to quantify X-ray of joints. Sharp reported a scoring system of joint erosion (JE) and joint space narrowing (JSN) on both hands and feet, and van der Heijde and Genant modified subject joints and score definition of JE and JSN in Sharp's method. Now, their modified methods go mainstream in clinical trials, in part because of their wide range (maximum of 448 in vdH score and 290 in Genant score) within bone and cartilage, which enable to evaluate the effect of a therapeutic on joint damage quantitatively. In addition, structural remission is defined as ≤ 0.5 in annual progression by vdH score. Globally standardized evaluation has contributed to clarify the effect of biologics on joint damage, which led the inhibition of radiographic progression to be a realistic target to treat. The most important in scoring is to evaluate radiographic changes. It could be possibly acceptable to rump the scores to manifest the gradient. A series of scored progression in each patient is represented on a cumulative probability plot, which comprehensively shows individual results and a proportion with repair or progression. In this educational lecture, practical procedure and pitfalls of van der Heijde's modified total Sharp score will be illustrated, including X-ray filming, reading, and data handling.

EL2

Diagnostic approach on periodic fever and fever of unknown origin in children

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Conflict of interest: None

In children, infectious diseases are frequent and neoplastic disorders such as leukemia, malignant lymphoma, and neuroblastoma are also relatively of high prevalence. Recent progress on the diagnostic imaging as well as identifying infectious agents is now changing the final diagnosis of "fever of unknown origin" and "periodic fever". Such progress highlights a new disease category, "autoinflammatory syndromes" that is caused by genetic disorders of innate immunity regulators as a cause of "fever of unknown origin" and "periodic fever". In this review talk, I will focus on the pediatric "fever of unknown origin" and "periodic fever" in a new era with modern clinical diagnostic procedures, especially on the pediatric autoimmune and rheumatic diseases including the autoinflammatory syndromes.

EL3

Cutaneous manifestation of collagen diseases

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Conflict of interest: Yes

Collagen diseases include many types of cutaneous manifestations such as erythema, photosensitivity, sclerosis, dermatitis, ulcers and so on. In this review, facial erythema will be focused from the viewpoints of diagnosis, pathogenesis and treatment of systemic or cutaneous lupus erythematosus. Facial erythema/ butterfly rash In SLE, cutaneous eruption is observed in 80% of patients and is the presenting sign in 60% of the cases. The most frequent cutaneous sign is an erythematous eruption over the cheeks and nose with a butterfly distribution. Butterfly-type erythematous lesions are not specific for SLE but are found in many diseases including dermatomyositis, discoid LE, atopic dermatitis, contact dermatitis and several viral diseases. Histology and direct immunofluorescence (IF) method are very helpful for differential diagnosis, in which immunoglobulin and/or complement component deposits are frequently observed at derma-epidermal junction of the skin of LE but not others Skin lesions are usually seen over the face. Annular erythema Annular erythema is found in patients with so-cold Ro-lupus group such as subacute cutaneous LE, neonatal LE, and Sjogren syndrome. They are characterized by typical clinical features and the presence of anti-SSA/Ro antibody in the sera. The lesions are scaly papules, which can evolve into either psoriasiform or a polycyclic annular lesion. Direct IF is also useful for Ro-lupus, in which staining pattern is somewhat different from facial erythema/ butterfly rash. Koebner phenomenon Koebner phenomenon is secondary to physical stimuli such as ultraviolet light, exposure to cold or hot, scratching etc. This is very important to prevent the exacerbation. Treatment Tacrolimus ointment, dapsone and hydroxychloroquine are dermatological ways. These treatments will be introduced.

EL4

Osteoporosis Treatment Update

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Conflict of interest: None

Osteoarthritis (OA) is characterized by cartilage degeneration and osteophyte formation in joints. Despite its high prevalence and social needs, there is no disease-modifying treatment for this disorder. This is because the therapeutic target is undetected, and this is because the molecular backgrounds remain unclear. Considering that most of risk factors approved so far are related to accumulated mechanical stress on joint, we believe that elucidating the signaling lying downstream of the mechanical stress will disclose the molecular backgrounds of OA. To realize it, several experimental OA models in mice by producing instability in the knee joints have been developed to apply approaches from mouse genetics. Although the mouse genetics studies revealed that proteinases like MMP-13 and ADAMTS-5 are the principal initiators of OA progression, clinical trials of the proteinase inhibitors have to date been unsuccessful for the treatment, turning the interest of researchers to the upstream signals of proteinase induction. These signals include endochondral ossification signals such as Runx2, C/EBPβ, carminerin, osteoprotegerin, β-catenin, syndecan-4, hedgehog, etc. Among them, HIF-2α (encoded by *EPAS1*) is an extensive transactivator during the entire endochondral ossification process in mice and humans. The proteinases produced during this process 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 at the embryonic and growth plate cartilage. 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 like HIF-2α might become therapeutic targets altering the course of this disabling disease.

EL5

New Japanese 2011 guidelines for prevention and treatment of osteoporosis

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Conflict of interest: Yes

In 1998, the first Japanese practice guidelines on osteoporosis was published. It has been updated several times, with the most recent being the full-scale 2011 edition and its abridged edition. The present guidelines provide information for the managements of primary osteoporosis in postmenopausal women and men over 50 years old, a summary of the evidence for the treatment of secondary osteoporosis, and a summary of the evidence for the prevention of osteoporosis in younger people. One of the key changes is revision of the criteria for initiation of pharmacological treatment, along with an introduction of the fracture risk factors used in FRAX®. The risk factors for fracture include low BMD, factors that contribute to a decrease in BMD, and deterioration of bone matrix, including lifestyle-related diseases. A prevalent fragility fracture is the most important among all these factors with the exception of low BMD. Family history of proximal femoral fractures significantly increases the fracture risk even in persons without a fragility fracture who have a "low bone mass" based on their BMD. These Guidelines detail the effect of each therapeutic agent used in Japan on BMD and the risk of vertebral fracture, non-vertebral fracture, and proximal femoral fracture, based on evidence from Japan and abroad. Each recommendation is also graded. In regard to some therapeutic agents, the effect on QOL is also described. For the selection of therapeutic agents, the full range of drug-related information must be considered: the efficacy of each medicine on BMD, fracture risk, QOL including pain, bone metabolic markers, risk of fall, as well as safety, including effects other than those on bone metabolism *per se* and adverse effects.

EL6

Adaptation and use of non-biological DMARDs

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Conflict of interest: Yes

The primary target for treatment of rheumatoid arthritis (RA) should be a state of clinical remission. The definition of remission proposed by ACR/EULAR is a strict standard compared with DAS28, which have been used frequently. It has been suggested that early diagnosis and tight control are useful concept of the treatment of RA. To achieve this goal, biological DMARDs including TNF inhibitors are used at early stage of RA. However a clinical algorithm for the use of biological DMARDs in RA is ineligible for all patients due to barriers to care including cost and side effects such as infection. Early RA patients with low disease activity and a few poor prognostic factors have a possibility to achieve a remission with the use of non-biological DMARDs. Non-biological DMARDs are useful drugs for maintenance of remission and enhancement of efficacy of biological DMARD. Thus rheumatologist should know the efficacy and side effects of each non-biological DMARDs including methotrexate (MTX) in the detail and perform the safety use of them. MTX is an anchor and more effective drug compared with other non-biological DMARDs and is necessary for the use of anti-TNF-α antibodies. Recently, we can increase the dose of MTX to 16mg/wk. in Japan and its usefulness increases. It is important how we increase the dose of MTX and judge the effect, and how we monitor side effects and deal with them. In addition, we have many other non-biological DMARDs as well as MTX in Japan and can apply them to combination therapy of non-biological DMARDs for tight control and patients with difficulty of the use of MTX. The selection of these drugs does not have the standard strategy. After all it is the most important to choose considering a characteristic of various DMARDs, and the knowledge is required while grasping the state of the patient. We present the combination therapy of DMARDs and appropriate clinical application based on a characteristic of various non-biologic DMARDs.

EL7

The overview of lymphocyte subsets for rheumatologists

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Conflict of interest: None

Common lymphoid progenitors develop to B and T cells, as well as to innate lymphoid cells (ILCs) discovered in the late 1990s. These cells contain several subsets to exhibit the different functions and each subset is linked to a unique transcription factor such as T-bet, Foxp3 or RORgt. ICs including natural killer cells, lymphoid tissue inducer cells and ILC2 reflect many functions of T helper (Th) cells. Recent advances in the study of $CD4^+$ Th cells clarified new subsets such as Th17 cells, regulatory T (Treg) cells and follicular helper T (Tfh) cells. The development and functions of these cells will be summarized in this lecture.

EL8

Pathophysiology and treatment of pulmonary hypertension in patients and model animals

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Conflict of interest: None

Three target pathways are considered to be important for the treatment of pulmonary arterial hypertension : endothlin (an endothlium-derined potent vasoconstrictor), NO(an endothlium-derined vasodilator), prostacyclin (PGI_2) pathways. Endothelin-1 acts via activation of two receptor subtypes, ET-A and ET-B receptors, both of which are coupled to various GTP-binding proteins depending on cell types. The development of ET-A and/or ET-B receptor antagonists as well as gene-manipulated animals greatly accelerated elucidation of physiological and/or pathophysiological roles of endogenous endothelin-1. When the production and release of endothelin-1 are increased, endothelin-1 contributes to the pathogenesis of, and stimulates the progression of various cardiovascular diseases. Pulmonary hypertension (PH) is associated with the increase in plasma endothelin-1 levels, which is strongly correlated with the severity of the disease. The endothelin receptor antagonists are remarkably efficacious in all animal models thus far investigated. Bosentan (ET-A a nd ET-B receptor dual antagonist) and ambrisentan (ET-A specific receptor antagonist) are now available for clinical treatment of PH. In atherosclerosis is as well as various kinds of vascular remodeling, endothelin-1 plays causing or progressing

roles in the diseases. From the early stages, the combined treatment with endothelin receptor antagonist, PDE-III inhibitor, PGI_2 (or its analogue) is considered to be more effective in improving survival of the patients with pulmonary hypertension.

EL9

MR imaging of rheumatic disorders

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Conflict of interest: None

Among many imaging technique used for rheumatic disorders, MR imaging (MRI) is unique, since it can visualize a joint as an organ. Application of MR imaging for rheumatic disorders started for evaluation of atlantoaxial subluxation in RA and for early diagnosis of osteonecrosis in SLE. Then, MRI was used for early diagnosis and quantification of inflammatory synovial volume in RA. After introduction of biologics, MRI has become used for early diagnosis, prognostication, and outcome measures of RA and spondyloarthropathy (SpA). In RA, MR findings can be a surrogate marker for physical examination. MR findings such as active synovitis, MR bone erosion, and bone marrow edema can be used to predict prognosis in RA. In this context, OMERACT RAMRIS has been developed. In SpA, MRI can demonstrate osteitis and enthesitis before classic radiologic findings become obvious. A new diagnostic criterion including MR findings has been proposed for early diagnosis of SpA by Assessment of SpondyloArthritis international Society. Although MR findings are not specific, it is used to determine an appropriate site for biopsy in dermatomyositis (DM) and polymyositis (PM). MRI also is utilized to investigate pathophysiology in the development of myopathy in these disorders. Osteoarthritis is a disease of whole joint. MRI is one of the most promising biomarker for its diagnosis and assessment of treatment outcome. Several MRI-image based compositional methods have been developed. For example, delayed, gadolinium-enhanced MRI can quantitate content of proteoglycan in the degenerated hyaline cartilage. Whole body MRI can be applied for complete assessment of arthritis and myositis in rheumatic disorders such as SpA and DM/PM. To the contrary, detailed images of small joints can be obtained by microscopic coil. MRI has opened a new window to see musculoskeletal manifestation of rheumatic disorders. In this session, applications of MRI for a wide variety of rheumatic disorders will be presented.

EL10

A collaboration with medical specialists in patient safety

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Conflict of interest: None

It is estimated that as many as forty thousand patients die every year due to medical harm, in Japan. We have to realize that medical harms might be occurred during medical practices. Multisectoral collaborations and early interventions are required to resolve medical problems so that we need to make good relationships with each other, especially in large general hospitals. In 2004, many problems regarding patient safety were surfaced as a result of a fatal accident which occurred by an overdose administration of Methotrexate in a national university hospital. Some important problems were pointed out in the accident analysis report. In that report, the analysis committee noted that this case was not reported to patient safety division immediately after the accident and a treatment-delay might be happened accordingly. Thus, team management skills like reporting, collaborating, communication are the essential components of patient safety as well as technical skills. Recently, these skills are called as "non-technical skills" which have become the cornerstone of the medical practices. In this session, I will introduce the hidden risk of medical practices and the idea of "non-technical skills" by explaining my experiences as a risk manager in a university hospital.

EL11

An update of treatment for SLE and lupus nephritis

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Conflict of interest: Yes

SLE is a chronic inflammatory disorder caused by autoimmune mechanisms which affects various organs including skin, joints, kidney and central nervous systems (CNS). SLE involving vital organs is often fatal and their dysfunction is associated with poor mortality and morbidity. Therapeutic strategy for severe/active SLE is composed of induction phase using aggressive immunosuppressive agents followed by maintenance phase to prevent relapses with minimum side effects. Steroid is still indispensable for both phases. Other immunosuppressants, including cyclophosphamide, azathioprine, mycophenolate mofetil, mizoribine, tacrolimus and cyclosporine A, are used in combination with steroids. As a result, 10-year survival has been markedly improved up to more than 90%. However, it is now important to control infection, bone diseases and cardiovascular events. These complications are related with steroid use or other immunosuppressants, and new therapeutic options with more favorable adverse effects are awaited. Through the progress in understanding pathophysiology of SLE, biological agents which target molecules regulating immune system have been developed. Belimumab is a successful example, which inhibits B cell cytokine BLyS and has received FDA approval for SLE in 2011. However, efficacy of belimumab appears marginal in the results of international phase-III trials. Moreover, patients with lupus nephritis or CNS lupus were not enrolled in these trials. Clinical trials on rituximab or abatacept have failed to achieve primary endpoints. Disease heterogeneity and a lack of unequivocal endpoints were thought to be obstacles in establishing efficacy of candidate drugs for SLE. Since 2000, there have been reported a number of clinical trials on lupus nephritis. Based on these results, guidelines for the treatment of lupus nephritis have been proposed. In this lecture, I will present our data on lupus nephritis and summarize recent progress in the treatment of SLE.

EL12

The best use of biologic anti-rheumatic agents in patients with rheumatoid arthritis- To select the right patients, the right agents, and the right time –

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Conflict of interest: Yes

The treatment of rheumatoid arthritis (RA) has made remarkable improvement. Diagnostic procedure is revised by the 2010 classification criteria for RA proposed by the American College of Rheumatology and the European League Against Rheumatism. The most important aim of the new criteria is to pick up the right patients who should start anti-rheumatic treatments immediately. The treatment strategy has been standardized to achieve the best outcome ('T2T strategy') in patients with RA as well as other chronic diseases (e.g., diabetes mellitus, hyperlipidemia, and hypertension). The aim of RA treatment is to achieve a clinical remission or low disease activity and their clinical definitions have been

established. Tight control to achieve and maintain remission is strongly recommended for all RA patients in clinical practice. The biologic anti-rheumatic agents (biologics) are the key drugs to treat RA to target. The majority of RA patients with inadequate response by non-biologic anti-rheumatic agents can achieve clinical goals by using biologics. The most important effects of biologics on RA are minimizing a bone erosion, and some cases could achieve drug free-remission ('cure') or autoantibody-free remission. TNF inhibitors include antibody (infliximab, adalimumab, and golimumab) and receptor (etanercept) agents, which have some different characteristics each other but are preferably used concomitant with methotrexate (MTX). Whereas the IL-6 receptor antagonist (tocilizumab) and CD80/86 inhibitor (abatacept) may have enough clinical effects on RA without MTX, the different therapeutic modification between both agents is shown. Six biologics can be used in clinical practice now and an additional biologic agent (certolizumab pegol) is going on market. We, rheumatologists, have some difficulties in selecting the right agents for RA patient. The best use of biologics in real world will be discussed for more effective treatment in patients with RA.

EL13

The utility of musculoskeletal ultrasound in the diagnosis and the monitoring of disease activity in rheumatoid arthritis

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Conflict of interest: Yes

The 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 ultrasound was shown to visualize both synovitis and bone lesions. This caused a paradigm shift in the imaging for RA as the strategy to directly assess the activity of synovitis was impossible with plain radiograph. In the diagnosis of RA, ultrasound is more accurate than patients' symptoms or joint examination to determine 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 such as DAS, SDAI, and CDAI, are not necessarily accurate due to the wide variability of joint examination, the influence by non-inflammatory pain, or the inflammatory response from other causes. It is especially difficult to evaluate synovitis activity in atypical cases, at lower levels of disease activity, or under corticosteroid use. Ultrasound, on the other hand, can visualize the activity of synovitis by means of the Doppler signals and more accurately predict joint damage progression. Utilizing ultrasound in monitoring disease activity in difficult cases or for difficult joints can improve the clinical outcome of RA.

EL14

Diagnosis and treatment for rheumatoid knees

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Conflict of interest: None

Rheumatoid arthritis (RA) is a systemic disease and often affects women with around 30 years of age. Typical rheumatoid patients initially show symmetrical joint swelling and pain in their small joints of fingers or wrist. RA also affects large joints including elbows or knees and the incidence of knee involvement is seemed to be relatively high, reaching to more than 50 %. When RA or anti-CCP and CRP are positive, diagnosis may be easily made. However, elderly-onset RA with mono-arthritis shows established osteoarthritis changes in the joints and on occasion it may make a precise diagnosis more difficult. Suppurative arthritis or some of degenerative knee disorders including crystal-induced arthritis, osteonecrosis of the knee and so on are listed as different diagnosis for RA knees because main lesion of these diseases is synovium and shows continuous knee joint swelling. Characteristic feature of osteonecrosis of the knee is sudden onset of pain which is aggravated by physical activities. Therefore, it may be important to understand the pathogenesis and the clinical features. Rheumatoid knees are basically treated with drug therapeutics and surgical treatments are indicated in cases without good response to medical treatments. Total knee joint replacements (TKA) are well recognized as most reliable surgical treatment for RA knees because of recent improvement of surgical techniques and design and materials of TKA and provide long-term good functional outcomes for RA patients. En bloc capsule-synovectomy additional to TKA is also known to reduce systemic disease activity of RA. After recent introduction of biological drugs, it has been noticed that the biologics remarkably suppress disease activity and some of the patients have achieved complete remission. Accordingly, joint preserving surgical treatments such as synovectomy have attracted more considerable attention for surgical treatment of RA knees.

EL15

Update and furture perspective of total hip arthroplasty

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Conflict of interest: Yes

Since the success of Charnley at 50 years ago, total hip arthroplasty (THA) has become popular as a treatment to improve the symptoms dramatically. It should be noted the survival rate of the initial Charnley THA were 94% at 10 years 50% at 30 years for the revision as the endpoint. Therefore, the survival rate of anew THA must exceed this figure.We have learned that only minor changes in an implant may dramatically change its performance and even small changes in the surgical technique may affect the long-term results. Because the short to medium term results have been improved as a whole, the number of operations of THA is rapidly increased. Although the number of revision will decrease if the survival of the primary THA is really improved, the actual number of revision still increased. A decrease of revision burden should be achieved in the near future. Many surgeons or companies have continued to make a lot of effort in order to improve performance and it is important to analyze the details of individual implants. Because the number of cases and the follow-up periods cannot be sufficient by the efforts of individual orthopedic surgeon, there is a limit to compare the performance of many implants by these surveys. Arthroplasty register system has been developed in many countries to solve this problem and become a useful tool for evaluating the outcomes of interventions and the materials used in arthroplasties, and to provide rapid feedback to practitioners and patients about any failure of THA, such as large head metal on metal implants. It is necessary for safety introduce of a new model that careful pilot study and feedback of the results of registry is required. As the outlook for the future, it will be necessary to continue these steady efforts, including the development of surgical training of the operator and medical care system in order to

achieve further improvement of the overall outcome of THAs.

EL16

Rehabilitation for the patients with rheumatoid arthritis

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Conflict of interest: Yes

Protraction of RA induces the disorders of joint function such as contractures and deformities causing the deterioration of the activities of daily living (ADL), which yields the change of a role in the home and the limitation of social participations. As there is not a curative treatment of RA, once functional disorders have developed, it cannot be recovered completely and a plural number of disorders make functional disabilities worse. In such case, it is difficult to restore the ambulation as far as secondary obstacles remain, even if the anti-rheumatic drugs are quite effective. AS a change of joint damage and functional disorder by RA, it is recently reported that disorder progresses from a disease onset rapidly within a few years. Therefore, it is proposed that adequate administration of methotrexate as an anchor drugs should be started initially and treatment of RA should be done based on the recommendations named as Treat to Target (T2T). Rehabilitation for RA patients includes the various kinds of exercises and approaches such as the physical therapy in early stage and the nursing home service with caregiver insurance in terminal stage of RA. In terms of the principles of T2T, aim of the treatment of RA is to let the patients improve their long-term QOL as much as possible during their lifetime through the restoration of body functions and the participation to social activities. Also, the decision making of treatment should be done under the consideration of the structural damage of the joints and the disabilities in ADL in addition to the evaluation of disease activities. Aim of the rehabilitation is completely same as that of T2T because it is to let the people with disabilities live as usual humankind by diminishing the difficulties in daily life and improve their conditions of QOL. It is therefore very important for rheumatologists to keep it in mind that RA is a people with difficulties to daily living and not just one with disease.

EL17

Neuropsychiatric signs and symptoms of collagen disease

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Conflict of interest: None

There are a number of neuropsychiatric conditions associated with collagen diseases. Their diagnosis is essential for rheumatologists. Collagen diseases may directly involve nervous system, such as in cases with SLE, polyarteritis nodosa and Hashimoto's thyroiditis. Neuropsychiatric diseases such as NMO, with elevated titers of anti-AQP4 antibodies, may co-exist with Sjogren disease. CNS symtoms of SLE may include psychiatric symptoms almost indistingushable from schizophernia or intractable epilepsy. This lecture will focus on diagnosis and management of such conditions with illustrative cases. New developments in the understanding of neurodegenerative diseases such as ALS or Alzheimer disease in the light of neuroinflammation similar to rheumatoid arthritis will also be covered.

EL18

Usefulness of Immunosuppressant therapy for connective tissue diseases

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Conflict of interest: Yes

Prognosis of connective tissue disease including systemic lupus erythematosus (SLE) and rheumatoid arthritis (RA) has markedly improved because of the recent progress of the diagnostic technology and the development of new therapy. Especially, an introduction of the active usage of immunosuppressant and the development of the new type of immunosuppressant have made a great contribution to achieve this issue. Although the prognosis of angitis such as Wegener granulomatosis and lupus nephritis has been improved by the usage of cyclophosphamide including its pulse therapy, clinical features such as type IV lupus nephritis, CNS lupus, and acute progressive interstitial pneumonitis in amyopathic type dermatomyositis are still remaining as intractable organ involvements. In addition, adverse reactions are also serious problems among the patients with connective tissue diseases treated with the immunosuppressant. On the other hand, the therapy for RA has been dramatically changed using biologic agents, and the aim of treatment becomes the induction of remission. But the biologic agents are not always available for RA patients because of their high costs and their adverse reactions. Therefore, it is needed to develop a new type of immunosuppressant which is targeting the particular molecule associated with immune disorders in connective tissue diseases, and a new approach to use the drugs. In this session, we will discuss about the usefulness of immunosuppressant therapy for connective tissue diseases based on the problems as mentioned above.

EL19

Management strategies of pain in rheumatoid arthritis

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Conflict of interest: None

Rheumatoid arthritis (RA) is often associated with pain affecting functionary. Disease-modifying antirheumatic drugs (DMARDs) and anti-inflammatory treatments may influence pain only to a certain degree, and additional pain treatment may be required. Interventional pain treatment and the use of opioids in musculoskeletal disease has been established in some areas. Although there are no controlled trials available, it is mostly accepted that opioids control pain from RA and they are being increasingly used. Many RA patients continue to experience pain despote their current treatment with nonopioid analgesics. The use of strong opioids has always been controversial, although increasingly more clinicians feel that opioids are well tolerated and effective and should be made available when nonopioids have failed to control pain. The conditions under consideration clinically fall into two mechanisms, inflammaion and other, the latter taken to include mechanical and neuropathic. A neuropathic mechanism should be considered where there are no signs of nociceptive pathology, specifically inflammation, but where there is allodynia or hyperalgesia to mechanical stimuli. The need for improved pain control in RA is heightened by the insidious and chronic nature of this disease. It is recommended that all clinicians regularly monitor pain levels in their patients and the use strong opioids and the interventional

methods as a further step in the treatment of pain from RA.

EL20

Autoantibodies - from basic aspects to clinical significance -

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Conflict of interest: None

Autoantibodies to various cellular components are the hallmarks of systemic autoimmune diseases. The development of new technologies for detecting autoantibodies has been able to identify more than 100 of autoantibodies and their target antigens. Such autoantigens have been clarified as intracellular enzymes and regulatory factors involving in gene replication, transcription, RNA processing and protein synthesis. Thus, the studies of autoantibodies are useful not only in clinical medicine but also in basic cellular and molecular biology. Moreover, the measurement of autoantibodies has a number of clinical usefulness, such as markers of diagnosis, disease subsets, disease activity and prognosis. Recently, several new autoantibodies are especially noteworthy. In rheumatoid arthritis (RA), anti-citrullinated protein autoantibodies (ACPA) show high disease specificity and reasonable sensitivity. ACPA may not only be useful as a new serological marker of early diagnosis and radiologic progression but also be involved in pathophysiology of RA. In polymyositis and dermatomyositis (PM/DM), autoantibodies correlate to specific subsets and clinical features. In particular, anti-aminoacyl tRNA synthetases antibodies are important to diagnose and manage myositis patients since they are closely associated with a common clinical manifestation called as “anti-synthetase syndrome” (myositis, interstitial lung disease (ILD), polyarthritis and mechanic’s hand). Recently, a novel autoantibody, termed anti-CADM-140, was found. This antibody is closely associated with clinically amyopathic DM with rapid progress ILD. The target antigen of anti-CADM-140 has been identified as IFIH1/MDA5 that is a cytoplasmic receptor of single-strand viral RNA. It is especially interested because some patients with PM/DM show preceding viral infection and such infection may be thought to cause production of autoantibodies and development of myositis.

EL21

Cytokines and it’s signaling

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Conflict of interest: None

Cytokines regulates many physiological responses and homeostasis; they influence the survival, proliferation, differentiation and functional activity of cells of the immune system, as well as of most other organ systems. Cytokine can activate a number of signal transduction pathways leading to regulation of a wide array of biological activities. One of these pathways, the Jak-Stat pathway, activates JAK kinases (JAK1, JAK2, JAK3 and Tyk2) associated with their cognate receptors. The activated JAKs phosphorylate the receptor cytoplasmic domains which creates docking sites for SH2-containing signaling proteins. One of these substrates of tyrosine phosphorylation is members of the signal transducers and activators of the transcription (STAT) family of proteins. The suppressors of cytokine signaling (SOCS) and cytokine-inducible SH2 protein (CIS) are a family of intracellular proteins, several of which have been shown to regulate the responses of immune cells to cytokines. Apparently, the discovery of the SOCS proteins has defined an important mechanism for the negative regulation of the cytokine-JAK–STAT pathway. In this session, I briefly over-reviewed a role of cytokines, the Jak-Stat pathway and negative regulation of SOCS in the T cell mediated immune responses.

EL22

Medical cooperation in treatment of rheumatoid arthritis

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Conflict of interest: None

Introduction. The treatment of rheumatoid arthritis varies dramatically. As it is a time to master even biologics and wide variety of drug treatment is possible even in the clinic, various complication may develop. In this presentation, I introduce the way how to prevent the various infections and how to cooperate with other medical facilities. Prevention efforts of infections in my clinic: I have created five bullets what symptoms should contact immediately, and what sign is dangerous as follows: 1) stifling, 2) fever over 38 °C, 3) frequent urination, back pain, chill, 4) strong abdominal pain, 5) not maintained consciousness. Eight items were distributed to all out patients which showed guidance to be a doctor within a few days. Specific guidance of the prevention of infection: Infection is a complication that cannot be avoided in treatment as the fate of BIO. As infection is indispensable, clear lifestyle must be taken as much as possible. I presented the nine items of cleanliness habits and nine items of infection prevention in the family. And also, I recommend actively influenza vaccination and pneumococcal vaccine. The practical medical cooperation for the treatment of rheumatic disease and complication. In fields of practical lesion related to rheumatoid disease, there are two cases of sudden change in life-threatening and the phenomenon caused by the disease itself. As the most important occasion that requires cooperation, there is a respiratory infection. Therefore, I am committed to building a partnership with respiratory physician from always. Especially, as the respiratory complication always need to urgent admission, I am trying to ask directory to hospital doctor. **Conclusion.** The therapy of RA become to complex and various complications are often occurred unanticipated. In this presentation, I introduce how to treat these incidental events in a clinic.

EL23

Early diagnosis and treatment of adverse drug reactions in patients given biologics

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Conflict of interest: Yes

Early diagnosis and treatment of adverse drug reactions in patients given biologics Treatment with biologics has significantly improved outcomes of patients with rheumatic diseases, but is sometimes hampered by their adverse drug reactions (ADRs). To harness biologics and provide best outcomes to patients with rheumatic diseases, proper risk management in clinical practice is mandatory. In Japan, all-patient postmarketing surveillance (PMS) programs were implemented for infliximab (n=5,000), etanercept (n=13,894), adalimumab (n=7,780), and tocilizumab (n=7,901), and the results from these studies revealed incidence and detailed characteristics of ADRs of these biologics. Among serious ADRs, infections and infestations, and respiratory, thoracic and mediastinal disorders showed high incidence rates. Malignancy, autoimmune disorders, and gastrointestinal perforations were rare, but should be paid special interest. Regarding drug retention rates of biologics, a longer observation period than that of all-patient PMS

is appropriate. Using the data from the Registry of Japanese Rheumatoid Arthritis Patients for Long-term Safety (REAL), we identified that ADR and insufficient effectiveness were major reasons to discontinue biologics in ~40% of patients for each. One third of these ADR were infections. These data indicate that management of infection is most important in patients given biologics. It has become an international consensus that risk for infection increases during the first 6 or 12months of the treatment and returns toward baseline after that period. Therefore, systematic screening before initiating biologics and careful monitoring during the first year are the keys to successful treatment with biologics. In this educational lecture, I would like to focus on infection, respiratory disorders, and malignancy during the treatment with biologics and discuss recent evidence about these ADRs, and early diagnosis and treatment.

EL24

Early diagnosis and personalized medicine in systemic sclerosis (SSc)

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Conflict of interest: Yes

SSc is a multisystem disease characterized by excessive fibrosis, microvasculopathy, and production of autoantibodies. Survival has been improved in past 20 years due to introduction of effective supportive therapies, such as ACE inhibitors for renal crisis and epoprostenol for pulmonary arterial hypertension. However, there is no treatment regimen that has been proved to modify natural course of the disease. This is due to lack of appropriate clinical trial design, highly heterogeneous clinical presentation among patients, and difficulty of discriminating a physiologic would-healing process from mechanisms for pathogenic fibrosis. Nevertheless, under these circumstances, we have to provide the best medical care to patients in clinics. For this purpose, subgrouping of SSc patients into several distinct disease subsets based on future organ involvement and prognosis is critical for deciding suitable treatment regimens. For example, in patients with diffuse cutaneous SSc (dcSSc), we should provide different treatment strategies according to disease duration, including very early edematous phase, early progressive sclerotic phase, and late atrophic phase. Especially, immediate introduction of treatment and the treat-to-target strategy are critical in patients with early dcSSc. In contrast, patients with late dcSSc usually require supportive therapies alone, like those with limited cutaneous SSc without progressive interstitial lung disease. Recently, preliminary criteria for early diagnosis of SSc have been proposed to encourage early intervention because SSc organ involvement is often irreversible once established. Patients with Raynaud's phenomenon without apparent skin sclerosis can be classified as having early SSc, if they have nailfold capillaroscopic findings typical of SSc or SSc-specific autoantibodies. Vasodilators such as calcium channel blockers may be used to treat patients with early SSc, but clinical trials are still underway.

EL25

Behcet's disease: progress in diagnosis and treatment

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Conflict of interest: None

Behcet's disease (BD) is characterized by recurrent aphthous stomatitis, uveitis, genital ulcers, and skin lesions. One of the most serious manifestations in BD is sight-threatening uveitis. Infliximab has been shown to be effective in suppressing the occurrence of uveitis attacks, and to have favorable implications for the visual prognosis. Another difficult manifestations of BD include vasculo-Behcet, neuro-Behcet [NB] and intestinal-Behcet. The use of infliximab for vasculo-Behcet is still controversial, since some reports suggest the thrombogenicity of infliximab. NB consists of acute and chronic progressive types, for which Japanese diagnostic criteria have been recently proposed. Attacks of acute NB are sometimes self-limiting. However, when the neurological manifestations are progressive and severe, administration of corticosteroid is necessary. No drugs have been demonstrated to be effective in preventing the occurrence of attacks of acute NB, although colchicine, low dose of steroids and various immunosuppressive drugs have been used anecdotally for this purpose. Some case reports suggest the efficacy of infliximab in preventing the recurrence of attacks, although controlled trials are required for confirmation. Chronic progressive NB is characterized by intractable, slowly progressive dementia and ataxia, with persistent marked elevation of cerebrospinal fluid (CSF) IL-6. Chronic progressive NB is resistant to corticosteroid, cyclophosphamide, or azathioprine, whereas low-dose weekly methotrexate has been shown to be effective. Recent studies have disclosed that infliximab inhibits the progression of neurological manifestations by decreasing CSF IL-6 in chronic progressive NB. As to intestinal-Behcet, there are increasing case reports, suggesting the efficacy of infliximab. However, further studies are necessary to confirm its efficacy with a larger numbers of patients.

EL26

Application of Regenerative Medicine to Musculoskeletal Diseases

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Conflict of interest: None

A new therapeutic trial to promote the natural healing potential of body itself for the natural induction of tissues regeneration and repairing, has been recently expected. The healing potential is based on the inherent ability of cell proliferation and differentiation. To realize this regenerative therapy, there are two practical approaches; cell therapy and tissue engineering. The tissue engineering is a biomaterial technology to artificially create a local environment which can enhance the cell ability for tissue regeneration. Various biomaterials are being used as the cell scaffold and delivery carrier of growth factors and drugs. If a key growth factor is supplied to the right place at the right time period and concentration, it is no doubt that the body system will initiate to physiologically function, resulting in the cell-based natural induction of tissue regeneration. One practically possible way to enhance the in vivo therapeutic efficacy of growth factor with in vivo short half-life period is to make use of drug delivery system (DDS) technology. We have designed biodegradable hydrogels for the controlled release of growth factors and succeeded in the growth factor-induced regeneration and repairing of various tissues. Some tissue regeneration trials with biomaterials have been clinically started to demonstrate the good therapeutic efficacy. The release system can be combined with cells or/and the cell scaffold to promote the therapeutic efficacy of tissue regeneration. In addition, the biomaterial technology is applicable to regenerative researches (the basic research of stem cells and drug discovery) which can scientifically support the regenerative therapy of next generation. In this paper, several concrete results on promoted regeneration of various tissues by the cell scaffold and DDS technologies and the regenerative researches are presented to emphasize significance of biomaterial-induced tissue engineering to realize regenerative medicine.

Meet the Expert

MTE1

The Most Appropriate Surgical Intervention for Patients with Rheumatoid Arthritis in the Era of Biologics

Jun Hashimoto, Shosuke Akita, Hideki Tsuboi, Makoto Hirao, Shiro Ohshima, Yukihiko Saeki
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Conflict of interest: Yes

The most appropriate surgical intervention keeps in step with the times. It could be changed under the influences of improvement both in the each surgical procedure and treatment other than surgery, change in the therapeutic goal of patients with disease, and variation of socioeconomic program. In the last decades, the procedures, materials, and designs in joint replacement surgery and in instrument for arthroscopic surgery have greatly improved. These advances in implant and surgical procedures have the potential for the further improved functional status of patients with rheumatoid arthritis (RA). On the other hand, the advent of biologics has revolutionized the management of RA and put new strategies for remission into practice. It also bestows several benefits on the patients with late phase RA of advanced joint disability. The reduced disease activity could decrease the fragility in bone and soft tissue resulted in easy procedure and handling in delicate surgery, and improve the preoperative anemia. The remission of RA also could provide the patients with the motivation for further functional or cosmetic recovery and for the better quality of life. Therefore, the advent of biologics also leads changes in the surgical treatment and indication of RA. However, notwithstanding these advances, disease control is still inadequate in many patients with RA. This situation requires the skill of varied surgical intervention, and pharmacotherapeutic skill succeeding in sustained control of RA activity. It means that speciality required for the rheumatologist and surgeons is enhanced. So, surgical treatment of patients with RA in Era of biologics need coordinated management by rheumatologists, surgical specialists, nurse and therapists working in a multidisciplinary team, and it must be continuously sophisticated since differences of opinion within the team may adversely affect patient care.

MTE2

Management of Liver Damages

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Conflict of interest: Yes

There are many mechanisms causing liver damages experienced in the clinical settings of the rheumatic diseases. The most common one is drug-induced liver damage. Methotrexate causes elevation of hepatic transaminase occasionally, which may be recovered by administration of folic acid. Liver damage is seen in some rheumatic conditions, like systemic lupus erythematosus and adult Still's disease. Liver damage may also be seen in the systemic viral infections, including 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. Covalentry closed circular DNA of HBV stays long in hepatic cells without massive proliferation, however, the balance between viral proliferation and immunological function attenuates after the immunosuppression and HBV proliferates (HBV reactivation). After finishing the immunosuppression, immunological competency attacks infected liver cells causing hepatitis (de novo hepatitis). Because this type of hepatitis may cause fatal fulminant hepatitis, it is the most important to screen the potentially risky patients before immunosuppression. Prophylaxis administration of entecavir may be necessary for the patients who show HBs Ab-positive and/or HBc Ab-positive. In this session, the management of liver damages in rheumatic diseases will be discussed with the audience.

MTE3

The proper use of MTX

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Conflict of interest: Yes

In 1990s, our protocol of methotrexate (MTX) use for patients with rheumatoid arthritis (RA) had been as follows: initiating with 5 mg/week, followed by dose-up by 2.5 mg/week every 4 weeks until 15 mg/week for tolerable and refractory patients. After the official limitation within 6-8 m/week of MTX between 1999-2010, MTX use up to 16 mg/week has been officially approved in February 2011. MTX treatment is indicated as the first-line disease-modifying anti-rheumatic drugs (DMARDs) for patients with poor-prognostic RA, as well as the second-line drug for those refractory to other DMARDs for 2-3 months. Consequently, MTX may be given for most of the RA patients except for mild subsets and contraindicated subpopulations. Before the initiation of MTX, RA disease activity, poor prognostic factors, as well as co-morbidities including latent tuberculosis and viral hepatitis should be intensively evaluated. The initial dose of MTX should be determined by the risk factors of the patients rather than their disease activity, while the dose increment may be based on the disease activity and severity for tolerable patients. Therefore, MTX can be started at a dose of 8 mg/week, followed by dose-up by 4 mg/week every 4 weeks until reaching 16 mg/week in patients without any risk factors, while the initial dose and dose increment should be reduced by 2 mg/week with prophylactic folic acid supplementation in those with risk factors such as older age and renal dysfunction. The safety monitoring includes lung injury, possible infection, cytopenia, liver dysfunction, lymphoproliferative diseases and gastrointestinal disturbance. The fact that the appropriate use of MTX is fundamental in RA treatment is further supported by the accumulating evidences for the critical role of MTX in the efficacy of biological agents. Therefore, we are going to intensively discuss about MTX treatment using RA case series of MTX monotherapy and its combination therapy with biological or non-biological DMARDs.

MTE4

Rehabilitation for the patients with rheumatoid arthritis

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Conflict of interest: Yes

Aim of the rehabilitation is to let the peoples with any disabilities live as usual humankinds by diminishing the difficulties in daily life. Protraction of RA induces the disorders of joint function. As a result, activities of daily living (ADL) are deteriorated, which

yields the limitation of social participations. Functional disorders have once developed, a plural number of it make disabilities worse. Therefore, in order to prevent the progression of these problems, RA rehabilitation includes the various kinds of approaches along their disease activities and progressions such as patient education, exercise therapy, application of splints and utilization of long-term care insurance. In late years, it is reported that the quick effect characteristics and the high effectiveness of biologics. When the structural remission following the clinical one has been successfully introduced by the biological agents, the problems confronting the execution of rehabilitation might be reduced. On the other hand, it is reported that the exercise in addition to the biologics have shown better effects on the functional recovery of upper extremities in comparison with the biologics alone. However, even if RA patients have achieved their clinical remission by biologics, joint destruction might progress rapidly by overuse of it when it had been damaged beyond the moderate stage. It seems that similar troubles such as tendon rupture during exercise may be observed in upper extremities. In conclusion, it must be emphasized that the execution of more prudent rehabilitation are very important even in the time of biologics mainly used for RA patients. To understand the rehabilitation for RA, follows are prepared. 1. To understand the impairments, disabilities and handicaps due to musculoskeletal disorders. 2. To understand the rehabilitation utilized for RA. 3. To advice the way of home-based exercise and protection for joint damage in daily life to RA patients.

MTE5

Clinical aspects of inflammatory myopathy

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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 How we make correct diagnosis What we should choose for initial treatment How we monitor the disease activity What we should choose after the failure of the first treatment

MTE6

Systemic scleorosis: diagonsis and treatment

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Conflict of interest: None

Systemic sclerosis is a heterogeneous disease that includes mild acrosclerosis and severe diffuse skin sclerosis. It is relatively easy to diagnose typical cases, although early cases and mild cases are sometimes difficult to diagnose. Furthermore, it is required not only to make a diagnosis but also to evaluate and predict each patient's clinical subset and prognosis. In this session, we will learn how to diagnose patients with systemic sclerosis, especially from skin symptoms as well as antinuclear antibodies.

MTE7

Respiratory infection in patients under immunosuppressive therapy for rheumatic diseases

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Conflict of interest: None

In the treatment of rheumatic diseases, the biologics and immunosuppressant are widely used, which causes impaired host defense. Since opportunistic infection can be life-threatening, the prophylaxis and treatment are the critical issue in the clinical practice of rheumatic diseases. It is sometimes difficult to differentiate lung infection from non-infectious lung complications such as drug-induced pneumonitis or alveolar hemorrhage. When a patient with long-term outpatient care for a rheumatic disease is complicated with pneumonia, the treatment strategy was according to the guideline for community-acquired pneumonia, which sometimes resulted in inappropriate antibiotic therapy. In 2011, the Japanese Respiratory Society published the guideline for nursing and healthcare-associated pneumonia (NHCAP), proposing pneumonia in a patient with long-term outpatient care to be treated as NHCAP. In NHCAP, a variety of pathogens including drug-resistant bacteria and the immunity status of the patient should be considered on introduction of antibiotics. Pneumocystis pneumonia (PCP) is one of the most common opportunistic infections. In PCP, the radiological features are similar to those in methotrexate pneumonitis, making the differential diagnosis difficult. In rheumatic patients with PCP, the levels of inflammatory cytokines in bronchoalveolar lavage fluid are higher than in AIDS patients with PCP. This could be the reason why PCP in patients with rheumatic disease show rapid progression and poor prognosis compared with PCP in AIDS patients. Since the increased risk of active tuberculosis associated with infliximab was reported, a tuberculosis screening and prophylactic isoniazid for a high-risk patient are recommended before introduction of the biologics. Non-tuberculous mycobacteriosis are also associated with the use of the biologics. In this presentation, the diagnosis and treatment of opportunistic lung infections in patients with rheumatic diseases are to be reviewed.

MTE8

MR imaging of rheumatic diseases

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Conflict of interest: None

The aim of this session is to experience image interpretation of various rheumatic diseases by case-based approach. The General Instruction Objectives (GIO) of the program is to understand MR findings of rheumatoid arthritis, spondyloarthropathies (SpA), and dermatomyopathy (DM)/ polymyopathy (PM). Three important MR findings in RA are well established; bone erosion, bone edema, and synovitis. Diagnosis of early RA has become possible using these MR findings. In addition, the role of MR imaging in the differential diagnosis of RA will be discussed. Although early diagno-

sis of RA in pre-erosive stage is becoming a reality owing to introduction of new diagnostic criteria, demonstration of bone erosion is still an important finding to diagnose erosive arthritis. For the early diagnosis of erosive arthritis, it is crucial to understand MR findings of bone erosion, and to differentiate it from its mimickers. Only MRI can demonstrate bone edema, which is depicted as area of signal alteration within the trabecular bone, with ill-defined margins and signal characteristics consisting water. Active synovitis is an area in the synovial compartment that shows post-gadolinium enhancement of a thickness greater than the width of the normal synovium. Depiction of active synovitis by enhanced MR images can be a surrogate marker of diagnosis of arthritis by physical examination. The earliest finding of SpA is osteitis at the enthesis. Since MR imaging can visualize osteitis before bony proliferative changes does occur, it is now used to make an early diagnosis SpA, and to evaluate response to biologics. MR findings of axial SpA including sacroiliitis will be discussed. MR imaging is used to make a diagnosis of DM/PM and other rheumatic disorders such as eosinophilic fasciitis. It is also used to find an appropriate site fore biopsy. Since fasciitis in DM/PM is now recognized as an important finding, these MR images will be presented.

MTE9

Treatment for refractory RA in daily practice

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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 RA classification criteria to classify patients with progressive arthritis and introduce methotrexate-based therapy in early stage disease. 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. Generally, randomized clinical trials are considered the gold standard for evaluation of the efficacy of newly developed agents. However, randomized clinical trials, which have strict exclusion criteria, are artificial, may not reflect efficacy and safety in the real rheumatology world. In addition, even recent clinical trials have shown that treatment with anti-TNF biologics in combination with MTX in early RA can lead to clinical remission in less than 50% of patients and the remaining half of the patients are either those notable to achieve clinical remission. Several factors are closely related with the refractory RA. Thus, 1) the presence of negative predictive factors including high titer of anti-CCP antibody, high disease activities, 2) drug resistance, 3) treatment intolerance, 4) comorbidities (chronic infectious diseases such as non-tuberculous mycobacterial infection, renal dysfunction, interstitial pneumonia, chronic hepatitis and so on), 5) other factors like economic problems. Further, some inconsistencies in therapeutic targets and strategies among rheumatologists have been recognized. These inconsistencies may be partly based on differences in attitudes among doctors caring for patients with RA. I would like to discuss these issues to be overcome for the better treatments of refractory RA in this meeting.

MTE10

Management of 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), thrombotic microangiopathy (TMA) and antiphospholipid syndrome (APS) 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? There are two TMAs; one is thrombotic thrombocytopenic purpura (TTP) related with reduced ADAMTS13 function. TTP could be successfully treated by plasma exchange with some exception. The ADAMTS13 activity was suppressed by anti-ADAMTS13-antibodies, therefore the effect of immunosuppressants should be discussed. The other groups is non-TTP. The treatment of Not-TTP TMA has not been established and is further difficult to treat. APS is basically thrombotic disorder. However, APS complicated with SLE has more heterogeneous clinical features compared with primary APS. Chorea, transverse myelopathy and serious thrombocytopenia could be complicated with thrombosis. How to treat such diseases? In this seminar, those topics will be discussed among the participants.

MTE11

How to use glucocorticoids

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Conflict of interest: Yes

History of glucocorticoid clinical use was initiated by Hench for patients with rheumatoid arthritis (RA) in 1948. Subsequently, glucocorticoids have played an important role in the treatment of rheumatic diseases such as systemic lupus erythematosus and RA, however, severe adverse events are usual, particularly at high doses. Lower risk/benefit ratio in the glucocorticoid therapy is a major target for every rheumatologist. Since glucocorticoids have a long history, many clinical evidences have been revealed by clinical trials. In contrast, empirical clinical uses of glucocorticoids are still common. I would like to summarize basic information of clinical pharmacology in this seminar first. I will then discuss with the participants about glucocorticoid use what was based on evidence or experience.

MTE12

Combination therapy of biologics and surgery

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Conflict of interest: None

It is recently general to use biologics for induction of remission and inhibition of bone and joint destruction in rheumatoid arthritis (RA). However the most important thing is that the quality of life (QOL) is improved by the recovery of joint function in RA patients. Biologics have the limitation of the efficacy for QOL im-

provement whatever the destruction of joint damage. It is valuable to assess the joint function based on the range of motion (ROM), however disease activity by general inflammation or sharp score are suppressed by biologics. Because the relief of pain in joint cannot always get the good ROM of joint in RA. It is clear that pathological locus is joint, however the role of the control of disease activity may be in bone marrow or general environment in RA. Therefore it is limit for surgery itself to treat RA dose not continue the efficacy of treatment. The combination therapy of biologics and surgery is powerful method to continue the efficacy of treatment in RA. For example, it is difficult how to treat the progressive joint destruction of shoulder (Larsen grade IV) in case of 20~30 years old patients achieved tight control and clinical remission by biologics. It is reported that synovectomy or arthroplasty are effective for the cases of toleration of biologics so far. However the indication or timing for surgery are important to know for good efficacy. Practical preparation for surgery with biologics and skill are explained in this lecture. Especially the function of upper limb focused on the shoulder is analyzed based on the QOL of patients. Furthermore using practical case studies, the position of surgery in treatment of RA with biologics will be discussed with audience together.

MTE13

Strategy to manage NSAIDs-induced gastrointestinal disorders

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Conflict of interest: None

NSAIDs are frequently prescribed for rheumatic diseases. NSAIDs work by inhibition of cyclooxygenase (COX) activity. COX-1 is structural enzyme which produces protective PGs. COX-2 is inducible enzyme which produces PGs relataed to inflammation and cancer. Serious side effects of NSAIDs such as gastrointestinal (GI) complications are known. In 1991, Japan Rheumatology foundation demonstrated 15.5% of gastric ulcer in patients with RA and OA who used NSAIDs during over 3 months. Risk facors of NSAIDs-induced gastric ulcer are elderly age, prior history of peptic ulcer, corticosteroid, high dose of NSAIDs and patients with severe general diseases. Moreover, possible risk factors are *H. pylori* infection, smoking, bisphosphonate and alcohol intake. Treatment of NSAIDs-induced ulcer is discontinuance of NSAIDs and administration of anti-ulcer drugs. In patients who can not discontinue NSAIDs, PPI and PG analogs (misoprostol) are useful. PPI and PG analogs are also useful for prevention of NSAIDs-induced peptic ulcer. Recently, lansoprazole and esomeprazole are approved as drugs for prevention of reccurent GI ulcer due to NAIDs in Japan. COX-2 selective NSAIDs such as etodolac and meloxicam are few in GI side effects. The frequency of cardiovascular events of celecoxib is the same as non-selective NSAIDs at postmarketing surveillance of 10,000 Japanese rheumatic patients. NSAIDs-induced lower Gl disorders of small intestine and colon are demonstrated. Their mechanism of NSAIDs-induced lower GI disorders is shown to be induced by inhibition of PGs production, enteric bacteria and bile. 71% of patients who were prescribed NSAIDs during over 3 months is endoscopically demonstrated small intestine disorders. Low dose aspirin which is administered for the prevention of cerebro- and coronary-vascular events is one of important factors for NSAIDs-induced GI ulcer. In this lecture, I would like to review recent evidence of NSAIDs including aspirin and COX-2 selective inhibitors.

MTE14

Rheumatic diseases of the elderly

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Conflict of interest: None

Rheumatologists may more frequently see elderly patients with rheumatic diseases due to longer life expectancy than before. In this session, I will have a brief talk for each main rheumatic disease in the elderly; giant cell arteritis (GCA), polymyalgia rheumatic (PMR), microscopic polyangiits, osteoarthritis (especially erosive osteoarthritis), and pseudo-gout. As PMR may be the most important rheumatic disease in the elderly, I will show a patient and would like to discuss about differential diagnosis between seronegative RA and PMR. 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). Low dose steroid is a mainstay of the treatment for PMR. However recent report about the efficacy of tocilizumab for GCA and PMR (Arthritis Care Res 2012; 64: 1720) seems to be attractive for elderly patients with other complications such as osteoporosis and diabetes. I'd like to discuss about this new treatment a little bit.

MTE15

Radiologic diagnosis of pulmonary involvement associated with collagen vascular diseases

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Conflict of interest: None

In collagen vascular diseases (CVD), various pulmonary complications often accompany. They include airway narrowing due to arthritis of neck joint, airway involvement of central and peripheral airways, interstitial pneumonitis and pulmonary fibrosis, vasculitis of pulmonary circulation and embolism, diffuse pulmonary hemorrhage, granuloma formation, respiratory muscle insufficiency and atelectasis, pneumothorax and pneumomediastinum. These complications sometimes occur one after another in the same patient. In addition, following therapy for CVDs itself, 1) opportunistic infections due to immunosuppression (virus, fungus including aspergillus and cryptococcus, nocardia, acid-fast bacillus, penumocistis, etc), 2) organizing pneumonia after infection, 3) drug-induced lung injury, 4) heart failure, also often occcur. Further, common lung disorders such as bronchial asthma, COPD, cancer, and community acquired penumonia are often observed in the same patient. In fact, the overall outcome of these factors is expressed as radiographic findings. Basically, any radiographic finding is not disease-specific. So it is very important to make diagnosis based upon clinical manifestations, laboratory findings, and sometimes response to therapy as well as radiographic findings. The prognosis of the pulmonary involvement associated with CVD depends on the pathophysiology of each involvement. From the clinical point of view, life threatening manifestations should be diagnosed as quickly as possible, and appropriate therapy should be conducted. In this lecture, first I would like to present some near-typical radiographic samples, then discuss how we proceed differential diagnosis for difficult cases.

MTE16

Osteoporosis update: diagnosis and treatment: how do we know bone quality?

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Conflict of interest: Yes

According to the present definition of osteoporosis, bone quantity, mineral density, and tissue material properties are important factors in determining bone strength. The proposed determinants of bone strength at the material level are the degree of mineralization of basic structure units, microdamage accumulation, and collagen cross-link formation. These are regulated by cellular activities and tissue turnover rate. Collagen cross-linking, a major post-translational modification of collagen, plays important roles in the biological and biomechanical features of bone. Collagen cross-links can be divided into lysyl hydroxylase and lysyl oxidase-mediated enzymatic immature divalent cross-links, mature trivalent pyridinoline and pyrrole cross-links, and glycation- or oxidation-induced non-enzymatic cross-links (Advanced glycation end products: AGEs) such as glucosepane and pentosidine. These types of cross-links differ in the mechanism of formation and in function. Material properties of newly synthesized collagen matrix may differ in tissue maturity and senescence from older matrix in terms of cross-link formation. Additionally, newly synthesized matrix in osteoporotic patients or diabetic patients may not necessarily be as well-made as age-matched healthy subjects. Data have accumulated that collagen cross-link formation affects not only the mineralization process, but also microdamage formation. Consequently, collagen cross-linking is thought to affect the mechanical properties of bone. Furthermore, recent basic and clinical investigations of collagen cross-links seem to face a new era. For instance, serum or urine pentosidine levels are now being used to estimate future fracture risk in osteoporosis and diabetes. In this review, we describe age-related changes in collagen cross-links in bone and abnormalities of cross-links in osteoporosis and diabetes that have been reported in the literature.

MTE17

Surgical Operation in Biologic Era: Basic seminar for rheumatic physicians

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Conflict of interest: None

The appearance of the biologic agents brought the remarkable progress to the therapy for rheumatoid arthritis (RA). Even if the basics of the medical treatment of RA are still three, medication, a surgical operation, and a rehabilitation therapy, it can be easily expected that the surgical remedy of RA will change quantitatively and qualitatively in the future. On the other hand, the misunderstanding that surgical treatment should be avoided as a result of not performing suitable medication may also be heard rarely. Therefore, this seminar explains a basic way of thinking of the operative treatment for RA and representative operations in each joint. We would like to reconfirm significance and positioning of the operative treatment in the biological preparation era. Therefore, the participant whom this seminar assumes are not surgeons with the experience for improvement of the operation ability and the confirmation of pit fall, but rheumatic physicians or young residents who intend to major in rheumatic surgery in the future. After outlining the fundamental view of a rheumatism operation in the first half part of this seminar, it is scheduled that an interactive lecture is done by discussing several clinical cases in the latter half. The timing of the consultation to the surgeon can be concretely imaged by displaying the cases in which the surgical timing has been missed. We also like to deepen recognition of the limit of biologic agents by presenting cases in which surgical operations are performed even if biological products are used.

MTE18

Clinical and basic researches for pathogenesis and treatment of osteoarthritis of the knee

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Conflict of interest: None

Osteoarthritis of the knee (OA knee) is deemed to be one of the degenerative knee disorders, which is often found in the elderly obese women with varus knees. In advanced stage, varus OA knees show lateral thrust in early stance phase. Pain worsened during or after weight-bearing activities. With development of bony changes such as osteophyte formation, loss of movement is appeared. As specific laboratory tests are not available, plain radiography is the gold standard for diagnosis and prognosis. Intervention of surgical treatments is required to patients who have difficulties in doing house-hold chores. OA is characterized by degeneration of articular cartilage, synovial inflammation and proliferative bony changes. Multiple factors are involved in the pathogenesis of OA, including mechanical influences, the effect of aging on cartilage and bony, hormonal events and genetic factors. These matters may make it more difficult to predict what kinds of the knee might be susceptible to OA and progress rapidly to the catastrophic stage. So far, the pathology of OA has long been thought to be cartilage-driven. Recent studies indicated an additional role of bone and synovial tissue. Repeated mechanical stress on cartilage leads to an imbalance in synthesis of extracellular matrix and apoptotic death of chondrocytes, and increased synthesis of MMPs and agrecanases may disturb the formation of matrix. Synovial macrophages stimulated by cartilage debris produce catabolic cytokines, starting synovial inflammation. On the contrary, observation during surgery showed cartilage repair tissue was found on the previously eburnated articular surface of the knees treated with osteotomy, indicating that reparative function may be initiated when the vicious environment of the articular cavity is altered. Further studies to delineate the pathophysiological mechanism will give us concrete clues to improve the functional outcomes in patients with OA.

MTE19

Practical use of musculoskeletal ultrasound for evaluating synovitis

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Conflict of interest: Yes

Among a range of pathologies that can be detected with musculoskeletal ultrasound, synovitis is the most important target to be evaluated in order to improve the clinical outcome of rheumatoid arthritis. Although synovitis is visualized as either synovial hypertrophy or synovial fluid with ultrasound, Doppler signals with in the thickened synovium represents ongoing inflammatory process and is the main target in the evaluation of synovitis activity. However, its accurate evaluation depends on the morphological assessment of synovium with gray-scale ultrasound since the extra-synovial blood flows are present in normal joints. The ultrasonographic assessment of synovitis is more accurate than that by clinical examination, and it improves the accuracy of diagnosis and disease activity assessment in rheumatoid arthritis. Especially in atypical or equivocal cases, ultrasound can directly influence the clinical decision and improve disease outcome. Although ultrasound can be performed for different purposes, such as technical practice, education of rheumatologists and patients, patient's request, and clinical research, sonographers needs to be aware of the exact purpose

during the examination. In this program, several case scenarios and images will be presented and various issues will be interactively discussed from indications for ultrasound to optimal machine setting. At the end of this program, participants will be able to: understand various possible purposes of performing ultrasound. understand mage conditions required for accurate assessment of synovitis. understand machine settings required for accurate assessment of synovitis. understand pitfalls in evaluating synovitis in different joint regions.

MTE20

Surgical treatment of the hand

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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 a few joints of the body, and the patient who pursue a higher level of ADL and QOL still exists. Manifestation of the disease in the hand has changed in this new era. It is uncommon to see a remarkable synovial proliferation and a severe pain, but in some of the patients, joint deterioration progresses accompanied with 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 it.", "Joint does not move.", "Deformity might recur." surgical treatment of the rheumatoid hand has been often hesitated to perform until now. But, we don't have to worry about them, if the reconstructive surgery was performed under an appropriate indication in a good timing, and if a postoperative hand therapy is performed well. Pain relief is usually provided by all 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 increases after flexor tenosynovectomy and tendon reconstruction for the rupture. When fusion is necessary, the patient wears a static splint to perform a simulation before the operation, and has her try whether she can use a hand well. Grip and pinch powers increase after fusion at the finger and the wrist joints. Prehension pattern improves after arthroplasty and balance restoration for a long standing deformity, despite increase in hand power is hardly to be provided. While recurrence of deformity rarely occurs due to suppressed local inflammation, progression of secondary arthrosis and tendon rupture due to over use of the hand are felt uneasy about.

MTE21

Management of renal complication

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Conflict of interest: None

Several rheumatic diseases, such as 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), gout, complicates renal diseases. (1) Small artery(arteriol-interlobar artery) damage are induced by AAV, SSc. (2) Glomerulonephritis/glomerulopathy, by AAV, SLE, MCTD and RA (amyloidosis). (3) Interstitial nephritis, by SjS and gout. We should treat careful management for these rheumatic diseases complicated with renal diseases. In this meeting, We will discuss on the management for AAV with renal involvements and lupus nephritis through of the intractable case presentation 1) AAV; Case1: Relapsed AAV patient without ANCA. Case2: Patient with Recurring AAV. Methods of early diagnosis, histological assessments, remission induction therapy, and predictive marker for relapse will be discussed. 2) Lupus nephritis;Case: Patient with Recurring lupus nephritis. Remission induction therapy based on histological differences of lupus nephritis, Methods of early diagnosis and treatments for relapse cases will be discussed. This meeting will help rheumatologists the understanding and the management of renal disease induced by rheumatic disease.

MTE22

Clinical examination of joints

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Conflict of interest: None

Graphic examinations of the joints by using ultrasonography and/or MRI have been widely employed lately. They are certainly useful to elicit valuable findings around the afflicted joints. However, thorough examination of the joints by inspection and palpation should be performed first, followed by these maneuvers to clarify the further pathology of the involved joints. To detect soft tissue swelling around a joint by palpation is the most important "first" clinical maneuver in establishing the diagnosis of rheumatoid arthritis (RA). The examiner should palpate each joint from the head to the toes (except for a hip joint which is too deep to reach). In performing this maneuver, one should always keep a textbook about clinical anatomy concerning the musculoskeletal and nervous system in hand so that one can guide oneself to pinpoint the involved sites i.e. if these are synovial membrane, synovial bursa, tendon sheath, enthesis, muscle membrane and so forth. The method of systematic examination of individual joints will be discussed at the session, with some referrals to certain key joints here. SHOULDER: Try to stand behind the examinee and grasp the whole joint with your full palms. In this position, it is much easier to demonstrate the presence of subacromial/subdeltoid bursitis, the most frequent sign of shoulder involvement in RA. ELBOW: Keep an eye on olecranon-fossa. Enthesopathy around the medial and lateral epicondyle should not be overlooked. HAND: Don't forget to examine the extensor-as well as flexor-tenosynovitis. Frequency of their involvement in RA is extremely high! KNEE: Atrophy of quadriceps muscles and contracture of hamstring muscles should be checked. Instability of the joint is also looked for. TOES: Metatarsophalangeal joints are frequent target of RA. Swelling of this small joint is notoriously difficult to discern. One has to keep touching this site, whether it feels normal or not, to improve one's ability in joint examination.

Workshop

W1-1

Gender difference of peripheral involvement in patients with psoriatic arthritis

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Conflict of interest: None

Psoriatic arthritis (PsA) is an inflammatory arthritis associated with psoriasis. PsA may affect as many as 5-30 % of patients with psoriasis. PsA affects men and women equally. However, gender difference in PsA has seldom been studied in Japanese patients with PsA. [Objective] The purpose of this study was to analyze gender difference of peripheral involvement in PsA by using skeletal radiographs. [Method] We compared the radiographic features of PsA, the changes in bone destruction score, and bone proliferation score between men and women. [Results] 57 men and 28 women were enrolled. The mean age/ disease duration of psoriasis/ disease duration of arthritis at radiographic evaluation of men and women were 49.3/ 11.6/ 6.4 years and 52.6/ 13.9/ 6.5 years, respectively. Juxtaarticular bone proliferation was seen most high frequency in both men and women. The proportion of men who had at least one finding of feet radiographs was higher than that of women. Neither the change of bone destruction score nor bone proliferation score was affected by gender using multivariate analysis. [Conclusion] Radiological foot involvement was more frequent in men than that in women.

W1-2

The feature of X-ray pictures of knee joints in rheumatoid arthritis and osteoarthritis analyzed using KOACAD system

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Conflict of interest: None

[Objectives] To clarify the difference of the feature of X-ray pictures of knee joints between in RA and OA, using KOACAD system. [Methods] 49 RA patients and 50 OA patients who was operated in the University of Tokyo Hospital since 2009 was retrospectively analyzed to use KOACAD system.Patient charasteristics and radiographic parameters were compared between OA and RA using the chi-square test for categorical variables and unipaired t test for numerical variables. Finally, we used logistic regression to test the association of knee radiographic features and OA, RA in the succession of patients. Multivariable models were used to adjust for age, sex, and confounding factors. [Results] A significant difference($p<0.05$) was recognized between RA and OA for lateral minimum joint space width, mJSW lat(mean ± SD in RA, OA 51.5±50.2mm^2, 130.3±69.9 mm^2), lateral joint space area(51.5± 50.2mm^2, 130.3±69.9 mm^2), medial osteophyte area of tibia(5.0± 8.0mm^2, 12.8±16.8mm^2), femorotibial angle(176.6±11.7°, 185.8±11.1°). By logistic regression analysis after adjustment, a siginificant difference was recognized for mJSW lat(odds ratio1.37, 95%CI: 1.03-1.88) [Conclusion] The difference of the feature of X-ray pictures of knee joints between in RA and OA was evaluated quantitavely analyzed using KOACAD system.

W1-3

Evaluating FDG-PET/CT findings between elderly-onset rheumatoid arthritis and polymyalgia rheumatica

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Conflict of interest: None

[Objectives] To analyze the differences in findings of FDG-PET/CT between elderly-onset rheumatoid arthritis (EORA) and polymyalgia rheumatica (PMR), which mimick each other in clinical presentation. **[Methods]** We retrospectively investigated 10 patients with EORA and 27 patients with PMR, who were admitted to our department between 2006 and 2012. **[Results and discussion]** The patients' median age at the time of undergoing FDG-PET/CT in EORA and PMR groups was 73.5 and 78.0 years, respectively, and the difference was not significant. We observed significant differences in the FDG scores between the groups for ischial tuberosities, spinous processes, atlanto-axial joints, elbows, and wrists. We observed no significant differences at shoulders and hips; however, specific uptake patterns were observed in each group: circular and linear uptake patterns were observed around the humeral head in the EORA group, whereas focal and nonlinear uptake patterns were observed in PMR group. Moreover, focal uptake in front of the hip joint, indicating iliopectineal bursitis, showed a tendency to be limited in the PMR group. **[Conclusion]** The differences in the degree of uptake at each resion and in uptake patterns at shoulders and hips could be useful in arriving at a definitive diagnosis.

W1-4

Imaging analysis of inflammation and bone metabolism in rheumatoid arthritis (RA) by using FDG-, and NaF PET

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Conflict of interest: None

[Objectives] Syonvitis causes joint destruction that is associated with altered bone metabolism in rheumatoid arthritis (RA). We investigated relationship between inflammation and bone metabolism by multiple imaging modalities. [Methods] NaF-PET, FDG-PET, US, MRI and X-ray of bilateral wrist and finger joints were comparatively analyzed in 7 RA patients who started or switched biologics at the entry, 6 months, and 12 months later. [Results] FDG signals were found in synovitis, recognized by physical findings and other modalities, more sensitively than USPD's and reduced in response to treatment. In joint bones adjacent to FDG uptake area, NaF was also accumulated, and strong signals were persistent in progressive bone erosion sites, determined by serial studies of MRI and/or Xp. Conversely, those were reduced in bone repairing site in a patient, associated with increased serum ostocalcin level. NaF was also accumulated in complicated osteoarthritis joints without FDG signals. [Conclusion] FDG-PET detects synovistis sensitively, whereas NaF was accumulated in both destructive and plastic bone lesions, irrespective of presence or absence of inflammation. Present study suggests both FDG and NaF PET contribute to accurate monitoring destruction and repairing of bone and joints in RA.

W1-5

Validity of Tomosynthesis for Evaluation of Joint Sspace Narrowing and Bone Erosions in Patients with 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 arthritic hands and wrists. [Methods] From July 2012 to October 2012, 20 patients with RA (female 14, male 6), who underwent radiography and tomosynthesis of hands and wrists, were included in this prospective study. Mean age was 62.2 years old and mean duration of disease was 71.1 months. One rheumatologist scored joints of the hands and wrists using modified Total Sharp Score from two imaging modalities. The correlation of scores between radiography and tomosynthesis was analyzed. [Results] Scores for total joints evaluated were 472 vs 806 for joint space narrowing and 244 vs 211 for bone erosion in radiography and tomosynthesis respectively. The correlation coefficients between scores of radiography and tomosynthesis in joint space narrowing, were 0.7070, 0.7579, and 0.6686 for total, carpal, and finger joints respectively. The correlation coefficients between scores of radiography and tomosynthesis in bone erosions were 0.7441, 0.8038, and 0.5178 for total, carpal, and finger joints respectively. [Conclusion] Tomosynthesis may be useful for evaluation of joint space narrowing and bone erosions in patients with RA.

W1-6

Automated Breast Volume Scanner (ABVS), a new automated ultrasonic device, is useful to examine joint injury in patients with rheumatoid arthritis

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Conflict of interest: None

[Objectives] ABVS is an ultrasonic device to be developed for the automated scanning for mammary glands. We have tried to explore the clinical application of ABVS toward the synovial lesion in RA patients. [Methods] 13 active RA patients of mean 53 y.o., whose mean disease duration 24 months and DAS28 6.02, were recruited. We have examined in total 130 MCP joints as well as 26 wrist joints at dorsal sites by both ABVS and conventional US. ABVS was scanned in a water tank. Presence of synovial hypertrophy (SH) and bone erosion (BE) by gray-scale were examined by both methods, and the association of both methods was calculated by kappa coefficient. [Results] The scanning time of ABVS was 2 min per patient. ABVS detected SH in 23 MCP joints and 20 wrist joints whereas conventional US detected SH in 18 MCP joints and 20 wrist joints. Kappa coefficient of SH was 0.80 in MCP joints and 1.00 in wrist joints, respectively. ABVS detected BE in 8 MCP joints and 12 wrist joints whereas conventional US detected BE in 5 MCP joints and 11 wrist joints. Kappa coefficient of bone erosion was 0.76 in MCP joints and 0.92 in wrist joints, respectively. [Conclusion] Present data have shown a substantial agreement of ABVS with conventional US to find SH and BE of wrist and finger joints in patients with RA.

W2-1

Diagnostic Impact of Magnetic Resonance Imaging of the Shoulder in the Diagnosis of Polymyalgia Rheumatica (2nd Report)

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Conflict of interest: None

Polymyalgia rheumatica (PMR) is an inflammatory rheumatic condition characterized clinically by aching and morning stiffness in the shoulders, hip girdle, neck, and torso in patients over the age of 50. There is no laboratory or other test, including ESR and CRP, specific for the diagnosis of PMR. The new EULAR/ACR provisional classification criteria for PMR were presented in 2012. Early studies reported a high prevalence of abnormal ultrasound and magnetic resonance imaging (MRI) findings in shoulders and hips in patients with PMR. The preliminary ACR/EULAR classification criteria recognized the possible value of ultrasonography in improving the correct classification of patients with suspected PMR. But MRI was not comprised in those criteria. We investigated the diagnostic impact of shoulder MRI for the diagnosis of PMR in addition to the provisional criteria. We analyzed 43 patients who were undergo shoulder MRIs for making diagnosis with PMR in our institute. The active regions are different between PMR and other rheumatic diseases. It is proved that MRI has added value for PMR diagnosis by the provisional classification.

W2-2

Usefulness of musculoskeletal ultrasonography for diagnosis of polymyalgia rheumatica

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Conflict of interest: None

[Objectives] The aim of this study was to investigate the findings of musculoskeletal ultrasonography (MSK-US) which efficiently distinguish polymyalgia rheumatica (PMR) from rheumatoid arthritis (RA). [Methods] The subjects of this study were 17 patients with PMR and 21 with RA. The diagnosis of PMR was made clinically by experienced rheumatologists. In shoulder US, long head biceps (LHB) tenosynovitis, subacromial-subdeltoid (SAD) bursitis and power Doppler (PD) signal were evaluated. In MSK-US of the wrist and finger joints, both gray scale (GS) and PD synovitis were graded on a semi-quantitative scale from 0 to 3.

In addition to these US findings, age, gender and laboratory findings (CRP, MMP-3, RF and anti-CCP antibody) were assessed. [Results] The patients with PMR had a significantly higher frequency of LHB tenosynovitis (p=0.0028) and lower grade of both GS and PD synovitis (p for trend = 0.0048, 0.0164, respectively). Multiple logistic regression analysis identified that low-grade (GS Grade≦1) peripheral synovitis (odds ratio 3.05, p=0.0157), absence of RF or anti-CCP antibody (11.33, p=0.0172), and presence of LHB tenosynovitis (7.46, p=0.0319) were associated with PMR. [Conclusion] MSK-US is a useful tool to distinguish PMR from RA.

W2-3

Quantitative assessment of rheumatoid arthritis with dynamic contrast-enhanced magnetic resonance imaging : Volume of sinovium and cemter of E-rate

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Conflict of interest: None

Objective: Using dynamic MRI in RA patients, we assessed enhanced synovial volume and distribution of enhancement rate, and examined the correlation with clinical response to the biologic agents. **Materials and methods:** Eight RA patients who were treated with biologics were examined with dynamic MRI of the dominant affected wrist and hand before and one year after the treatment. Wrist and metacarpophalangeal (MCP) joints II-V were scored using OMERACT-RAMRIS and calculated the volume of synovium and distribution of the E-rate. Distribution of the E-rate was evaluated by voxel-by-voxel analysis (E-rate mapping), and estimated the center of the distribution (center of E-rate). These data were compared to the changes of clinical activity score (DAS28-CRP) and matrix metalloproteinase 3 (MMP-3). **Results:** In each joint, synovial volume had correlation with OMERACT-RAMRIS synovitis score. Volume of synovium, center of E-rate and OMERACT-RAMRIS synovitis score has same correlation with DAS28-CRP. **Conclusion:** Assessment of volume of synovium and center of E-rate might be useful in the assessment of clinical improvement in response to the biologic agents same as OEMRACT-RAMRIS score.

W2-4

MRI assessment of treatment effects in patients with rheumatoid arthritis after switching of biologic therapies

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Conflict of interest: None

[Subjects] Subjects were 16 patients (14 women, 2 men; age range, 45–83years; mean, 59.2years) with rheumatoid arthritis who switched biologic agents because of insufficient treatment effects. [Methods] MRI images of the hands were taken before biologic therapy, before switching, and after switching. After switching, subjects were divided into a low disease activity group (Group L; DAS28 less than 3.2) and a moderate/high disease activity group (Group H; DAS28 at least 3.2). The RAMRIS (rheumatoid arthritis MRI scoring) system was used to obtain MRI scores for bone erosion, bone edema, and synovitis. [Results] The mean MRI scores in Groups L (9 patients) and H (7 patients) for bone erosion, bone edema, and synovitis were as follows: 23.8 and 16.6, 16.7 and 16.3, and 9.9 and 6.9, respectively, before biologic therapy; 21.9 and 21.1, 19.1 and 19.1, and 10.0 and 8.0, respectively, before switching biologics; 17.1 and 22.3, 9.3 and 16.7, and 4.8 and 6.4, respectively, after switching biologics. In Group L, synovitis and bone edema scores significantly improved (before vs. after switching). [Conclusions] Both synovitis and bone edema scores improved in cases where switching of biologics was effective. MRI is useful in assessing treatment effects in patients after switching medications.

W2-5

Analysis of Shoulder Joint Destruction in Rheumatoid Arthritis Patients Treated with Biologics

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Conflict of interest: None

[Objectives] The aim of this study was to assess risk factors for shoulder joint destruction in rheumatoid arthritis (RA) patients being treated with biologics using the MRI and 18FDG-PET (PET) findings. [Methods] Twenty-nine shoulders in 30 patients with RA were assessed using PET and MRI before starting biologics and six months later. The XP findings were assessed before starting biologics and two to three years later. The CRP, ESR and MMP-3 levels, and the DAS28-ESR, DAS28-CRP, CDAI and SDAI scores were also assessed. We compared these parameters between the progression of joint destruction group (P group) and no progression group (N group). [Results] The SUV max, synovitis and rotator cuff tear on MRI before biologics treatment were significantly higher in the P group than the N group. The SUV max and synovitis detected by MRI after biologics were also significantly higher in the P group. The CRP, ESR and MMP-3 levels and disease activity showed no significant differences between the two groups. [Conclusion] The detection of synovitis by PET or MRI is more important than the disease activity and serum inflammation markers when assessing the potential for the progression of shoulder joint destruction.

W2-6

Comparison of palpation, contrast-enhanced MRI with maximum intensity projection, and joint echo to the hand arthritis in rheumatoid arthritis

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Conflict of interest: None

[Objectives] To compare the usefulness of palpation, contrast-enhanced MRI, and joint echo to hand arthritis in rheumatoid arthritis (RA). [Methods] 24 RA patients (48 wrist joints and 240 MP joints) were included. In palpation, swelling or tenderness was recorded. In MRI, the maximum intensity projection (MIP) images were used, and in the echo, the images of Gray Scale (GS) and Power Doppler (PD) were done. The positive ratio of each examination and the kappa coefficient as a coincidence rate of each examination were calculated. [Results] The positive ratios of palpation, MIP, GS, and PD were 46, 65, 52 and 52% respectively at the wrist joints, and 5, 12, 32 and 7% respectively at MP joints. The

coincidence rates of palpation and MIP, palpation and GS, palpation and PD, MIP and GS, MIP and PD, GS and PD were 0.47, 0.29, 0.46, 0.33, 0.66, and 0.42 respectively at the wrist joints, and0.26, 0.12, 0.16, 0.23, 0.52, and 0.13 respectively at the MP joints. [Conclusion] Compared with palpation, MRI and a joint echo showed high positive ratios. As compared with the wrist joint, the judgment according to palpation at MP joint was difficult. Although MIP and PD were remarkable coincidence rates, they were comparatively low coincidence rate except this.

W3-1

Changes in foot pressure after toe plasty in the patients with rheumatoid arthritis

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Conflict of interest: None

[Objectives] The objective of this study is to clarify the effectiveness of toe plasty for the treatment of painful callosities at the planter aspect of the forefoot by measuring foot pressure in the patients with rheumatoid arthritis (RA). [Materials and Methods] Peak foot pressure and integrated foot pressure of the 8 feet in 6 patients with RA were measured using F-scan II®(Niita Co.) before the operation, 4~5 weeks and 3months after the operation, and they were compared with those in 15 healthy controls. The foot prints were divided into 6 segments, including lateral-forefoot, medial-forefoot, lateral-midfoot, medial-midfoot, lateral-hindfoot, medial-hindfoot. [Results] Preoperative peak pressure and integrated pressure were higher in the forefoot segments than those in the hind foot segments. Similar pattern was noted in the healthy controls. The foot pressure decreased in the forefoot segments and it increased in the hind foot segments 4~5 weeks after the operation. Three months after the operation, a tendency to move from hindfoot segments to lateral-midfoot and forefoot segments were seen in the distribution of foot pressure. [Conclusion] Measuring foot pressure using F-scan II®is a useful tool to evaluate effectiveness of toe plasty in the patients with RA.

W3-2

Assessment of plantar pressure distribution after forefoot surgery in patients with rheumatoid arthritis

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Conflict of interest: None

[Objectives] In RA, satisfactory postoperative results are reported in both (1) Hallux MTP-joint arthroplasty (Swanson implant)+2nd-5th toes metatarsal head resection arthroplasty and (2) Hallux Scarf osteotomy+2-5th toes metatarsal shortening osteotomy. Meanwhile, the effect of preserving metatarsal head on plantar pressure remains unknown. [Methods] 3 feet of healthy volunteer, 12 feet of RA patients who underwent operation (1) (3 male 9 female; age 62.4 y; postoperation duration 6.8 y), and 13 feet of RA patients who underwent operation (2) (13 female; age 62.0 y; postoperation duration 3.9 y) were enrolled. Walking plantar pressure through 2nd to 6th steps was assessed by F-SCAN II®(Nitta Co., Ltd.). [Results] Plantar pressure distribution of hallux MTP-joint was 13.1±2.2% in healthy volunteer;operation (1) 7.0±2.5%;operation (2)10.6±2.8% ((1) vs. healthy volunteer ; $P<0.001$ / (1) vs. (2); $P<0.01$). On the other hand, Plantar pressure distribution of 2nd-5th toes MTP-joints was 19.2±1.2% in healthy volunteer;operation (1) 20.4±5.7%;operation (2)12.4±3.5% ((2) vs. healthy volunteer or (1); $P<0.01$). [Conclusion] In RA patients, operation (1) was associated with decreased plantar pressure of hallux MTP-joints. On the other hand, operation (2) was associated with decreased plantar pressure of 2nd-5th toes MTP-joints.

W3-3

Relationship of radiological findings between hallux valgus and fore · mid · hind foot deformity in rheumatoid arthritis cases

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Conflict of interest: None

[Objectives] To confirm the relationship of radiological findings between HV and fore·mid·hind foot deformity in rheumatoid arthritis cases [Methods] X-ray pictures of 160 RA feet were evaluated. 1st MTP Larsen grade, 2nd MTP dislocation, HV·M12·M15 angle, metatarsus primus varus (MPV) angle, M12 diastasis, angle between talus and navicular (pronated foot deformity), Tibio-Calcaneal (TC) angle, distance between the axis of tibia and calcaneus (offset of calcaneus) were measured. [Results] M12 angle and HV angle correlated (R^2=0.7) in the group without 2nd MTP dislocation (D0), while correlated (R^2=0.7) only in cases of mild HV (<40) in dislocation (D2) group. The mean HV angle in D0 was 21±14.1, 45±16.8 in D2: significantly larger ($P<0.001$). Larsen grade and HV angle did not correlate in D0 cases, while did in D2 cases (R^2=0.3). MPV angle correlated with M12/HV angle (R^2=0.5), while M12 diastasis didn't. Pronated foot deformity correlated with HV angle in case of severe HV (>40) in D0 group (R^2=0.3). Offset of Calcaneus had no direct relationship to HV, but correlated with M12 angle (R^2=0.3), and pronated foot deformity (R^2=0.5). [Conclusion] In RA cases, not only midfoot effect, but also lateral offset deformity of hindfoot,1st MTP change and 2nd MTP dislocation worsen HV.

W3-4

Influence of foot involvements to ADL and QOL in RA patients

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Conflict of interest: None

Objectives: To clarify the influence of foot involvements and their progress to ADL and QOL in RA patients. **Methods:** We investigated the RA patients in our hospital cross-sectionally (271 patients and 542 foot) using X-ray films. Larsen grade was checked for 12 joints in foot and ankle. Of 271 patients, 212 patients and 424 foot were assessed for ADL and QOL using JSSF (Japanese Society for Surgery of the Foot) RA foot ankle scale and MHAQ. ANCOVA analysis was used for adjustment of RA disease duration. **Results:** Cluster analysis revealed that 542 feet were divided into 5 clusters and named according to each characteristic joint destruction distributions as normal type, forefoot type, mid-

foot type, mid-hindfoot type, and combined type. Distribution map of each cluster by duration of disease revealed that midfoot type had its climax in 5-10 years of disease periods and suggested the rapid progression from midfoot type to mid-hind or combined type. ADL and QOL in mid-hindfoot type and combined type were markedly decreased compared to other types. **Conclusion:** The progress from midfoot type to mid-hindfoot type or combined type markedly decreased the ADL and QOL. We consider that prevention of this progress by early intervention is one of the important elements in RA foot treatments.

W4-1

Results of joint-preserving surgery combined with Weil's shortening metatarsal osteotomy for rheumatoid forefoot deformity

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Conflict of interest: None

[Objectives] Resection arthroplasty has been widely used for rheumatoid forefoot deformity. However, considerably high rate of recurrent pain or deformity has been reported. We report clinical results of joint-preserving surgery combined with Weil's shortening osteotomy for rheumatoid lessor toe deformity. [Methods] We reviewed 22 feet of 14 patients who underwent surgical corrections of rheumatoid forefoot deformity. The mean follow up was 16.1 months. The mean age was 62 years old.Surgical procedures consist of Weil's osteotomy for lessor toes in all patients combined with Nakagawa's two-dimensional metatarsal osteotomy for hallux valgus in 15 feet.Clinical results were evaluated by JSSF scales and radiologically with HVA and IMA. [Results] The mean JSSF hallux score and lessor scale improved from 22.5 to 95.1 and form 13.3 to 93.4. The mean HVA and IMA decreased from 37.9°to 0.9°and from 16.1°to 4.4°. [Conclusion] Joint-preserving surgery could successfully correct rheumatoid forefoot deformity both clinically and radiologically with a low rate of residual painful callosities or recurrent deformity. Furthermore, it preserves the MTP joint range of motion and function of forefoot during stepping contributing to improved activities of daily living of rheumatoid patients.

W4-2

The result of arthroplasty for rheumatoid forefoot deformity by matatarsal oblique osteotomy

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Conflict of interest: None

[Objectives] We have been performing metatarso-phalengeal (MTP) joint preservative surgery for rheumatoid forefoot deformity since 1998. We assessed the result of this surgery. [Methods] This study included 40 feet in 26 patients (24 females, 2 males) could been observed more than 5 years after operation in total 65 feet in 38 patients. Their average age at operations was 58 years (41 to 74), the mean follow up was nine years (5 to 12). Surgical methods : We have treated for rheumatoid foot have painful callosities on the soles, Great toes : 31 feet underwent Swanson toe implant, remaining 9 feet Mitchell's osteotomy. II-V lateraltoes underwent shortening oblique osteotomy of the metatarsal neck and reduced dislocation of MTP joint. We evaluated feet radiologically and clinically. [Results] Recurrence of a dislocation of the MTP joint occurred in one foot that had pain, in 2 feet observed nonunion of the metatarsal necks, but had no symptom. Two feet had further surgery, one was for recurrence of a dislocation of the MTP joint and another one was for infection of the Swanson implant. [Conclusion] MTP joint preservation keeps the shape of the foot, a good long-term results were obtained. The improvement in deformities, function and cosmetic appearance caused patients satisfactory.

W4-3

Arthroscopic arthrodesis 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. The purpose of this paper is to investigate short term result. [Methods] We retrospectively studied 9 ankles of 9 RA patients. There were 3 males and 6 females. The mean age at the operation was 12.6 years old, and the mean disease duration was 12.6 years. Pre-operative mean dorsi-flexion was 5 degrees, and mean planter-flexion was 27 degrees. Larsen grade was classified IV in 5 and V in 4 ankles. The mean follow-up period was 2.6years. We used traction apparatus and two arthroscopic portals. The talo-tibial joint was debrided arthroscopically and fixed with 4-5 cannulated cancellous screws under fluoroscopic control. After surgery the ankles were immobilized for 4 weeks, and the patients were allowed to walking with ankle brace. 5-6 weeks after surgery. [Results] No surgical complication was observed. All patients achieved pain-free walk after 7.8 weeks and complete bone union after mean 12.4 weeks after surgery. The mean JOA score significantly improved from 39.4 preoperatively to 52.3 postoperatively. [Conclusion] Arthroscopic arthrodesis is a minimum invasive and reliable surgical treatment for rheumatoid ankle without severe varus-valgus deformity or bone loss.

W4-4

Clinical results of modified Scarf osteotomy for severe deformity of hallux valgus in patients with rheumatoid arthritis

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Conflict of interest: None

We investigated clinical results of modified Scarf osteotomy for severe deformity of hallux valgus in patients with rheumatoid arthritis. 12 RA patients (13 feet) were assessed after an average follow-up of 12.5 months. X-rays of feet were taken pre and postoperatively at the final follow-up. JSSF hallux scale were measured before and after surgery and the angle of HV (HVA), M1M2 (M1M2A) and M1M5(M1M5A) were also examined, moreover, the deviation of sesamoid bone were scored using Hardy's classification. In results, the mean JSSF hallux scale was 32.1 points preoperatively and 90.5 points at final follow-up, respectively. The mean HVA were 45.6 degrees pre-operatively and 10.5 degrees at final follow-up. The mean M1M2A were 14.9 degrees pre-operatively and 3.9 degrees at final follow-up. The mean M1M5A were 37.6 degrees pre-operatively and 22.1 degrees at final follow-up. The results of these measurements were improved in all cases after operation. Finally, positions of the sesamoid bone were improved in all cases at final follow-up using Hardy's classification. In conclusion, our results show that modified Scarf osteotomy will be beneficial methods for severe deformity of hallux valgus in patients with rheumatoid arthritis.

W4-5

Clinical outcome and mortality after total hip arthroplasty in hemodialysis patients

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Conflict of interest: None

[Objectives] We retrospectively evaluated the clinical outcome and mortality after total hip arthroplasty (THA) and clarified its usefulness in hemodialysis (HD) patients. [Methods] We evaluated 8 HD patients (8 hips) with chronic hip arthropathy who underwent THA (1 cemented, 7 cementless). They were followed up for a minimum of 2 years. The average age at THA was 57 years. The average duration of HD before THA was 8.5 years. Average postoperative follow-up period was 8.2 years. [Results] Four patients (50%) died an average of 7.8 years after THA. Revision THA was done in 1 hip with aseptic loosening 2.6 years after the primary cemented THA. Thus, we observed a 50% overall mortality rate and 87.5% implant survival rate. Clinical results were evaluated by the JOA score and the D'Aubigne & Postel hip score. Both of the average scores were significantly improved to 73.0 and 14.5 postoperatively from 41.1 and 8.8 preoperatively, respectively. [Conclusions] THA in HD patients can be associated with substantial local and general risks as well as high rates of mortality. Fifty percent of the patients died, however, 87.5% of the THA survived and were well functioning with significant improvement. Thus, THA can be an acceptable treatment and improve quality of life even in HD patients.

W5-1

The prognosis of patients with mutilans-type rheumatoid arthritis given many artificial joint arthroplasty in lower limbs

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Conflict of interest: None

[Objectives] We examined the prognosis of patients with mutilans-type RA operated many artificial joint arthroplasty in lower limbs. [Methods] 92 patients (8 men,84 women) with mutilans-type RA that the subject was under the treatment in our hopital between 1981 and 2011. The method examined performed surgery, complications, fatal cases. [Results] The surgery contents 89 THA(144joints), TKA 92(173 joints), TAA 12(14 joints). 3 joint replacement group (JRG)41cases, 4JRG 45 cases, 5JRG 4 cases,6 JRG 2 cases. The revision surgery was performed in 25 patients,and it was most of loosening. 11 patients underwent spinal operations. The complications were systemic; as for the osteoporosis, hypertension and anemia,local;as for loosening, dislocation and infection. A fatal case was 32 patients, and the cause of death was respiratory failure, sepsis, order of renal failure. At the cumulative survial rate, a significant difference was found in presence or absence of amyloidosis. [Conclusion] A new mutilans-type RA decreased by treatment such as the biological agent, but it seemed that the complications and prognosis required attention with the existing cases.

W5-2

Predictive factors of contralateral TKA in primary unilateral TKA in RA

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Conflict of interest: None

[Objectives] We have perfomed TKA for a knee of stronger symptom in RA patients who have indication of bilateral TKA. But we have experienced a case who needed a staged TKA or one who didn't need a contralateral TKA. So we investigated predictive factors that can judge a need for contralateral TKA at primary unilateral TKA. [Methods] This study involved 20 patients in RA who underwent TKA (12 in bilateral group, 8 in unilateral group). 132 patients in OA were treated as control. The rate of a staged TKA, patient backgrounds, clinical course, clinical evaluation, and imaging evaluation were studied. [Results] The rate of a staged TKA was 60% in RA and 43.9% in OA. There were statistically different in age, contralateral ROM and JOA score preoperatively, and the difference of FTA between operated knees and contralateral knees in OA. There was only statistically different in CRP level at day 14 postoperatively in RA, but bilateral group had a tendency of lower contralateral JOA score and greater difference of FTA. [Conclusion] These results suggest that CRP level, contralateral JOA score preoperatively, and the difference of FTA might be predictive factors for contralateral TKA at primary unilateral TKA in RA.

W5-3

The effect of ankle stability for kinematics in 2-component total ankle arthroplasty

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Conflict of interest: None

[Objectives] Many prostheses for total ankle arthroplasty (TAA) have been developed around the world. Though in current studies three-component, mobile prosthesis have been major, in Japan, two-component, semi-constrained alumina ceramic total ankle arthroplasty (TNK Ankle) had been most performed since 1991 and led to improved clinical outcomes. This study investigated in vivo kinematics of TNK Ankle using radiographic devices to understand biomechanical conditions of prostheses. [Methods] Between 2007 and 2008, twenty-one patients (20 women and 1 man, 19 OA and 2 RA) having TAA with TNK Ankle examined with fluoroscopy at postoperative 1 year. Weight-bearing lateral dynamic view was imaged between forced dorsiflexion and plantarflexion. Simultaneously varus and valgus stress and anterior drawer radiographs in implanted ankles were obtained. Each fluoroscopic image was analyzed with 3D-2D model registration technique. [Results] The components had enough range of dorsoplantar flexion and some flexibility for rotation in frontal and horizontal plane. Besides, some correlation between ankle stability and range of movement in each direction obtained. [Conclusion] To take advantage of simple mechanism, two-component TAA would need further biomechanical studies for better clinical outcomes.

W5-4

Long term result of TKA in rheumatoid arthritis

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Conflict of interest: None

[Objectives] We report long-term results(over 10 years) of total knee arthroplasty (TKA) for the treatment of rheumatoid arthritis (RA). [Methods] Fourteen patients with Thirty- seven knees were examined.Clinical results were evaluated using the Knee Function

Scoring System developed by three universities. Radiographs were evaluated for the loosening, sinking and insert-wear of TKA. Post operative complication were evaluated. [Results] The function score significantly improved from 47.6 to 83.6 points. The extension of knee joint improvesd from -20 to 0 degree after surgery. In radiographic evaluation, 6 patients 7 knees Osteolysis, 1 tibial loosening, 11 patiects 13 knees insert-wear were found. Postoperative complication were 1 infection, 9 patients 9 knees revision TKA. Infection case were recoverd by arthroscopic debridement. Revision TKA were caused by 1 loosening and 9 Insert were. [Conclusion] Clinical result and ROM were improved. Infection is only 1 knee and recoverd by arthroscopic debridement. Insert wear cases were caused by the problem of inplant design.

W5-5

A change of the patients background of total hip arthroplasty for the patients with rheumatoid arthritis

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Conflict of interest: None

[Objectives] When the joint destruction is inhibited in rheumatoid arthritis (RA) by a biological drug, and, as a result, the number of the surgery will decrease in future.We investigated the RA patients performed total hip arthroplasty (THA) in reacent 12 years. [Methods] We investigated the THA of patients with RA performed at our hospital during December, 2011 from January, 2000. We investigated number of THA cases every each year, age at surgery, duration of RA, medication and evaluation of pre-operative X-rays. [Results] The total number of the primaly THA were 561 cases, and RA were 54 cases (9.6%). The number was a tendency to decrease. There were few changes in the patients background with age at surgery and duration of RA. The steroid rate of use decreased. On the other hand, the MTX rate of use and the rate of use of the biological drug increased. A case of Larsen grade5 decreased by the X-rays evaluation. [Conclusion] The THA case for RA decreases in 2000's, and the patients background changes, too.

W6-1

Prognostic factors in dermatomyositis complicated by acute or subacute interstitial pneumonia that was treated with combination therapy of cyclosporine (CSA) and prednisolone (PSL)

Kentaro Isoda[1], Kenichiro Hata[1], Tohru Takeuchi[1], Shuzo Yoshida[1], Takeshi Shoda[1], Takuya Kotani[2], Shigeki Makino[1], Toshiaki Hanafusa[1]
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Conflict of interest: None

[Objectives] To evaluate the prognostic factors in dermatomyositis complicated by acute or subacute interstitial pneumonia (DM-A/SAIP) that was treated with the combination therapy of CSA and PSL. [Methods] This study included the patients admitted to our hospital from March 2004 to April 2012. All patients were treated with the combination therapy of cyclosporine (3.5-4.5 mg/kg/day) and prednisolone (0.75 mg/kg/day). The prognosis in 24 weeks and prognostic factors in DM-A/SAIP were retrospectively evaluated. [Results] 29 patients were enrolled into this study. (mean age:59.0±10.0, male:female=6:23, A:SA=10:19). 10 patients had anti-Jo-1 antibodies. 14 patients were initiated with intravenous cyclophosphamide. 23 patients survived and 6 patients died. (4 died of aggravation of IP and 2 died of infection.) Serum ferritin levels before the initiation of therapy were significantly higher in dead group (1788.25±203.56 ng/ml) than survival group (253.30±108.81 ng/ml) (*P<0.005*). $AaDO_2$ before the initiation of therapy were significantly larger in dead group (157.7±33.41 mmHg) than survival group (29.2±14.2 mmHg) (*P<0.01*). [Conclusion] High ferritin levels and large $AaDO_2$ before the initiation of therapy are possibly prognostic factors in DM-A/SAIP.

W6-2

The curative effect of rheumatic disease associated lung interstitial pneumonitis by Deep inspiratory breath hold PET/CT

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Conflict of interest: None

[Objectives] This study examined contributions of deep inspiratory breath hold (DIBH) -FDG-PET/CT to clinical assessment of ILD in rheumatic diseases. [Methods] We assessed ILD in 24 patients with collagen diseases,who had follow-up examinations by using DIBH-PET/CT. [Results] Baseline PET scan results were positive in 16 patients and negative in 8 patients.17 patients(11 FDG positive,6 FDG negative) were treated and 7(5 FDG positive,2 FDG negative) patients were not treated.6 patients had been treated previously upon first PET scan.Overall, patients with a positive PET scan result had higher KL-6 level than patients with a negative PET scan. Following initiation of treatment, decrease in C-reactive protein and KL-6 level was larger in patients with initial positive PET scan result than in patients with negative PET scan result.Follow-up PET scan, performed in 16 patients with initial positive PET scan result, completely normalized in 7 patients. 8 of 11 patients (73%) with positive baseline were treated successfully, compared to 2 of 6 patients (33 %) with negative baseline. [Conclusion] Deep inspiratory breath hold PET/CT is useful for monitoring of activity in rheumatic disease associated lung interstitial pneumonitis.

W6-3

Aggressive therapy of Pulmonary fibrosis in myeloperoxidase antineutrophil cytoplasmic antibody associated vasculitis

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Conflict of interest: None

[Purpose] We investigated the prognosis and prognostic factors of pulmonary fibrosis in myeloperoxidase antineutrophil cytoplasmic antibody associated vasculitis. [Methods] Among patients of pulmonary fibrosis in microscopic polyangiitis with myeloperoxidase antineutrophil cytoplasmic antibody in whom remission was induced in our hospital between 2001 and 2012. [Results] The subjects consisted of 14 males and 18 females. The average age was 71.8 years (range: 59 to 75 years). At starting of the therapy, MPO-ANCA 379±486EU, KL-6 692±551U/ml, Aa-DO2 33.6±58, %FVC 80.9±18%, %DLco/VA 61.5±19%, RV/TLC 42.0±8.4%. Initial HRCT findings were 25 UIP pattern and 7 non-UIP. Using the Kaplan-Meier life table method, the 5-year survival rate was estimated to be 85.5%. [Conclusion] The prognosis of pulmonary fibrosis in myeloperoxidase antineutrophil cytoplasmic antibody associated vasculitis was good, and aggressive therapy of withim-

munosuppressive agent were useful.

W6-4

There are differences among interstitial pneumonia(IP) treatments associated with 4 collagen vascular diseases of our institute

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Conflict of interest: None

[Objectives] We aim to know how differ IP treatments of PM/DM, RA, SSc and MPA. [Methods] On September 30, 2012, we reviewed clinical data of 4 disease's patients with IP of our institute. [Results] Total IP patients were 267 with 71 males. There were 58 PM/DM, 69 RA, 94 SSc, 25 MPA and 21 combined disease patients. The means of KL-6, %VC and %DLCO is 493, 96, 42 in PM/DM. 456, 90, 37 in RA, 597, 89, 38 in SSc, 576, 80, 29 in MPA. In PM/DM patients, 38 received cyclosporine (CyA), 6 tacrolimus (Tac), 8 azathioprine (AZP), 2 no anti-IP therapy. In RA, 1 received CyA, 6 Tac, 2 AZP, 61 no anti-IP therapy. In SSc, 4 received CyA, 10 Tac, 21 AZP, 61 no anti-IP therapy. In MPA, 2 received Tac, 13 AZP, 10 no anti-IP therapy. [Conclusion] There were no prominent diffences of KL-6, %VC and %DLCO among 4 disease. In PM/DM patients, there is high frequency of anti-IP therapy, and CyA treatment.

W6-5

Clinical characteristics of interstitial lung disease associated with adult Still's disease

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Conflict of interest: None

[Objectives] Interstitial lung disease (ILD) is a rare complication of Adult Still's disease (ASD). Some patients progress to AIP. However clinical characteristics and treatment strategies of ILD with ASD are not established. To clarify the clinical characteristics and treatment strategies of ASD-associated ILD (ASD-ILD). [Methods] We retrospectively investigated 84 patients who were diagnosed with ASD. We extracted the patients with ILD in ASD and reviewed the clinical characteristics of the ASD-ILD. [Results] ASD-ILD was identified in 7 cases (8.3%) and tended to occur in older female. HRCT showed marked interstitial thickening in all cases. There were neither honeycomb formation nor lung volume loss. ASD-ILD showed two clinical subtypes. Four cases had a shorter time from ASD onset to the detection of ILD, higher levels of serum ferritin and rapidly progressive ILD. The other cases had a long time to the detection of ILD and stayed asymptomatic. ASD-ILD cases frequently complicated with HPS and had a higher relapse rate of ASD. [Conclusion] In a case report, marked lymphocytic infiltration to lung tissue interstitial tissue was reported. The thickening of interstitial lung tissue was most characteristic findings of ASD-ILD. Histologic investigation is definitely needed.

W7-1

The clinical features of pulmonary arterial hypertension associated with connective tissue diseases: analysis of 26 cases

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Conflict of interest: None

[Objectives] Pulmonary arterial hypertension (PAH) is a life-threatening complication in connective tissue diseases (CTD). The aim of this study was to clarify the clinical features of PAH-CTD. [Methods] Patients with PAH-CTD, diagnosed by right heart catheterization between 1997 and 2012, were included in this retrospective study. [Results] This study comprised 26 patients including 11 with systemic sclerosis (SSc), 8 with systemic lupus erythematosus, 4 with mixed connective tissue disease, and 3 with other CTD, followed up for 30 (2-173) months. Three years overall and event-free survival rate were 86% and 49%, respectively. WHO functional class (FC) III or more at baseline ($p = 0.01$), complication of interstitial lung disease ($p = 0.02$), and no improvement of WHO FC at 12 weeks after the initiation of the treatment ($p = 0.04$) were identified as independent poor prognostic factors in Cox regression analysis. Nine out of 12 non-SSc patients treated with corticosteroids achieved one or more improvement of WHO FC at 12 weeks after the initiation of the treatment. [Conclusion] Early diagnosis and treatment are important for better prognosis of patients with PAH-CTD. Non-SSc patients should be considered to treat with vasodilators and immunosuppressive therapy.

W7-2

Enforcement criteria of right heart catheterization at the screening of the connective tissue diseases associated pulmonary hypertension

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Conflict of interest: None

[Objective] The right heart catheterization (RHC) is a gold standard for diagnosing connective tissue diseases associated pulmonary hypertension (CTD-PH), but the suitable criteria for the patient selection for RHC is not yet established. The aim of this study is to establish the enforcement criteria for RHC based on noninvasive tests. [Methods] A retrospective study was made of 28 RHC data from 20 CTD patients between 2008 and 2012, analyzing their blood test, pulmonary function test, and doppler echocardiography. [Results] The cut-off level in each parameter corresponding to mPAP≧ 25mmHg on RHC was developed by using ROC curve (cut-off point; BNP 38pg/ml, %DLCO 53%, %FVC/%DLCO 1.58). The sensitivity / specificity in BNP, %DLCO, and %FVC/%DLCO were 67%/62%, 75%/57%, 88%/43%, respectively. Based on these results and ESC/ERC guidelines (2009), we developed our RHC enforcement criteria; 1) with systolic pulmonary arterial pressure (sPAP) on echocardiography ≧50mmHg, or 2) with sPAP 37-50mmHg and meeting cut-off level either of BNP, %DLCO, %FVC/%DLCO or has unexplained dyspnea. We prospectively carried out screening for 44 SLE, 33

SSc, 2 MCTD patients and one patient corresponded to this criteria. [Conclusion] These results suggest that this criteria is valid.

W7-3

The survey of pulmonary artery hypertension associated with connective tissue disease (CTD-PAH)

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Conflict of interest: None

CTD-PAH had a lower survival rate compared with IPAH before. However, the prognosis in CTD-PAH is improving by changed strategy of diagnosis and treatment. REVEAL study provided new strategy of diagnosis and treatment. It is important to investigate medical practice for CTD-PAH in Japan to improve the strategy of treatment and diagnosis. (Method) We used our registry of CTD-PAH enrolled by 7 facilities in Kagawa prefecture. The following factors were examined retrospectively; (1)underlying disease (2)PAH diagnosis (3)UCG (4)RHC (5)treatment (6)prognosis. (Result) 35 cases were analyzed. As for underlying disease, MCTD was most frequent (40%). The rate of non-SSc was 80%. The patient diagnosed using RHC was only 60%. The others were diagnosed by UCG only (40%). As for use of PVDs, 25% CTD-PAH patients were treated with combination of PVDs at the initial therapy. However, the frequency of RHC and the PVDs combination therapy at the initial treatment were increasing in several years. Immunosuppressive therapy was conducted using GC, CY, TAC, AZA, TCZ. (Discussion) The strategy of diagnosis and treatment were changed within several years. However, there exists many issues to be discussed about the frequency of RHC, the indication of immunosuppressive therapy and when to start the therapy.

W7-4

Clinical characteristics of patients with rheumatoid arthritis complicated by interstitial lung disease and airway disease: examination of the IORRA cohort study

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Conflict of interest: None

Objective: To demonstrate the clinical manifestations of patients with RA complicated with interstitial lung disease (ILD) and airway diseases (AwD) such as bronchiectasis and middle lobe syndrome. **Methods:** The subjects were self-reported to have lung diseases in the IORRA study in April 2008. Their diagnosis of lung diseases was confirmed by their medical records. Disease activity (DAS28), physical function (J-HAQ), respiratory symptoms and use of methotrexate (MTX) and prednisolone (PSL) were evaluated. **Results:** Of the 5,349 subjects, 5.0% had ILD alone (ILD+ group), 2.1% had AwD alone (AwD+ group), 0.2% had both ILD and AwD (ILD+/AwD+ group), and 92.4% had neither (ILD-/AwD- group). The mean DAS28/J-HAQ; 3.6/1.00 in the ILD+ group, 3.9/0.96 in the AwD+ group, 4.9/1.92 in the ILD+/AwD+ group, were higher than those in the ILD-/AwD- group (3.3/0.70) ($p<0.01$, respectively). The respiratory symptoms (cough/sputum/sinusitis) were more frequently present in the ILD+ group (19%/24%/13%), AwD+ group (37%/50%/26%), ILD+/AwD+ group (45%/55%/18%) than in the ILD-/AwD- group (5%/8%/8%) ($p<0.001$). No trend was observed in the use of MTX or PSL. **Conclusion:** The results of the large-scale cohort study suggest that the presence of lung lesions might affect the condition of RA.

W7-5

Study on background and deteriorioration of the Nontuberculous mycobacteria(NTM) in the collagenosis patient

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Conflict of interest: None

Objections: We studied the characteristic of a collagenosis patient complicated with NTM. Mothods:1602 collagenosis patients who visited in our hospital a year from September, 2011, we analyzed 12 case when we juged that has a diagnosis of NTM by the diagnostic criteria of the Japanese society for tuberculosis/ the Japanese respiratory society.We compared 5 that the chief physician took as exacerbation with 7of non-exacerbation. Results: In all 12 cases, the breakdown of the original illness is RA 8, 10 cases include PSL use the past And 1 case using infliximab. Among exacerbation group, 1 case did not have the use of DMARDs in SS, and the others were RA2, SLE1, MPA1. 5 was MAC in exacerbation group.We accepted an existing lung disease recognized it to 4 in the exacerbation group and 3 in the non-exacerbation group.We accepted hollow shadow in CT in 3 in exacerbation group.The exacerbation group all cases gave an antibiotic treatment.It was 1 case in exacerbation group to have given an antibiotic treatment at the time of exacerbation, and there was one recrudescent after NTM completion of treatment.It was 4 cases by an antibiotic treatment improvement, to be unchangeable. Conclusion: The NTM exacerbation group accepted an existing lung disease and a hollow lesion to a high rate.

W8-1

The features of TRAPS in Japan

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Conflict of interest: None

[Objective] TRAPS is an autosomal dominant inherited disorder associated with *TNFRSF1A* gene mutations. Most of the reported families are of European and a few of Asian including Japanese. The purpose of this study is to find undiagnosed TRAPS patients and elucidate the features of TRAPS in Japan. [Methods] The Ministry of Health, Labor and Welfare study group for TRAPS conducted a national survey. We sent survey questionnaire to the doctors in the hospitals with more than 200 beds and asked whether they had the patients suspected of TRAPS. All the patients that were suspected as TRAPS underwent genetic test if they agreed. [Results] Up to November 2012, 151 patients underwent genetic test. T61I, V136M and S321I variants were identified in 8, 1 and 1

patients, respectively. All of these variants were not reported from counties other than Japan. TRAPS patients in Japan have less symptoms other than fever such as abdominal pain than ones in other countries. *TNFRSF1A* variants are subdivided into structural and non-structural mutations, which cause pathologically and clinically different TRAPS. We conducted experiments with cell line to examine how the variants we identified affect the structure of TNFR1. [Conclusions] TRAPS in Japan is genetically and clinically unique.

W8-2

Genomic analysis of patients with primary hypertrophic osteoarthropathy (PHO)

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Conflict of interest: None

[Objectives] We previously reported 3 cases of PHO in this meeting (52th JCR). Recently, responsible genes (*HPGD*, *SLCO2A1*) were identified in this disease. [Methods] In this study, we analyzed the genomic DNA derived from 4 PHO patients (complete type; 1 patient, incomplete type; 3 patients). [Results] We identified *SLCO2A1* mutations in all PHO patients. Moreover, *MEFV* mutations (P369S/R408Q, R202Q/G304R) were seen in 3 PHO patients. [Conclusion] These results suggest that PHO should be caused by *SLCO2A1* mutations and *MEFV* mutations might be one of the risk factors for inflammatory responses in this disease, especially in 3 PHO patients.

W8-3

Genomic analyses in the patients with unknown fever

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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. Autoinflammatory syndrome is known to be important for the differential diagnosis of unknown fever. We examined the responsible genes including *MEFV* and *TNFRSF1A* in the genomic DNA derived from 330 patients with unknown fever. We diagnosed as FMF (M694I) in 16 patients (5.3%) and detected another *MEFV*mutations, such as E84K, R202Q, E225K, R304R, R354Q, P369S, and R408Q in 52 patients (17.3%) out of 301 genomic analyses. We identified *TNFRSF1A* mutations, such as T61I, C88Y, and V125M in 13 patients. These results suggest that we could not detect the *MEFV* and *TNFRSF1A* mutations in 73.2% of the patients with unknown fever.

W8-4

Clinical characteristics in 11 patienents of adult and elderly-onset Familial Mediterranean fever (FMF)

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Conflict of interest: None

FMF is the autoinflammatory disease with periodic fever and symptoms of serositis, such as abdominal, chest pain and joint pain. While it's considered a rare in Japan, some patients has atypical periodic fever (more 3 days and/or not always once a month) and no serositis. We experienced 11 cases who developed variant FMF. The average of onset is 52.5±15.8 y/o and diagnosis is 57.2±11.6 y/o. While 10 cases have fever, all cases have arthritis and 5 cases have muscle pain, no patients complain chest or abdominal pain. They have one or more mutations of MEFV, which is responsible for the development of FMF. They are all exon 2 mutations consisting of E148Q (7 pts), L110P (3 pts), R202Q (2 pts), G304R, E369S and R408Q (each 1 pt). Their comlications are gout, type 1 diabetes mellitus (DM), type 2 DM, chronic kidney disease, adult onset Still's disease, IMAM (inflammatory myopathy with abundant macrophages), RS3PE syndrome and SLE. It's not only these diseases may trigger the onset of FMF, but also FMF may modify these diseases. It's noteworthy that corchicine improved inflammatory symptoms and serological findings dramatically in 6 of 7 cases. It's important that FMF might be developed also in the elderly without family history, and so we have to diagnose and treat as soon as fast.

W8-5

Analyses of polymorphisms of the MEFV gene in patients with periodic fever

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Conflict of interest: None

[Objectives] Hereditary autoinflammatory disease is characterized by periodic fever, rashes, polyarthralgia, myalgia, abdominal pain and inflammatory reactions. Several gene polymorphisms and mutations may contribute to the pathogenesis of autoinflammatory disease. In the present study, we explored the frequencies of several single nucleotide polymorphisms (SNPs) of the MEFV gene in patients with periodic fever. [Methods] One hundred sixty three patients with periodic fever were enrolled. Periodic fever are defined as more than 3 episodes of fever (> 38°C) expanding more than 3 days. Patients with infection, collagen diseases, and malignancy were excluded. All patients are Japanese. Genomic DNA was extracted from all of patients with informed consent. We performed direct sequencing to analyze the MEFV gene. [Results] We found 77 patients with mutations of MEFV gene. The non-synonymous SNPs (case count) are E89K (1), L110P (14), E148Q (50), R202Q (4), G304R (4), P369S-R408Q (15), S503C (3), and M694I (7). [Conclusion] We conclude that familial Mediterranean fever is an important differential diagnosis concerning patient with periodic fever in Japanese.

W8-6

The effect of colchicine treatment after *MEFV* gene analysis in Japanese patients with familial Mediterranean fever

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Conflict of interest: None

[Objectives] Familial Mediterranean fever (FMF) is a hereditary disorder characterized by recurrent attacks of fever with peritonitis, pleuritis, and arthritis. Although colchicine treatment is effective in most patients in Mediterranean area, the effect of colchicine in Japanese patients is unknown. [Methods] We investigated clinical response to colchicine treatment in 113 patients who have some *MEFV* gene mutation. We considered whether colchicine was used, dosage and administration, and the effectiveness by genotypes. The effect of colchicine classified remarkably effective (attacks almost free), effective (attacks relief), no effect, and discontinue by side effects. [Results] For the patients with M694I mutation(41 patients), colchicine was received about 75% patients and those of them were all remarkably effective or effective. A number of patients with compound heterozygote of L110P/E148Q and E148Q heterozygote only (45 patients) were effective though some patients didn't use colchicine because attacks are not severe. The effectiveness was limited for the patients with compound heterozygote of P369S/R408Q. None of them were remarkably effective. [Conclusion] The effect of colchicine treatment was different by genotypes. These findings may be helpful at the treatment.

W9-1

Longitudinal Change in Treatment Modality and QOL among RA Patients treated at the clinics affiliated to Tochigi-Rheumatism-Network (TRN)

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Conflict of interest: Yes

[Objectives] To examine the longitudinal change in QOL and to correlate it to treatment modality among RA patients treated at the affiliated clinics to Tochigi-Rheumatism-Network (TRN). [Methods] During 4 months from Sept. to Dec. every year since 2007, a patient treated at a clinic affiliated to TRN was asked to fulfill a questionnaire on age, sex, disease-duration, global-health (GH), and the doctor in-charge was asked to write usage and amount of methotrexate (MTX) as well as usage and type of biologics. [Results] Eighty-one clinics are affiliated to TRN now. Six-hundred and 20 questionnaires were collected from 23 clinics in 2007. The number increased gradually, year by year, up to 1,627 from 39 clinics in 2011. MTX was used in 58.4% at the average dose of 5.95 mg weekly in 2007; the numbers increased to 70.7% and 7.82 mg, respectively, in 2011. The average level of mHAQ decreased from 0.359 in 2007 to 0.294 in 2011; GH also decreased from 30.0 mm to 26.3 mg. [Conclusion] TRN seems to be effective in the treatment and management of RA patients residing in Tochigi Prefecture. The good relationship of Win (hospital) - Win (affiliated clinic) – Win (patient) is established and hospital and healthcare clinic co-operation (HHC) is needed in every field of medicine and district.

W9-2

Relation between yearly change of physical function (ΔHAQ) and affected joint region by multivariate regression analysis: A Nationwide study based on the *NinJa* (National database of rheumatic diseases by IR-Net in JAPAN) 2011

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Conflict of interest: None

[Objective] We reported HAQ was highly impacted by large joints last year. We analyzed which joints related to ΔHAQ. **[Methods]** Total joint indices (TJI) were calculated as described (Rheumatol Int 2012:32;2569). Serial registered data (2010~11) were extracted from *NinJa* excluding patients received orthopedic surgery. Correlation between ΔHAQ and TJI by multivariate regression was examined using 79 patients who fulfilled stage I, RA duration ≦1 yr and ΔHAQ<0, where ΔHAQ can be considered as ΔactHAQ, on the assumption that HAQ can be separated into actHAQ, which relates to disease activity, and damHAQ, which represents irreversible joint damage. A multivariate regression model to estimate ΔdamHAQ was obtained applying 4161 data. **[Results]** ΔactHAQ correlated with TJI of upper/small joints negatively and with ΔTJI of large joints positively. ΔdamHAQ was positively correlated with class, Δclass and TJI of large joints. ΔactHAQ significantly declined in patients with RA duration≦1 yr, high disease activity, RA progression and ΔDAS<-0.6. ΔdamHAQ significantly elevated in patients with RA duration>1 yr, high disease activity, RA progression and ΔDAS>1.2. **[Conclusion]** ΔactHAQ was related to TJI of upper/small joints and ΔTJI of large joints. ΔdamHAQ was connected to TJI of large joints.

W9-3

Assessment of work productivity and activity impairment in patients with rheumatoid arthritis in the Institute of Rheumatology Rheumatoid Arthritis (IORRA) cohort

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Conflict of interest: None

[Objectives] Indirect costs of RA due to losses such as reduced productivity are an important social issue. [Methods] In RA patients who participated in the IORRA study in October 2011, a cross-sectional analysis was conducted to determine the influence of RA on work performance as assessed using the Work Productivity and Activity Impairment (WPAI) questionnaire. [Results] Of 5700 patients with RA, 2162 patients (37.9%) were paid workers. The absenteeism rate, presenteeism rate, and activity impairment were 2.5%, 16.1%, and 19.8%, respectively. The absenteeism was weakly correlated with the DAS28, J-HAQ, and EQ-5D scores. The presenteeism and activity impairment were moderately or strongly correlated with these scores. Among RA patients with high J-HAQ (>1.5), the absenteeism rate, presenteeism rate, and activity impairment were 11.7%, 44.1%, and 53.0%, respectively, and were significantly worse compared with 2.2%, 9.9%, and 11.1%, respectively, in RA patients with low J-HAQ (<0.5). [Conclusion] In Japanese patients with RA, work productivity and activity impairment were strongly correlated with the extent of physi-

cal disability and QOL. The study results indicated that the key to reduce the indirect costs is to control RA before it can cause physical disability and impaired QOL.

W9-4

Assessment of problems on evaluating ADL and factors militating ADL in Japanese RA patients

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Conflict of interest: None

[Objectives] mHAQ had been developed as follow up tool to evaluate ADL of RA patients. In Japanese RA patients, mHAQ score often deviated largely from HAQ score. The aim of this study was investigating the factor causing the deviation of mHAQ and HAQ score, and the factor carrying a lot of weight on HAQ score. [Methods] ACR coresets were collected at the same time in outpatients RA clinic of our institution from September to November 2012. Total of 348 patients data were included to this study. The factors causing the deviation of HAQ and mHAQ and influencing the HAQ were assessed. [Results] The mHAQ score was significantly lower than HAQ score. The most deviated question was 3, and next was 8. In the back ground factor review influencing the HAQ score, Steinblöcker's stage classification was more strongly correlated with HAQ than class. In the disease activity components, patient'sVAS and tenderness joint count were strongly correlated with HAQ. [Conclusion] In Japanese RA patients, if use mHAQ, changing the extract question from F to G in Question3, and from S to T in 8 improved the reproducibility to HAQ. Recently, swelling joint count is weighted in clinical examination, but to achieve functional remission, pain and tenderness joint should be recognized as important indicator.

W9-5

Evaluation of the effect of working to QOL in rheumatoid arthritis patients who achieved clinical remission

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Conflict of interest: None

[Objectives] In this study, we evaluated the effect of working to QOL in rheumatoid arthritis patients who achieved clinical remission. [Methods] 34 patients who achieved clinical remission (DAS28CRP<2.6) were included. General health assessment VAS (GH-VAS), Health assessment Questionnaire (HAQ), The Disabilities of the Arm, Shoulder and Hand (DASH), EQ5D were administered in patients. [Results] 14 patients were at work (group W) and 20 patients were not (group N). Comparison of average GH-VAS between 2 groups, there was not significant difference (group W/N: 1.9±1.6/1.7±1.6).On the other hand, Comparison of average HAQ and DASH, these in group W were significantly higher than in group N (HAQ: 1.0±0.9/0.4±0.6 P<0.05, DASH: 30.0±26.5/12.1± 15.8 P<0.05). Simple regression analysis revealed correlation between HAQ and EQ5D in group W, but not revealed in group N. [Conclusion] In this study, RA patients who achieved clinical remission were assessed. These results suggested that functional disability is more influence on patients who are at work than those who are not.

W9-6

Investigation of factors influencing physical function mid-term status after total knee 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. [Methods] We identified 77 patients (10 men, 67 women) registered with NinJa who underwent TKA in 2004, 2005, or 2006, and who had a 5-year follow-up without any other surgical procedures. The numbers and values of candidate factors were compared between the 34 cases with better mHAQ scores (group B) and the 32 cases with worse mHAQ scores (group W) at the five year follow-up relative to the baseline score. Examined factors included sex, age, disease duration, stage, class, mHAQ, CRP, ESR, PtPainVAS, PtGVAS, DrVAS, DAS28, CDAI, and SDAI. [Results] A significant difference ($p<0.05$) was recognized at baseline between groups B and W for age (61.2 and 65.6 years old, respectively), mHAQ (1.10 and 0.77, respectively) and DrVAS (4.79 and 3.65, respectively). CRP tended to be lower in group B (1.70) than in group W (2.83) ($p = 0.067$). Not only the lower limb scores, but also the upper limb mHAQ scores improved in group B. [Conclusion] Our results suggest that the effect of TKA on physical function improvement continues for a mid-term duration even among RA patients with relatively high physical dysfunction when patients are relatively young and the inflammation status is controlled.

W10-1

Evaluation of hepatitis B virus (HBV) infection in rheumatoid arthritis patients treated with biologics

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Conflict of interest: None

Objectives: The aim of this study was to examine the safety of biologics therapy in patients with rheumatic disease and hepatitis B virus (HBV) infection. Methods Patients with past HBV infection were included in the study. All patients showed hepatitis B surface antibodies (anti-HBs) and of negative serum HBV DNA. Using biologic were 3 infliximab, 1 etanercept and 1 abatacept. Results: Five patients showed HBsAg-negative and anti-HBc-positive serology indicative of past HBV infection. Among these 5 patients, two viral reactivation was observed in patients while using MTX with infliximab. However all of them showed elevation of HBV-DNA, only one showed elevation of aminotransferase. Withdrawal of biologics and treated with entacavir in these two patient, it showed negative HBV-DNA again and no development of acute hepatitis nor fulminant hepatitis. Conclusions: Regular monitoring of both serum aminotransferase levels and HBV-DNA were useful to detect reactivation of HBV.

W10-2

Re-introduction and Continuation of Biologics after Episodes of Infectious Diseases

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Conflict of interest: None

Purpose: There are reports regarding infectious diseases (IDs) after introduction of biologics (BIOs), however, only a few reports describe the treatment after the episode of IDs. We here report how the patients were treated after the episodes of IDs. Method: Out of 156 patients with rheumatic diseases introduced with BIOs between May 2005 to November 2011, 59 patients were analyzed in whom episodes of IDs developed which needed specific treatment. Seventeen severe infectious disease episodes (SIE) which needed hospitalization were mainly analyzed. Results: The SIE included pneumonia in 5, pneumocystis pneumonia in 2, pulmonary cryptococcosis in 3, skin infection in 3, and others. The BIOs under use were IFX in 6, ETN in 9, and ADA in 2, respectively, and there were no differences in the incidence of SIE episodes among BIOs. Eight patients stopped receiving BIOs, whereas 7 patients stopped BIOs temporarily and restarted them. The incidence of SIE was 5.3/100pt-year and that after 1 SIE was 6.3/100pt-year, no significant differences. Other patients continued BIOs during and after non-SIE without any troubles. Conclusions: BIOs can be re-introduced in patients in whom SIE developed without high incidence of infection.

W10-3

Autopsy review for rheumatoid lung disease and nontuberculous mycobacteriosis

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Conflict of interest: None

Background: In our previous report (JCR, 2008), 13% of 430 RA patients had chronic lower airway diseases (CLAD), and nontuberculous mycobacteria (NTM) in sputa were detected in 1/4 of the CLAD patients. This study investigated autopsy findings in our RA patients retrospectively in special reference to rheumatoid lung disease and mycobacteriosis. **Patients**: Of 141 deceased RA patients registered in our database, 15 patients had been autopsied. All the specimens were reviewed for lung pathology. **Results**: Causes of death in 15 patients included 4 bacterial pneumonias and 3 infection-induced interstitial pneumonias (IP). Ten patients had lung involvement of RA (3 bronchiolitis, 5 bronchiectasis, 6 IP). Two patients had tuberculosis (Tb) and one patient had NTM disease (NTMD) in their history. One NTMD patient was treated for RA by etanercept in 2004, and by infliximab since 2005, which was discontinued because of mild NTMD flare. He received anti-M. avium therapy until 2008, and 4 sessions of tocilizumab therapy in 2008. He died of bacterial pneumonia in 2012 without clinical flare of the NTMD. None of the 15 patients showed active mycobacteriosis at autopsy. **Conclusion**: Active NTM disease may be infrequent even in RA patients having lower airway disease, i.e., common NTM carriers.

W10-4

Efficacy and safety of proper oral methotrexate dose in rheumatoid arthritis patients with infliximab therapy

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Conflict of interest: None

BACKGROUND: Clinical, structural and functional remission become targets for infliximab therapy from Japanese study such as RECONFIRM and RISING in patients with established rheumatoid arthritis (RA). OBJECTIVE: Proper oral methotrexate dose with infliximab therapy has no evidence. To aim of this study is to analyse oral methotrexate dose and disease activity with infliximab therapy regarding efficacy and safety and to determine proper oral methotrexate dose. METHOD: 644 patients with RA who had received infliximab treatment enrolled this study. RESULTS: The mean BL-MTX dose was 9.56mg/week: 82% of these was more than 8mg/week. DAS of week 22 and week 54 was corrrelated with BL-MTX dose. There was no significant difference between delta DAS and BL-MTX dose of BL-22w and BL-54w. DAS of week 54 was significantly corrrelated with that of week 22. Higher dose of BL-MTX led to remission and low disease activity of week 22. The group of BL-MTX dose ≥12mg led to lower DAS of week 22. The rate of remission and loe disease activity was highest in the group of BL-MTX dose ≥12mg. CONCLUSION: Proper oral methotrexate dose with infliximab therapy is more than 12mg/week before the therapy from this analysis.

W10-5

Biologics therapy for rheumatoid arthritis patients administrated Entecavir

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Conflict of interest: None

[Objectives] Prescription of nucleoside analogs is recommended for RA patients who are positive of hepatitis B surface antigen (HBs-Ag) by guideline. We repot six cases of biological therapy under the prescribed nucleoside analogs (Entecavir). [Methods] Six RA patients who are positive of HBs-Ag at screening test were prescribed Entecavir under controlled hepatologist. After HBV-DNA decreased under 2.1 log copies/mL, we started biological therapy. We investigated the HBV markers and genotype at pre-treatment and change of amount of HBV-DNA, HBs-Ag and alanine aminotransferase (ALT). [Results] The average age was 54.7 year, disease duration of RA was 10.9 and DAS28-ESR was 5.51. Biologic agents were one Infliximab, two Etanercept, two Adalimumab, and one Tocilizumab. HBs-Ag of pre-treatment was minimum 12.2 and three cases were over 2000. Amount of HBV-DNA was 4.28 log copies/mL and ALT was 20.2 U/L at pre-treatment. Reactivation of HBV was not confirmed during 2.1 years started biologics. DAS28-ESR was 3.16 at final follow-up. [Conclusion] We can choose the biologic agent as one of the useful treatment for HBV carrier, if the patients take nucleoside analogs simultaneously under the control of hepatologist.

W10-6

Malignant lymphoma in Rheumatoid Arthritis Patient Taking Biologic Therapies in the TBC Registry

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Conflict of interest: None

[Objectives] Rheumatoid arthritis (RA) patients have a high incidence of malignant lymphoma (ML). Although it has been well known about the MTX related ML, there is uncertainty regarding the adverse effect of biologics including ML. [Methods] All patients enrolled in the TBC registry were studied. The crude incidence rate (IR) of ML was calculated as cases per 1,000 patient-years (p-y). [Results] 9 cases were detected in 1,933 patients (4,670 p-y). Mean age was 65 and mean RA duration was 16.4 years. All cases took concomitant MTX. Mean time to onset of ML from biologics initiation was 21 weeks, and within 8 weeks in 5 cases. Histologic types were DLBCL in 6, MALT lymphoma in one, and unknown in 2 cases. Spontaneous resolution with stopping drugs was seen in 3 cases. IR in male was 2.8, and 1.9 in female. IR in the patients with etanercept was 0.4, 2.3 with infliximab, 5.6 with adalimumab, 22.1 with golimumab, 22.8 with abatacept, and no case with tocilizumab. [Conclusion] Since the time to onset of ML was quite short and 3 cases of spontaneous resolution were seen, some cases should have been MTX-related ML. IR was higher in male. Etanercept showed lower IR than infliximab and adalimumab. Further study is necessary for IR with golimumab and abatacept due to their short p-y.

W11-1

Etanercept decreases serum oxidative stress in patints with rheumatoid arthritis

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Conflict of interest: None

【Introduction】 In this study, the effect of etanercept (ETN) on RA disease activity score and serum oxidative stress was examined utilizing Free Radical Elective Evaluator.【Patients and Methods】 Eleven refractory RA patients treated with preexisting disease modifying anti-rheumatic drugs and were newly introduced with ETN were selected. In each patient, disease activity score (DAS)28(4)-ESR, C-reactive protein (CRP), ESR, MMP-3, and d-reactive oxygen metabolites (d-ROM) were examined just before introduction, and 3, 6, 12 months after introduction of ETN. The acquired data were statistically analyzed with t-test and single regression analysis.【Results】 ETN improved DAS28(4)-ESR. It was 4.7 on introduction, and was significantly decreased to 3.0 after 3 months, and then 2.6 after 12 months, respectively. ETN also decreased d-ROM value significantly from 393 U.CARR. on introduction to 327 U.CARR. after 6 months. MMP-3 was significantly decreased from 279 to 138 ng/ml after 6 months. D-ROM was significantly correlated with DAS28, CRP, ESR, and MMP-3, respectively.【Conclusion】 These data suggest that oxidative stress is strongly associated with tumor necrosis factor in pathogenesis of RA. D-ROM value is supposed to be a useful marker of RA disease activity.

W11-2

Exploration of new rheumatoid arthritis disease activity marker by using DNA microarray

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Conflict of interest: None

[Objectives] Although C-reactive protein and DAS28 are widely used for the assessment of rheumatoid arthritis (RA) disease activity, establishment of more specific and sensitive indicators is greatly desired in the aspect of strict judgment of drug efficacy and investigation of the pathogenesis. We conducted exploration of new RA activity markers by DNA microarray. [Methods] We analyzed peripheral blood gene expression profile in 402 RA samples (212 RA cases) by using Whole Human Genome DNA Microarray 4x44k (Agilent). After the multiple steps of statistic procedures, many candidate genes were selected as disease activity marker. [Results] Most correlated gene to DAS28 in the expression level measured by microarray was FAM20A (Family with sequence similarity 20, member A). Average of P value in two probes of this gene are extremely low (2.64E-42 and 4.87E-31, respectively). Microarray results were significantly correlated to reanalysis by quantitative PCR for validation (R^2=0.53). FAM20A expression level was significantly elevated in RA samples compared as that in healthy and disease controls and the change by infliximab administration in RA patients were also significantly correlated to DAS28. [Conclusion] FAM20A is considered to be a promising candidate as new RA activity marker.

W11-3

The evaluation of the IFX and TCZ therapy for patients with rheumatoid arthritis using FDG-PET/CT

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Conflict of interest: None

[Objectives] The FDG-PET can detect the inflammation of patients with rheumatoid arthritis (RA) and evaluate the disease activity of RA patients. Although both infliximab (IFX) and Tocilizumab (TCZ) are the biological preparation by the intravenous drip infusion to RA, the features differ a little. We carried out the FDG-PET/CT scan for RA patients with these two biologics, at baseline and six monthes after the initiation of the therapy, and compare the FDG uptake with the disease activity evaluated by the conventional prameters, and examine the difference among these methods. [Method] 31 RA patients (17 IFX, 14 TCZ, males 6, females 25, age 59.2 ± 12.6 years, disease duration 13.5 ± 13.0 year) were included. FDG uptakes were represented by maximum standardized uptake value (SUV). Total SUV was calculated. [Result] DAS28 before and after the treatment are IFX group 5.26±0.99, 3.87±1.04, and TCZ group 4.74±1.54 and 2.79±1.37. Total SUV are IFX group 25.6±7.0, 19.7±6.3 and TCZ group 24.4±9.5,

19.5±6.3. There was no significant difference in the disease activity before the treatment among both groups. Total SUV was significantly decreasedsix months after the initiation of those therapies. [Conclusion] There was no significant difference to the change of SUV between IFX and TCZ.

W11-4

Relation between infliximab efficacy and the parameters at the initiation of infliximab

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Conflict of interest: Yes

[Objective] Anti-CCP antibody and RF are the bad prognosis factors in the treatment of rheumatoid arthritis (RA). The aim of this study is to evaluate whether those parameters such as anti-CCP antigen, RF, and MMP-3, correlate the efficacy of infliximab treatment. [Methods] One hundred and forty-two RA patients were enrolled this study. Female were 113 and male were 29. Average age was 55.2 years old. We divided these cases into 2 groups; responders and non-responders. [Results] Responders were 89 cases (62.1%) and non-responders were 53 cases. In non-responders group, ant-CCP antigen positive rate and RF positive rate were higher than those in responder group. [Conclusion] When infliximab is initiated in RA patients, anti-CCP antigen positive cases need to be treated more tightly.

W11-5

Changes of the risk for serious adverse events in patients with rheumatoid arthritis receiving TNF inhibitors; analyses from the REAL database

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Conflict of interest: Yes

[Objectives] To investigate changes of the risk for serious adverse events (SAEs) in Japanese rheumatoid arthritis (RA) patients who were treated with TNF inhibitors (TNFI). [Methods] We compared 630 RA patients who started TNFI from 2005 to 2007 (2005 group, 566 patient-years [PY]) and 304 patients in and after 2008 (2008 group, 241 PY) in the REAL database. Types and incidence rates of SAEs during the first year of TNFI treatment were analyzed. [Results] In the 2008 group, patients had significantly shorter disease duration, lower disease activity, and less advanced Steinbrocker's stages, and received significantly higher dosage of methotrexate and lower dosage of oral corticosteroids. The crude incidence rate ratios comparing the 2008 group with the 2005 group for SAEs and serious infections (SIs) were 0.88 (95% CI 0.59-1.30) and 0.46 (0.20-1.02), respectively. The Cox proportional hazards analysis revealed that the 2008 group had significantly lower risk for SIs than the 2005 group (HR: 0.42 [95% CI, 0.18-0.99], p=0.046) after adjusting for baseline characteristics. [Conclusion] These results indicate that improved risk managements of TNFI treatment and education of RA patients as well as selection of patients for the treatment decreased the incidence of SIs.

W11-6

Safety profile of Certolizumab pegol in Japanese Rheumatoid Arthritis clinical trials

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Conflict of interest: Yes

[Objective] The safety of certolizumab pegol (CZP) in Japanese RA patients (pts) was evaluated. **[Methods]** Two 24-week double-blind, placebo-control, randomized trials (DBT) in pts with active RA followed by open label extension (OLE) studies were conducted. **[Results]** In DBT, total of 355 pts were treated with CZP, and 191 patients were assigned to placebo (PBO). 75.8% and 62.8% of pts treated with CZP or PBO experienced adverse events (AE). Most common AEs were nasopharyngitis, eczema, and upper respiratory tract infection. Only 3.4% of pts experienced severe AE. Serious AEs were observed in 7.3% and 2.1% of pts treated with CZP and PBO, respectively, with serious infections in 2.3% and 0.5% of pts. Incidences of injection site reaction-related events were relatively low. No TB was reported. One patient treated with CZP without MTX died due to aortic dissection rupture (Not likely related). In OLE, 3 cases of malignant neoplasm were reported (0.74 per 100 patient-years), incident rates of AEs were similar to DBT. **[Conclusion]** The most common AEs in patients treated with CZP were infections and infestation, the majority were mild to moderate. No new safety signals were detected in DBT and OLE.

W12-1

Soluble Toll-like receptor levels in the sera of adult onset Still's disease

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Conflict of interest: None

[Objectives] Adult-onset Still's disease (AOSD) is a systemic inflammatory disease of uncertain etiology. It is suggested that bacterial or viral infection participates in the development of AOSD. Toll-like receptors (TLRs) are a family of receptors that recognizes microbial-associated molecular patterns from diverse organisms. We measured soluble TLRs in the sera of AOSD patients to investigate the role of TLRs in AOSD. [Methods] We measured serum TLR levels in 10 patients with active AOSD and 10 controls. [Results] TLR2, TLR5, and TLR9 levels were significantly increased in patients with AOSD. TLR2 values correlated with ferritin and LDH, and TLR5 values correlated with ferritin, LDH and soluble IL-2 receptor levels in AOSD patients. These data suggest that TLR activation may play a role in the develop-

ment of AOSD.

W12-2

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] Seventy-three patients with AOSD who were treated in our hospital enrolled in this study. The patients group consisted of 26 men and 47 women. We classified the patients with AOSD into 2 groups; RA-subtype (n = 15) who met the revised criteria of American College of Rheumatology clinical diagnostic criteria for RA and nonRA-subtype (n = 58) 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, knee, MCP, MTP joint arthralgia were more frequently observed and cervical spine, hip, DIP joint arthralgia and radiographic findings were more frequently observed than RA and were accompanied by an osteosclerosis lesion to a high rate.

W12-3

Study of clinical and dermatopathological findings about dermatomyositis and pururigo pigmentosum like eruptions in adult onset still disease

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Conflict of interest: None

[Objectives] Importance of dermatomyositis and pururigo pigmentosum like eruptions in adult onset still disease (AOSD) was studied. [Methods] Two our patients and 17 patients reported in Japanese and English literature of AOSD with dermatomyositis and pururigo pigmentosum like eruptions were enrolled. [Results] Distribution of age and male female ratio were similar to common AOSD. Only 1 patients complicated malignancy. Eruption appeared prior to fever in 5 cases, in many cases eruption and fever were admitted at the same time. Eight patients had only atypical eruption. Histpathologically neutorophil infiltration in upper dermis and single cell keratinization in epidermis were recognized. Former is common, latter is very specific and diagnostic. [Conclusion] Rheumatologists should pay attention to AOSD suspected patients with eruption similar with dermatomyositis and pururigo pigmentosum.

W12-4

Usefulness of tacrolimus for refractory Adult-Onset Still Disease

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Conflict of interest: None

[Objectives] To evaluate the usefulness of Tacrolimus (TAC) for refractory Adult-Onset Still Disease (AOSD). [Methods] We got informed consent and tried TAC for 6 corticosteroid (CS) resistant AOSD patients in the period from November 2011 to November 2012. [Results] (1)22years, a pregnant female. This case failed in high dose CS remission induction therapy, but achieved clinical remission after TAC additon. (2)41years, female. This case failed in high dose CS remission induction therapy and Etanercept was not effective. But she achieved clinical remission after TAC addition. (3)32years, female. This case failed in CS pulse remission induction therapy, but achieved clinical remission after TAC and methotrexate (MTX) addition. (4)38years, female. This case repeated recurrence, but TAC enabled to reduce CS dose. (5)61years, female. This case repeated recurrence and MTX, Infliximab (IFX) were not effective. But TAC enabled to reduce CS dose. (6)63years, male. This case repeatd recurrence and MTX, IFX, Tocilizumab were not effective. We tried TAC, but stopped it because of elevation of creatinine and potassium value. [Conclusion] TAC was useful for 5 patients in 6. It can be one of the options for refractory AOSD.

W12-5

Four Cases of Adult-onset Still's Disease Treated with Tocilizumab

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Conflict of interest: None

Tocilizumab (TCZ) has been shown to be effective in treating adult-onset Still's disease (AOSD) in several reports. We will present four new cases of AOSD treated with TCZ along with a review of the literature. Case 1: A 25 year-old male with AOSD was treated with steroids, cyclosporine (CsA), and methotrexate (MTX) but CRP levels did not normalize. Treatment with TCZ resulted in remission. Case 2: A 19 year-old female with AOSD was treated with steroids and CsA. She had a relapse four months later, and after increasing CsA and steroids, TCZ was begun. The day after the first treatment, fever and hyperferritinemia developed. Macrophage activation syndrome was suspected but successfully controlled with a course of methylprednisolone pulse therapy. Steroids and CsA are being tapered without further relapses. Case 3: A 60 year-old female was diagnosed with AOSD and treated with steroids. Eight months later, she experienced a relapse, and MTX was added. She had another relapse eleven months later, and TCZ was begun. Steroids and MTX are being tapered successfully. Case 4: A 48 year-old female was diagnosed with AOSD. She experienced multiple relapses despite treatment with steroids, MTX, and CsA. When she had another relapse at the age of 57, TCZ was started with favorable results.

W12-6

Successful of humanized anti–interleukin-6 receptor antibody (tocilizumab) therapy for a case of familial Mediterranean fever complicated by AA amyloidosis

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Conflict of interest: None

[Objectives] Familial Mediterranean fever (FMF) is a cause of AA amyloidosis and is the most frequent type of familial amyloidosis. Colchicine has proved to be an effective treatment for FMF. However, treatment for patients who are refractory to colchicine remains controversial. [Methods] We encountered patients who was shown to have AA-amyloidosis by biopsy of the kidney and stomach. Treatment for this disease was investigated. [Results] Colchicine was administered first to a 51-year-old man with AA-amyloidosis. However, his arthralgia and nephropathy showed progression. Therefore, a humanized anti–interleukin-6 receptor antibody (tocilizumab) was administered at a dose of 8 mg/kg monthly. After 2 years, his serum creatinine decreased from 2.3 mg/dL to 1.5 mg/dL, CRP decreased from 2.5 mg/dL to 0.0 mg/dL, and proteinuria improved from 2.5 g daily to 0.2 g daily. His arthralgia also subsided. Repeat biopsy of the stomach showed the disappearance of AA-amyloidosis. [Conclusion] This case suggests that treatment with tocilizumab can achieve significant improvement and represents a new therapeutic option for patients with FMF and AA amyloidosis if colchicine is not effective.

W13-1

Presence of Peripheral Arthritis Prevents Radiographic Spinal Damage Progression in Ankylosing Spondylitis: Observation Study of Korean spondyloArthropathy Registry (OSKAR) Study over 5 years

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Conflict of interest: None

[Objectives] To determine presence of peripheral arthritis can affect the structural damage in patients with ankylosing spondylitis (AS). [Methods] A total of 915 patients with AS from the Observation Study of Korean spondyloArthropathy Registry (OSKAR) cohort were enrolled. We used a two-step approach. First, all OSKAR data were analyzed in relation to the history of peripheral arthritis on cross-sectional survey. Second, we retrospectively analyzed the radiographic spinal progression for 5 years according to the presence or absence of peripheral arthritis. the mSASSS were examined by two experienced radiologists to validate the results. [Results] On cross-sectional survey, in spite of adjusting for multiple comparisons by Bonferroni correction, the patients with history of peripheral arthritis had fewer mSASSS unit than those without history of peripheral arthritis (19.56±1.06 vs 22.67±0.81, p=0.005). In a retrospective analysis over 5 years, the mean progression of mSASSS in patients with peripheral arthritis was 3.26±0.58 units, while that of mSASSS in patients without peripheral arthritis was 4.97±0.44 units (p=0.024). [Conclusion] The patients with the peripheral arthritis had slower radiographic spinal damage progression than those without peripheral arthritis.

W13-2

The efficacy of infliximab in ankylosing spondylitis in Japan and analysis of predictor of good responce

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Conflict of interest: None

[Objectives] To evaluate the efficacy and safety of infliximab to active ankylosing spondylitis (AS) patients in Japan and identified clinical predictors of good clinical response. [Methods] AS patiens with high disease activity despite of conventional therapy received 3 or 5mg/kg infliximab at weeks 0, 2, 6, and then every 6 to 8 weeks. Response to infliximab was evaluated at 6, 30, 54 weeks using BASDAI (Bath Ankylosing Spondylitis Desease Activty Index), BASFI (Bath Ankylosing Spondylitis Functional Index), CRP and ESR. Predictor of good response was analysed with BASDAI, BASFI, age, disease duration at the time of administlation. [Results] Of 17 patients, 11 (64.7%) patients respond good courece, BASDAI decreased 5.8 to 1.7 at 54 weeks. Six patients were respond at 6 weeks but then effect was attenuated at 30 and 54 weeks. CRP and ESR were decreased in responder, but in non-responder CRP and ESR were increased at 30 and 54 weeks. Predictor of good clinical response were lower CRP, lower BASFI, higher BASDAI. [Conclusion] Infliximab was effective in active AS patients with 64.7%. Greater CRP concentration s, lower functional damage and high disease activity at administration were associated with good clinical responses.

W13-3

The efficacy of biologic agents in spondyloarthritis

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Conflict of interest: Yes

[Objectives] We acessed spondyloarthritis (SpA) and estimated the effect of anti-tumor necrosis factor (TNF) therapy with SpA. [Methods] All eleven patients fulfilled the criteria of modified New York criteria for the diagnosis of ankylosing spondylitis (AS). We examined blood test, radiography, MRI, HLA typing check, cytokine test, and physical exmination including BASDAI. We used infilimab in one patient, and adalimumab in ten patients. [Results] All patient showed good responce to the anti-TNF therapy. There was no HLA-B27 positive patients in our cases. The positive typing were B7, B44, B51, B52 and B61, especially B61 positive cases showed severe bamboo-spine spondylosis in radiography. All cases are still under controlled. [Conclusion] The evaluation of anti-TNF therapy in SpA patients are exellent in short term clinical results. The phenotype of AS may different in Europian countries and Japan.

W13-4

A case of ankylosing spondylitis (AS) successfully treated with rituximab

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Conflict of interest: None

We present a case of 38-year-old man with back pain and difficulty of neck flexion and extension since 2002 and recurrent uveitis since 2009. He was diagnosed as AS by X-ray finding which had already shown ‘bamboo spine’ at the first visit to our hospital in February 2010. His symptoms continued after administration of 8 mg/w methotrexate, 5 mg/d prednisolone and NSAIDs, so we started infliximab (IFX) in June 2010. IFX led him to a marked im-

provement, but the appearance of severe numbness in upper and lower limbs forced to discontinue IFX. Next, we switched IFX to etanercept (ETN). However, the response to ETN was less impressive than IFX and furthermore the numbness relapsed. Then we treated him with 700 mg Rituximab (RTX) intravenously at week 0 and 2. After infusions of RTX, his BASDAI score was promptly improved from 6.39 to 3.56. Thereafter, he remained free of symptoms, could taper prednisolone and discontinued methotrexate without numbness. RTX was reported to be effective in TNF blocker-naïve patients with AS in a clinical trial. Moreover past studies have shown the infiltration of B cell into the subchondral bone marrow of the spine of AS patients. RTX might be an optional therapy for AS patient with difficulty of the administration of TNF alpha inhibitors.

W13-5

A clinical study of eight cases demonstrating relapsing polychondritis

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Conflict of interest: None

【Objectives】8 patients with Relapsing Polychondritis (RP) were analyzed.【Methods】8 patients consisted of 4 males and 4 females, with ages of onset ranging from 30 to 78. Duration from onset to diagnosis varied from 2 months to 22 months.【Results】At onset, auricular chondritis was detected in 5 patients, scleritis in 1 patient, conjunctivitis in 2 patients, eruption in 1 patient, arthritis in 1 patient, nasal septum cartilage deformation in 1 patient. Concurrence of the internal organs lesion was neurological disorders in 2 patients, ileocecum ulcers in 1 patient. In the initial treatment, the oral steroid was administered to all patients, and all of them responded to. But, as dose reduction of steroid, 5 cases were relapsed and 3 of 5 cases were received steroid pulse therapy. After the relapse, 4 of 5 cases were received immunosuppressive drugs. These included cyclophosphamide pulse in 2 cases, methotrexate in 3 cases, cyclosporine in 2 cases, azathioprine in 2 cases, mizoribine in 1 case, and 3 of 4 cases were controlled. One case which complicated the ileocecum ulcers responded to infliximab.【Conclusion】Our 8 patients with RP responded to steroid therapy in the initial treatment, but many of them were relapsed as dose reduction of steroid, and included severe cases.

W13-6

Experience of biological agents in refractory relapsing polychondritis

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Conflict of interest: None

(Case report) A 32-year-old woman had medical examinations for pain and swelling of nose from October 2011. She was diagnosed as relapsing polychondritis by nose biopsy January 2012. Prednisolone therapy was started, but chest computer tomography (CT) revealed the upper and lower respiratory tract stenosis. She noticed a breathing difficulty and nasal continuous positive airway pressure (CPAP) support was started. Then, steroid pulse (mPSL 1000mg per day) for three days following 1 mg/kg of oral prednisolone were done. Cyclophosphamide (CPA) pulse therapy was also used on March. However, the treatment worked temporarily, symptom turned worse. Chest CT appeared no improvement of the respiratory tract stenosis. Because of arthralgia, 8 mg/week of MTX was started with prednisolone tapering from July 2012. Etanercept therapy was added for two months, dyspnea and CT findings turned worse. The tracheotomy was enforced, biological agents was changed to infliximab from October. The improvement of the respiratory tract lesion was confirmed in CT. The relapsing polychondritis with respiratory tract stenosis is extremely rare and the standard treatment is not established. This is a valuable case using the biological agents for the treatment, so we report with literatures consideration.

W14-1

Targeted deep resequencing implicates innate immune responses in Behçet's disease pathogenesis

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Conflict of interest: None

[Objectives] Behçet's disease (BD) is an inflammatory disease characterized by oro-genital ulcers, uveitis, and skin inflammation. It has been debated whether the innate immunity is involved in the pathogenesis of BD but genetic evidence to support this hypothesis is sparse. Genome-wide association study (GWAS) is a powerful means for identifying loci with common variants, associations due to rare and low-frequency variants could be missed. **[Methods]** In the current study, non-synonymous variants identified by deep exonic resequencing of 10 genes identified by GWAS (*IL10*, *IL23R*, *CCR1*, *STAT4*, *KLRK1*, *KLRC1-4*, and *ERAP1*) and 11 genes involved in innate immunity (*IL1B, IL1R1, IL1RN, NLRP3, MEFV, TNFRSF1A, PSTPIP1, CASP1, PYCARD, NOD2*, and *TLR4*) were evaluated. **[Results]** Non-random distribution of rare and low-frequency variants in Japanese and Turkish BD cases and controls (n=4919) implicated BD susceptibility-associated rare and low frequency variants in *IL23R* and *TLR4* in both the Japanese and Turkish populations and in *MEFV* in the Turkish population. Carriage of *MEFV*-M694V, known to cause recessively inherited familial Mediterranean fever, conferred risk in Turkish samples (OR=2.65, $p=1.79x10^{-12}$). **[Conclusion]** The findings implicate innate immune and bacterial sensing mechanisms in BD.

W14-2

Relationship between IL-23 receptor and Th17 related cytokines in patients with Behcet's disease (BD)

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Conflict of interest: None

[Objectives] We have demonstrated that CD4+ T cells were hyperactivated to both Th1 and Th17 related cytokines and the frequencies of Th17 cells and Th1/Th17 cells were increased in peripheral blood obtained from patients with BD. We investigated the role of IL-23 receptor (IL-23R) in BD pathogenesis which is essential to maintain Th17 cells. [Methods] We purified peripheral memory CD4+ T cells from 5 BD patients and 7 normal controls and we stained the cells with anti-IL-23R, anti-IFNγ and anti-IL-17 for flowcytometry. [Results] The frequencies of Th17 cells and IFNγ+ IL-17+ (co-producing) T cells were relatively high in BD patients compared to normal controls without significance. Linear regression models were used to analyze the results and we estimated that p-values between the frequencies of IL-23R+ cells and Th17 cells and between those of IL-23R+ cells and co-producing T (Th1/Th17) cells were 0.058 and 0.081, respectively. We cultured the memory CD4+ T cells in the presence of IL-23 and the cell numbers were remarkably decreased in 2 BD patients. [Conclusion] Recently several GWAS studies identified IL-23R gene as a BD susceptibility gene. Taken together the results of our study, the overexpression of IL-23R on CD4+ T cells play a role in the pathogenesis of BD.

W14-3

Comprehensive analysis of protein expression in peripheral blood mononuclear cells from patients with Behcet's disease

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Conflict of interest: None

[Objectives] To elucidate the pathophysiology and establish biomarkers in Behcet's disease (BD). [Methods] Peripheral blood mononuclear cells (PBMCs) were obtained from 16 patients with BD, 16 patients with rheumatoid arthritis (RA), and 16 healthy control subjects (HC). Proteins extracted from PBMCs were separated by 2-dimensional gel electrophoresis. [Results] By quantitative analysis of the obtained 563 protein spots, intensity of 14 spots and 98 spots was at least 1.2-fold higher in the BD group than in the HC group and in the RA group, respectively ($p<0.05$). Similarly, intensity of 9 spots and 17 spots was at least 1/1.2-fold lower in the BD group than in the HC group and the RA group, respectively ($p<0.05$). We completely discriminated between the BD and HC groups and between the BD and RA groups by multivariate analysis of intensity of 23 spots and 35 spots, respectively. The protein spots that showed significantly different intensity and were also used in the multivariate analysis contained proteins functionally related to cytoskeleton, transcription/translation, T cell activation, bone turnover, regulating apoptosis, and microbial infection. [Conclusion] The identified PBMC-derived proteins may play key roles in the pathophysiology and serve useful biomarkers for BD.

W14-4

Efficacy of Quantitative Analysis of Brainstem atrophy on MRI for Diagnosis of Chronic Progressive type Neuro-Behçet's Disease

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Conflict of interest: None

[Objectives] This study was designed early diagnosis and evaluation of disease activity of chronic progressive neuro-Behçet's disease (CPNB). [Methods] MRI recorded at the diagnosis and at various periods thereafter were evaluated in patient with acute type NB (n=10), CPNB (n=10), non-NB (n=8), and NPSLE (n=8). MRI scans of age- and sex-matched control patients for CPNB (n=10) were also studied. The areas of brainstem was measured on mid-sagittal sections of T1-weightened images of brain MRI. [ResultsThe areas of brainstem was found to be lower in CPNB than in the other 4 groups. On ROC analysis, the sensitivity/specificity of the areas of brainstem for diagnosis of CPNB against non-CPNB was 70.0%/94.4% at 614.9 mm^2. The time kinetics analysis demonstrated that brainstem atrophy progressed during the first 2 years from the initial diagnosis of CPNB. Brainstem atrophy progressed at significantly greater degree in CPNB patients with continuous elevation of CSF IL-6 compared with whom CSF IL-6 levels were kept bellow 20pg/ml. [Conclusion] The data suggest that MRI might effective for early diagnosis and for evaluation of the disease activity of CPNB. It is suggested that brainstem atrophy might progress due to CNS inflammation mediated by IL-6 during the early phase of CPNB.

W14-5

Study on the retention rate, efficacy and safety of infliximab in 20 patients with refractory Entero-Behcet's disease

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Conflict of interest: None

[Objectives] Entero-Behcet's disease (BD) is often complicated by serious comorbidity. Although corticosteroids (CSs) and immunosuppressants are used for treatments, refractory entero-BD is difficult to be managed. [Methods] In this study, infliximab (IFX) and MTX was administered to 20 patients who were diagnosed with entero-BD based on colonoscopy and were refractory to the conventional treatments. The primary endpoint was the retention rate at 1 year and secondary were safety, healing rate of ulceration on colonoscopy and the improvement in Disease Activity Index for Intestinal Behcet Disease (DAIBD). [Results] The mean age was 42.3 (15 female) and 10 patients had a history of relapse and 6 had a history of perforation. Retention rate at 1 year was 90 %, but 2 discontinued because of insufficient efficacy. No severe adverse effects were observed. Among 3 patients showed relapse. 2 were switched to etanercept. The healing rate of ulceration on colonoscopy was 65 %. DAIBD was significantly decreased from 73.5 to 25.8 ($p<0.05$). The dose of CS was reduced from 11.9 mg to 2.6 mg. [Conclusion] The IFX therapy for entero-BD appeared a high retention rate, tolerability and efficacy judged from endoscopic observation, DAIBD scores and tapering of CS dose.

W14-6

Draft of recommendations for the management of vasculo-Behcet's disease in Japan

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Conflict of interest: None

[Objectives] Vascular involvement, especially in arterial and pulmonary systems, is one of the most serious manifestations of Behcet's disease, but the therapeutic strategy has not established. The purpose of this study is to propose a clinical guideline of vasculo-Behcet's disease in Japan. [Methods] Clinical statements were generated based on more than 170 literatures which had been published in the last 5 years and the important references and clinical data of 105 patients in Behcet's Disease Research Committee of Japan. [Results] The diagnosis relies on Japan Criteria The vascular lesions should be identified by imaging modalities including angiography, CT, MRI/MRA, ultarsonograhy, PET/CT, and pulmonary scintigram. Corticosteroids and immunosuppressants play a major role in pharmacological therapies, while anticoagulation and anti-platelet therapy be cautious especially in patients with pulmonary lesions. Surgical treatment is required for impending rapture of aneurysms with pre- and postoperative immunosuppressive therapies. Endovascular therapy and anti-TNF antibody are alternative. [Conclusion] Although there is few literatures with high evidence, it is important to generate consensus based recommendations for Japanese patients with vasculo-Behcet's disease.

W15-1

A case of a different type of lymphoma emerged in a patient with rheumatoid arthritis after the remission of a lymphoproliferative disorder related to methotrexate therapy

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Conflict of interest: None

An 80-year-old woman was diagnosed as RA in her seventies. 18 months ago, she was diagnosed as MTX related lymphoproliferative disorder (LPD) (diffuse large B cell lymphoma) and the interruption of MTX led to the cure of the symptoms. Since then, she was treated by rituximab (RTX). One month ago, she was performed a surgical procedure due to a traumatic fracture. After surgery, her general condition worsened and she was transferred to our hospital. Physical and laboratory examinations led to the suspicion of infection and disseminated intravascular coagulation. She was treated by several antibiotics without response to therapy. Laboratory investigations revealed a high level of soluble interleukin-2 receptor and a positive value of serum EBV PCR and a relapse of the LPD was suspected. High dose steroid and RTX therapy was initiated but there was no response and she was died. The autopsy showed many malignant cells, like Reed-Sternberg cells (CD15+, CD20-, CD30+, EBER+), invaded many organs especially the liver and spleen. As far as we know, in all the previously reported cases, the histopathology of the relapse LPD consisted on similar types of tumor cells found in the initial LPD. Our case is the first report showing two different types of LPD emerged in a patient with RA.

W15-2

Clinical outcomes and serum KL-6 levels in rheumatoid arthritis patients with interstitial lung disease treated with biologics

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Conflict of interest: None

[Objectives] Pre-existing lung disease is a risk factor for adverse events related to biologics. Safety must be considered when using biologics in rheumatoid arthritis (RA) patients with interstitial lung disease (ILD). [Methods] and [Results] Biologics were administered as follows: etanercept (ETN) alone in 3 patients, a switch from infliximab (IFX) to ETN in one, tocilizumab (TCZ) alone in 2, IFX/TCZ in one, IFX/adalimumab (ADA)/TCZ in one, and ETN/TCZ in 2 patients. IFX was discontinued because of *Pneumocystis* pneumonia in one and ETN was discontinued because of aspiration pneumonia, and so on in 4 patients, respectively. In the short- term (2 or 3 months), mean serum KL-6 increased from 648.4 to 676.0 U/ml in ETN therapy (n=5), and from 858.2 to 1130.8 U/ml in TCZ therapy (n=5). In the long- term (one or 2 years), it increased from 685.8 to 1198 U/ml in ETN therapy (n=4), but decreased from 858.2 to 621.8 U/ml in TCZ therapy (n=5). KL-6 increased immediately after discontinuation of ETN in 3 patients. A switch from ETN to TCZ decreased KL-6 in 2 patients. [Conclusion] Biologics are useful in RA patients with ILD, and may control ILD exacerbation. However, it is crucial to monitor adverse effects.

W15-3

Characterization of interstitial pneumonia developed after using biologics in rheumatoid arthritis

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Conflict of interest: None

OBJECTIVE: To assess characteristics of interstitial pneumonia (IP) associated with biologics in 226 RA patients using 55 infliximab (IFX), 79 etanercept (ETN), 24 adalimumab (ADA), 47 tocilizumab (TCZ), 1 golimumab and 20 abatacept. METHODS: Medical records of all the patients were systematically reviewed. RESULTS: 7 (1 IFX, 5 ETN and 1 ABT) patients developed abnormal findings on HRCT which were consistent with IP. All of the 7 patients had preexisting lung disease. All patients showed bilateral diffuse heterogeneous ground glass opacity. Compared to the patients have no lung adverse effects, there is a statistical significant higher in age (Ave. 66.8year-old vs. 57.6, $p=0.02$), and availability of exist lung diseases ($p<0.001$). There were no worsening of IP in TCZ treated patient with preexisting lung diseases. CONCLUSION: This report suggests that RA patients with preexisting lung disease and older patients must be aware of IP associated with biologics.

W15-4

Histopathological examination of the rheumatoid peripheral neuropathy

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Conflict of interest: None

[Objevtives] The objective of this study is to clarify the rheumatoid peripheral neuropathy by examining histopathology of the terminal branch of the posterior interosseous nerve (PIN) at the wrist. [Materials and methods] Thirty - nine wrists in 39 patients with rheumatoid arthritis (RA) were operated during the period between March 2011 and December 2011. At the operation, PIN was resected as a denervation, and it was examined histopathologically. Relationships between histopathological findings of the nerve and disease activity, age, disease duration, and synovial histopathology (Rooney's score) were investigated. No patient had symptomatic neural deficit including entrapment neuropathy. [Results] There were focal fibrosis of the nerve (n=16, 41%), myxoid change (n=12, 31%), segmental demyelination (n=30, 77%), absence of segmental axon (n=31, 79%), increased number of perineural vessels (n=3, 8%) and deposition of amyloid (n=2, 5%). There was not a significant relationship between histopathlogical findings of the nerve and each parameter. [Conclusion] Subclinical peripheral neuropathy was proved histopathologically at the wrist in the patients with RA.

W15-5

Assessment of estimated glomerular filtration using Creatinine and Cystatin C in patients with rheumatoid arthritis

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Conflict of interest: None

[Objectives] The estimated glomerular filtration rate (eGFR) using creatinine (Cr) may be overestimated in patients with RA due to their loss of muscle mass. Recently, Cystatin C (CysC) has been focused on as a useful marker of renal function. This prompted us to clarify the factors affecting the discrepancy between eGFR using Cr (eGFRcr) and that using CysC (eGFRcys). [Methods] 229 RA patients were enrolled in this study. We calculated eGFRcr/eGFRcys as a marker of the discrepancy of renal function. We divided patients into two groups: group A with a ratio<0.8, n=36, and group B with a ratio□0.8, n=193. We searched for associated factors. [Results] In all patients no significant difference was noted between eGFRcr and eGFRcys. The average age (years), body weight (kg), disease duration (years), serum albumin (mg/dl), DAS28-CRP and SDAI of the patients in group A were 70.1, 51.8, 18.3, 3.9, 2.24, 10.17 and while those in group B were 60.2, 56.6, 9.5, 4.2, 1.70 and 5.55, respectively, and showed significant differences between the two groups. [Conclusion] The renal function of the patients with high age, low body weight, long disease duration, malnutrition and high disease activity was overestimated by eGFRcr. Thus, particular attention is needed to assess renal function in RA patients.

W15-6

Lung diseases in male patients of rheumatoid arthritis (RA)

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Conflict of interest: None

[Objectives] In male RA patients, the prevalence of lung diseases (LDs) in comparison with that in female, including usual IP (UIP), nonspecific IP (NSIP), organizing pneumonia (OP), emphysema, pleuritis, and pulmonary hypertention (PH), and their clinical features were studied. [Methods] Patients of RA who visited our hospital from Jan., 2006 to Oct., 2012 were included. LDs were diagnosed based on the medical records and XP/CTs. Brinkman index (BI), serum RF, KL-6 levels and ANA and Sjogren syndromecomplication (SjS) were examined. [Results] LDs were observed 43/84 (51%) in male and 13/100 (13%) in female patients ($p<0.05$). In male, combined pulmonary fibrosis and emphysema (CPFE) were observed in 19, UIP/NSIP in 6, OP in 3, emphysema without IP in 16, pleuritis in 4. In female, they were in 1, 3, 1, 3, and 1, respectively. In male patients with and without LDs, the age was 73±10 vs. 64±13, BI 800 vs. 400, RF 382 vs. 49 U/mL, and KL-6 421 vs. 220 U/mL. They were all significantly higher in the former; higher prevalences of positive ANA and SjS were also seen. No acute IP exacerbation was seen. PH was complicated in 2 CPFE patients, both having SjS. [Conclusion] LDs were seen more prevalently in male patients, and among them CPFE was major.

W16-1

The effectiveness of a recombinant immunotoxin against folate receptor β in bleomycin-induced experimental scleroderma

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Conflict of interest: None

[Objectives] Accumulating evidence indicates a crucial involvement of macrophage in the pathogenesis of systemic sclerosis. Here we determine the presence of folate receptor β (FRβ) -expressing macrophages in bleomycin (BLM)-induced scleroderma and assess the anti-fibrotic effects of depletion of FRβ-expressing macrophage by a recombinant immunotoxin conjugated to an anti-FRβ antibody (anti-FRβ-PE38). [Methods] Skin fibrosis was induced by local injection of BLM in C3H/HeJ mice. Mice were divided into three groups (n=10 in each) and were administered anti-FRβ-PE38 (*Pseudomonas* exotoxin A) or VH-PE38 (control protein) or vehicle alone intravenously. Skin fibrosis was evaluated by skin thickness and hydroxyproline content, and the number of skin macrophages and mRNA level of transforming growth factor (TGF) β1 were assessed. [Results] The anti-FRβ-PE38 strongly reduced the number of FRβ-expressing macrophages in BLM induced scleroderma, and dermal thickness and hydroxyproline content in treated group were significantly lower compared with the other groups. The mRNA level of TGF-β1 in the treated group tended to be decreased. [Conclusion] FRβ-expressing macrophages may play a crucial role in the development of experimental scleroderma, and an anti-FRβ-PE38 has potent anti-fibrotic effects.

W16-2

Increased cell surface expression of DNAM-1 (CD226) on $CD8^+$ T lymphocytes from patients with systemic sclerosis

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Conflict of interest: None

[Objectives] DNAM-1 is well known as a susceptibility gene for systemic sclerosis (SSc). The aim of this study was to evaluate the expression of DNAM-1 on lymphocytes from SSc patients (pts) and to identify the role of DNAM-1 in the pathogenesis of SSc. [Methods] The expression of DNAM-1 was analyzed by flow cytometry (FCM) on $CD4^+$, $CD8^+$ and $CD19^+$ lymphocytes from 17 SSc pts and 6 healthy controls. The intracellular cytokine production and CD107a degranulation by $CD8^+$ T cells with or without DNAM-1 were measured by FCM after *in vitro* stimulation. The cytotoxicity of $CD8^+$ T cells against HUVECs was assessed with or without anti-DNAM-1 neutralizing antibody. [Results] There was significantly higher percentage of DNAM-1 positive $CD8^+$ T cells from SSc pts. Higher level of DNAM-1 expression was associated with anti-Scl-70 antibody, interstitial pneumonia and a lower value for the percent predicted vital capacity. The production of IL-13 was significantly increased in DNAM-1 positive $CD8^+$ T cells. The cytotoxicity against HUVECs was partially suppressed in the presence of anti-DNAM-1 neutralizing antibody. [Conclusion] These findings indicate that DNAM-1 positive $CD8^+$ T cells is involved in the pathogenesis of SSc via endothelial cell injury and the production of profibrotic IL-13.

W16-3

IL-13 receptors and signaling in the dermal fibroblasts from patiets with systemic sclerosis

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Conflict of interest: None

[Objectives] The aim of the present study was to investigate the fibrotic effects of IL-13 on the collagen production by skin fibroblasts, and to evaluate the signal transduction of IL-13 in the cultured skin fibroblasts. [Methods] We examined the expression of IL-13Rα1 and IL-13Rα2 on skin fibroblasts by flow cytometry, and western blot analyses. Skin fibroblasts from patients with SSc were cultured with indicated concentrations of IL-13 and TNFα for various periods. Procollagen type I C-peptide and TGF-β1 levels were measured using ELISA. mRNA expression of COLlA1, COL1A2, TGF-b1, CTGF were also measured by real-time qPCR. Various specific inhibitors were used for evaluation of IL-13-mediated signaling. [Results] With the flow cytometric analysis, we revealed the expression of IL-13Ra2, but didn't detect IL-13 Ra1. Western blot analysis revealed expression of both receptors. With IL-13 stimulation, the phosphorylation of STAT6 and was induced, and IL-13 plus Jak /Tyk inhibitor(s) suppressed the phosphorylation of STAT6. We observed IL-13 increased collagen production in 72 hours ($p = 0.009$) compared to no stimuli. [Conclusion] IL-13 may be a potent stimulator of collagen production in skin fibroblast and IL-13 signaling pathway would be a potential target for the new treatment of SSc.

W16-4

Reactive hyperemia index assessed by EndoPAT and serum PlGF associate with complications of systemic sclerosis

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Conflict of interest: None

[Objectives] We evaluated the association between reactive hyperemia index (RHI) assessed by EndoPAT, serum biomarkers and complications of SSc. [Methods] Thirty patients with SSc (20limited type, 10diffuse type) were enrolled. They were examined by Chest X-ray, echocardiography, respiratory function test, blood test including autoantibodies and NT-proBNP, endothelial function test (RHI), skin assessment (mRSS). In addition, serum levels of PlGF were measured by ELISA. [Results] The mean of age was 63y.o. and that of disease duration was 3ys. Complications were interstitial pneumonia (IP) in 13patients, PH in 3patients, and digital ulcer (DU) in 6patietns. Anti-Tpo-1 was positive in 6patients, anti-centromere in 20patieints, and anti-U1-RNP in 2patients. The mean of mRSS was 6 points. The mean of RHI was 1.5, which was low as compared with healthy and was very low in patients complicated by DU. The RHI inversely correlated with mRSS ($r=-0.4$, $p<0.05$). The serum PlGF were higher in SSc patient, especially diffuse type, as compared with healthy ($p<0.01$). RHI was lower ($p<0.01$) and the serum PlGF were higher ($p<0.01$) in patients complicated by IP than in the other patients. [Conclusion] Low RHI may be one of risk factors of DU. PlGF is suggested to associate with fibrosis of skin and lung.

W16-5

Study on the Usefulness of Exercise Echocardiography for the Early Diagnosis of Pulmonary Hypertension(PH) in Systemic Sclerosis(SSc)

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Conflict of interest: None

[Objectives] PH frequently occurs in SSc and worsens prognosis. Reductions in the pulmonary vascular bed not detectable in patients at rest may become detectable with increased pulmonary blood flow brought on by exercise. We therefore decided to investigate whether echocardiography performed with the patient exercising, i.e., exercise echocardiography, facilitates the early diagnosis of PH in SSc patients. [Subjects] We investigated 34 SSc patients with a resting tricuspid pressure gradient (TR-PG) of no greater than 36 mmHg and 30 healthy individuals as controls. [Methods] During supine bicycle exercise, transthoracic echocardiography was used to determine TR-PG in a state of maximum exercise stress. Right heart catheterization was performed on subjects whose differences in resting and maximum exercise tricuspid pressure gradient (ΔTR-PG) indicated an increase of at least 35

mmHg. [Results] TR-PG and ΔTR-PG under exercise stress were both higher in SSc patients than controls. Six of the SSc patients had a ΔTR-PG of at least 35 mmHg, and PH was confirmed in the two patients who consented to right heart catheterization. [Conclusion] For diagnosis of PH in SSc, exercise echocardiography appears to be useful for reducing the false negative results with resting echocardiography.

W16-6

Characterisation of the EULAR Scleroderma Trials and Research (EUSTAR) group database: an analysis of more than 9,000 scleroderma patients

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Conflict of interest: None

[Objectives] As systemic sclerosis (SSc) is a rare rheumatic disease, only multicenter collaboration is able to foster disease-related research. EUSTAR, founded in 2004, developed a Minimal Essential Data Set to collect data on SSc patients based on yearly follow-ups. [Methods] To reveal the profile of the EUSTAR cohort, baseline visit data from all SSc patients registered in the database were analysed using descriptive statistics. In 2008, the databank has been reorganized to include new items such as different treatment strategies. [Results] 9165 patients have been registered so far and 7655 fulfilled the preliminary ACR diagnostic criteria. The main disease characteristics like Raynaud's phenomenon (95.4%), antinuclear antibodies (92.9%, in 35.7% against centromeres, in 33.1% against topoisomerase I), and digital ulcers (32.2%) were frequent at baseline. The foremost immunosuppressant therapies included corticosteroids (45.3%), cyclophosphamide (15.9%), and methotrexate (13.7%) and were prescribed significantly more frequent in the diffuse subset. [Conclusion] Based on the collective work of 174 centres worldwide, the EUSTAR database sets a unique standard with respect to a rheumatic orphan disease and provides a great quantity of information on the clinical face of SSc.

W16-7

CD34+ selected and unmanipulated autologous HSCT for systemic sclerosis: Comparison for 4 years

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Conflict of interest: None

[Objectives] Recent phase III study has revealed that CD34+ selected autologous hematopoietic stem cell transplantation (auto-HSCT) causes longer event-free survival than conventional intravenous cyclophosphamide pulse therapy in patients with severe systemic sclerosis (SSc)(JM van Laar et al. EULAR 2012). However, optimization of the transplant regimen is necessary due to 10% of transplant-related mortality. The aim of this study is to compare the efficacy and safety of CD34+ selected auto-HSCT with those of unmanipulated auto-HSCT in SSc patients for 4 years after HSCT. [Methods] Nineteen patients with SSc received auto-HSCT with (n=11) or without (n=8) CD34+ selection. [Results] CD34+ selected auto-HSCT was more effective on skin sclerosis and more strongly associated with viral infection than unmanipulated auto-HSCT for 4-years after HSCT. The effect on interstitial pneumonia was not different between two groups. A death due to disease progression at 20 months and one relapse at 36 months were observed after CD34+ selected auto-HSCT. A death due to relapse at 38 months and two relapses at 12 and 24 months were observed after unmanipulated auto-HSCT. [Conclusion] Treatment intensity of auto-HSCT is positively associated with efficacy and negatively associated with safety.

W17-1

The *IL12RB2* gene is a novel candidate susceptible to systemic sclerosis in the Japanese population

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Conflict of interest: None

[Objectives] In this study we explored the association of a single nucleotide polymorphism (SNP) of the *IL12RB2* gene with susceptibility to SSc in the Japanese population. [Methods] Two hundred thirth-five patients with SSc, and 322 healthy controls (HC) were enrolled in this study. Three SNPs (rs1495965, rs924080 and rs3790567) in the *IL12RB2* gene were determined by allelic discrimination with the use of each specific TaqMan probe. [Results] Only a SNP (rs1495965) was significantly associated with susceptibility to SSc in the Japanese population. At rs1495965, the C allele showed a significantly higher frequency in patients with SSc than in controls ($P = 0.008$; odds ratio, 1.37; 95% confidence interval, 1.1-1.7). In this study, we didn't support an association of *IL12RB2* rs3790567 with SSc, as previously reported in Caucasian populations. In particular, the clinical subsets of SSc showed a more significant association between the C allele and dcSSc ($P = 0.008$) and ILD-SSc ($P = 0.005$), Topo-SSc ($P = 0.003$). [Conclusion] The *IL12RB2* gene was one of susceptibility-genes in patients with SSc. Our results strongly suggest that this SNP may be a powerful indicator for the severity of skin and lung involvement in patients with SSc.

W17-2

Role of platelets in the fibrotic process of systemic sclerosis

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Conflict of interest: None

[Objectives] Fibrosis is an important physiological process in the wound healing, and platelets play an important role, especially in the earlier step. Our aim is to identify the role of platelets in the pathogenesis of SSc. [Methods & Results] Twenty-two patients with SSc and 23 healthy controls were involved. mRNA expression profile of 168 genes assumed to be associated with SSc (chemokines and their receptors and genes associated with vascular biology) were screened by RT2 Profiler™ PCR array and compared between pooled RNA samples from platelets of 10 SSc and those of 10 healthy controls. Expression of candidate genes were confirmed by semi-quantitative PCR combined with densitometry and by quantitative PCR. As a result, 14 genes were selected as candidates by the PCR array, and CXCL5 was identified as a gene upregulated in platelets of SSc, confirmed by both semi-quantitative and quantitative PCR. Protein level of CXCR5 was also upregulated in SSc by immunoblot. Interestingly, fibronectin production was

enhanced by addition of CXCL5 in the culture of skin fibroblasts. [Conclusion] These results suggest that phenotypically-altered platelets are recruited to the sites of microvascular injury, and promote induction of fibrosis by releasing CXCL5 in the disease process.

W17-3

Antifibrotic effects of sildenafil in scleroderma fibroblasts

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Conflict of interest: None

[Objectives] The phosphodiesterase (PDE) inhibitor sildenafil has the vasodilatory effect in vascular smooth muscle cells by increasing levels of intracellular cyclic guanosine monophosphate (cGMP) and has been used for pulmonary arterial hypertension (PAH). Antifibrotic effects of PDE inhibitors in such as cardiac, lung fibroblasts and kidney mesangial cells have already been reported, but those in dermal fibroblasts remain unclear. The purpose of our study is to examine antifibrotic effects of sildenafil in scleroderma fibroblasts. [Methods] Scleroderma fibroblasts were treated with sildenafil or soluble guanylate cyclase (sGC) stimulator BAY 41-2272. Intracellular cGMP levels were measured by EIA method. Furthermore, col1a1, col1a2, IL-6 and TGF-β1 mRNA levels were measured by quantitative RT-PCR. [Results] Both sildenafil and BAY 41-2272 increased levels of intracellular cGMP and suppressed the expression of col1a and col1a2. They also increased the expression of TGF-β1 and only sildenafil increased the expression of IL-6. [Conclusion] Antifibrotic effects of sildenafil in scleroderma fibroblasts were confirmed. Sildenafil might be a novel therapeutic strategy and these effects were independent of TGF-β in our study.

W17-4

Evaluation of utility of pulmonary function tests (PFTs) and B-type natriuretic peptide (BNP) as screening tools for pre-capillary pulmonary hypertension in patients with systemic sclerosis (SSc)

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Conflict of interest: None

[Objectives] We evaluated if PFT parameters and BNP, in combination with or without echocardiography, are useful for PH screening in SSc patients. [Methods] This single-center observational study enrolled 115 consecutive SSc patients between 2008 and 2012 (Screening cases) and 14 SSc patients between 2001 and 2012 with confirmed precapillary PH (pre-PH) (Incident cases). Screening program based on estimated pulmonary arterial pressure (esPAP) by echocardiography was performed in screening cases. For PH suspected cases, pre-PH was confirmed by right heart catheterization. All patients also underwent BNP measurement and PFTs including %FVC, %DLCO, and %DLCO/VA. Receiver-operating characteristic curve analysis was performed to obtain sensitivity and specificity at optimal cut-off value. [Results] Individual screening parameters were compared between 110 patients without pre-PH and 19 with it consisting of 14 incident and 5 newly identified cases. esPAP was the best parameter with sensitivity of 100% and specificity of 95% at the cut-off of 45 mmHg. When %DLCO and BNP were combined with esPAP, the specificity was slightly increased to 96%. [Conclusion] Addition of PFT and BNP to echocardiography slightly improves diagnostic accuracy in echocardiography-based screening program for PH.

W17-5

Investigation of Acute renal failure in 18 patients with systemic sclerosis

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Conflict of interest: None

[Purpose]: Scleroderma renal crisis (SRC) is serious complication in systemic sclerosis. We aimed to elucidate the clinical feature and prognosis of SRC. [Patients and Methods] We reviewed clinical charts of 21 patients who developed acute renal failure (ARF) and/or proteinuria/hematuria from 1995 to 2012 in our hospital. Outcome measures were requiring hemodialysis (HD), patients' survival and SRC-related mortality. [Results] Of 21 patients, 3 were eliminated because of exacerbation of heart failure and dehydration. We selected 18 patients in this study. 8 were hypertensive SRC (HSRC; high diastolic blood pressure (BPd), high plasma renin activity (PRA) and presence of fundus hypertonics). 10 were normotensive SRC (NSRC; normal BPd, normal PRA). 8 of 10 NSRC patients were diagnosed of antineutrophil cytoplasmic antibodies-associated glomerulonephritis, and improved their renal function by initial therapy. 8 (6 HSRC, 2 NSRC) were diagnosed of TMA (thorombotic microangiopathy) based on the presence of hemolytic anemia and low plasma ADAMTS13 activity. Of these 8 patients with TMA, 5 died and 2 required HD. [Conclusions] Our results demonstrated that coexistence of TMA in SRC patients affect the prognosis. It is important that early diagnosis and treatment intervention for SRC with TMA.

W17-6

Evaluation of pathogenesis of Chronic Kidney Disease (CKD) in patients with systemic sclerosis

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Conflict of interest: None

[Objectives] To evaluate the frequency and pathogenesis of chronic kidney disease (CKD) of patients with systemic sclerosis (SSc),We studied the renal function in patients with SSc of Kitamoto-Kamata (KK) scleroderma data base. [Methods] SSc153cases (mean age 63.8years old, mean disease duration 12.7 years, dc SSc 28%, We followed the eGFR and urinalysis during 36 months in these SSc patients. [Results] Mean estimated glomerular filtration rate (eGFR) were significantly decreased from 73.1±19 to 69.6±20.6 mℓ/分/1.73 m^2 (P=0.027. Over 10% decrease of eGFR showed 28% patients with SSc. Patients with hematuria and proteinuria included only 9.8%. SSc patients satisfied of CKD criteria(under eGFR60ml/min/1.73 m^2 or renal disorder(proteinuria etc.) were 71% of patients with SSc. Factors related with CKD showed female, age, renal dysfunction started examination, cardiac dysfunction, and corticosteroids administration. There are no relation between digital ulcer, type of autoantibody, and interstitial pneumonitis. Only two patients were scleroderma renal crisis. [Conclusion] Chronic renal dysfunction of patients with SSc gradually progressed, not scleroderma renal crisis. It is important clinical findings in treatments of patients with SSc.

W18-1

RORγt overexpression 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 isolated from B6 or Tg were transferred into immunized B6 mice, and then clinical course of arthritis was assessed. [Results] 1) CIA was significantly suppressed in Tg mice compared with B6 mice. 2) IL-17 production from CII reactive T cells was significantly increased in Tg mice. 3) Higher expression of RORγt was observed in Tg mice. Foxp3 expressing $CD4^+$ T cells also expressed RORγt, and higher expression of CCR6 was observed on $ROR\gamma t^+Foxp3^+CD4^+$ T cells in Tg mice. 4) Severity of arthritis tended to be suppressed in B6 mice transferred with lymph node cells derived from Tg mice, compared with that from B6 mice. [Conclusion] CIA was significantly suppressed in Tg mice, although IL-17 production from CII reactive T cells was increased. The results of cell transfer experiments showed that inhibitory cells might exit in Tg mice.

W18-2

TIARP negatively regulates arthritis via the inhibition of NF-κB and STAT3 signaling

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Conflict of interest: None

[Objectives] TIARP is dominantly expressed in macrophages (Mφ) and synovium, however, little is known about their role. To define the role of TIARP in the development and pathogenesis of arthritis, we generated TIARP-deficient ($TIARP^{-/-}$) mice. **[Methods]** (1) We investigated several organs in $TIARP^{-/-}$ (C57BL/6 (B6)). (2) Mφ were cultured with TNFα or IL-6. The levels of IL-6 production and NF-κB/STAT3 signaling were analyzed. (3) We examined the susceptibility of $TIARP^{-/-}$ to collagen-induced arthritis (CIA), and the effects of anti-IL-6R or anti-TNFα mAb. (4) We also tested the susceptibility of GPI-induced arthritis (GIA) (DBA/1). **[Results]** (1) B6 $TIARP^{-/-}$ developed spontaneous synovitis, had high production of serum IL-6, and increased $CD11b^+$ cells. (2) $TIARP^{-/-}$ Mφ showed enhanced TNFα-induced IL-6 production, sustained degradation of IκBα, and increased IL-6-induced STAT3 phosphorylation. (3) CIA was clearly exacerbated, accompanied by marked neutrophil and Mφ infiltration. Treatment with anti-IL-6R but not anti-TNFα, prevented the development of $TIARP^{-/-}$ CIA. (4) GIA was also exacerbated in DBA/1 $TIARP^{-/-}$. **[Conclusion]** TIARP might be a negative regulator in arthritis by suppressing proinflammatory cytokines production and their downstream signaling such as NF-κB and STAT3.

W18-3

IL-21 signaling plays critical roles in the development of collagen-induced arthritis

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Conflict of interest: None

[Objectives] IL-21 is a T cell-derived cytokine whose receptor is expressed on variety of cells in immune system. IL-21was reported to be involved in the development of Th17 cells and follicular helper T cells, as well as in antibody production of B cells, all of which could be involved in the development of autoimmune diseases. In order to clarify the roles of IL-21 signaling in the pathogenesis of autoimmune arthritis, we investigated the development of collagen-induced arthritis (CIA) in IL-21 receptor (IL-21R)-deficient mice. [Methods] IL-21R-deificient or wild type C57BL/6 mice were immunized with chicken type II collagen (CII) emulsified in CFA on day 0 and were given boost injection with CII on day 21. [Results and Conclusion] We found that IL-21R-deficient mice were resistant to the development of CIA. CII-specific antibody production was severely impaired in IL-21R-deficitent mice, which is consistent with the reduction of germinal center B cells. On the other hand, development of Th17 and Tfh cells was largely unaffected by the absence of IL-21 signaling. Thus, IL-21 signaling is critically involved in the development of CIA mainly by inducing pathogenic autoantibody production of B cells.

W18-4

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. [Method] Wild-type (WT) and S1P3-deficient (KO) mice backcrossed 9generations to DBA/1J mice were immunized with bovine type II collagen (CII), and disease susceptibility and severity were assessed over time. The severity of the arthritis was assessed using an established semiquantitative scoring system of 0–4: 0=normal, 1=mild, 2=moderate, 3=severe and 4=most severe. The cumulative score for all four paws of each mouse (the maximum score is 16) was used as the arthritis score to represent overall disease severity and progression in an animal. Mice were sacrificed and their paws were fixed in 4% buffered formaldehyde. Paraffin sections of paws stained with hematoxylin and eosin (H&E) were systematically scanned in a microscope and histopathological changes were scored based on cell infiltration, cartilage destruction and bone erosion parameters. [Result] S1P3 KO mice exhibited significant attenuation of arthiritis score, and also less inflammation compared with WT mice. [Conclusions] These results indicate that S1P3 receptor signaling plays an important role in the development of murine collagen-induced arthritis model.

W18-5

CSF-1 Dependent Defective Kidney Repair Triggers Nephritis in Lupus-Susceptible Mice

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Conflict of interest: None

[Objectives] Macrophages (Mø) are central to inflammation and require colony stimulating factor (CSF)-1 for survival, proliferation and activation. Our prior studies indicate that CSF-1 is upregulated in tubular epithelial cells and hastens renal tubular repair following ischemia/reperfusion (I/R) in mice. Paradoxically, CSF-1 drives lupus nephritis (LN) in MRL-*Fas*^{lpr} mice. We hypothesized that CSF-1 dependent Mø-mediated inflammation after I/R leads to LN in MRL-*Fas*^{lpr} mice. [Methods] Using MRL-*Fas*^{lpr} mice genetically constructed to express differing levels of CSF-1: TgC/+ (high), wild type (moderate), and op/op (none), we compared parameters of kidney injury after I/R. [Results] We detected defective renal tubular repair in MRL-*Fas*^{lpr}mice compared to normal mice after I/R. Moreover, I/R triggered early-onset LN in MRL-Fas^{lpr}mice. Defective renal repair and early-onset LN was most pronounced in TgC/+ mice. Moreover, we did not detect tubular pathology, an increase in Mø and early-onset LN in MRL-*Fas*^{lpr} mice deficient in CSF-1. [Conclusion] CSF-1 mediates defective Mø mediated renal repair and non-resolving inflammation, that hastens the onset of LN. This suggests that CSF-1 expands Mø that are responsible for triggering LN.

W18-6

Protective roles of myeloid-derived suppressor cells in autoimmune arthritis murine models through inhibiting pro-inflammatory immune response of CD4$^+$ T cells

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Conflict of interest: None

[Objectives] Myeloid-derived suppressor cells (MDSCs) have a myeloid origin and an ability to suppress T cell responses. MDSCs in cancer have been studied in detail, but the roles of MDSCs in autoimmune disease remain controversial. Here we investigate the roles of MDSCs in autoimmune arthritis using collagen-induced arthritis (CIA) mouse models. [Methods] We first determined the number of MDSCs in CIA mice by flow cytometry. Next, we cultured MDSCs isolated by magnetic cell sorting with CD4$^+$ T cells. We investigated CD4$^+$ T cell proliferation and differentiation by flow cytometry, and cytokines by ELISA. Finally, we transferred MDSCs into CIA mice and evaluated the severity of arthritis. [Results] MDSCs significantly accumulated in the spleens of CIA mice at the peak of the disease. MDSCs inhibited CD4$^+$ T cell proliferation and differentiation into Th17 cells. Moreover, MDSCs inhibited the production of IFNγ, TNFα, and IL-6, whereas MDSCs promoted IL-10 production. Adoptive transfer of MDSCs significantly decreased the severity of the disease and the number of CD4$^+$ T cells and Th17 cells in the draining lymph nodes. [Conclusion] In CIA mouse models, MDSCs suppress the progression of arthritis. These observations suggest that MDSCs could be exploited for new cell-based therapies.

W19-1

Treatment of polymyositis models dependent on CD8 T cells by inhibiting CD28-CD80/86 costimulation

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Conflict of interest: None

[Objectives] CD28-CD80/86 inhibition between T cells and APCs directly blocks the activity of CD4 T cells but not that of CD8 T cells in an allogeneic mixed lymphocyte reaction. When we evaluated the effect of CD28-CD80/86 inhibition by CTLA-4 Ig on C protein-induced myositis (CIM) mice with cytotoxic CD8 T cells engaged in the muscle injury, the myositis was ameliorated. The effect of CTLA-4 Ig after the onset of CIM suggested that CD28-CD80/86 inhibition suppressed CD8 T cells independently of CD4 T cell help. Thus, we evaluated the direct effect of CD28-CD80/86 inhibition on CD8 T cells with a modified myositis model. [Methods] Dendritic cells pulsed with a C-protein origin peptide, which specifically binds to MHC class I K^b, were transferred to mice to activate CD8 T cells and to induce myositis (DCIM). DCIM mice were treated with CTLA-4 Ig (1mg/every 3 days) or with BSA. DCIM was histologically evaluated 7 days after DC transfer. [Results] The histological score of DCIM was significantly lower in the groups treated with CTLA-4 Ig than those treated with BSA ($p<0.05$). [Conclusion] DCIM is ameliorated by CD28-CD80/86 inhibition. Since DCIM is caused by direct activation of CD8 T cells, the result elucidates that CD28-CD80/86 inhibition directly suppresses CD8 T cell function.

W19-2

Evaluation of disease activity using the Myositis Disease Activity Core Set in Japanese patients with polymyositis/dermatomyositis

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Conflict of interest: None

[Objectives] To evaluate disease activity using the Myositis Disease Activity Core Set proposed by the International Myositis Assessment & Clinical Studies Group (IMACS) in Japanese patients with polymyositis (PM)/dermatomyositis (DM). **[Methods]** Twelve patients with PM/DM were enrolled in this study. Disease activity was measured using the Myositis Disease Activity Core Set, which is composed of patient global activity assessment (PGA), evaluator GA (EGA), health assessment questionnaire (HAQ), manual muscle testing (MMT), myogenic enzyme measurements, MYOACT, which evaluates extra-muscle symptoms using the VAS, and MITAX, which evaluates both muscle and extra-muscle symptoms. **[Results]** The PGA score was correlated with HAQ (r_s = 0.67, P = 0.03) and inversely correlated with the MMT score (r_s = -0.76, P = 0.02) before treatment. The following factors were significantly improved after treatment: PGA (P = 0.03), EGA (P = 0.004), HAQ (P = 0.03), creatine kinase (P = 0.04), MYOACT (P = 0.02) and MITAX (P = 0.0003). However,

the MMT score did not significantly improve after treatment. **[Conclusions]** Disease activity was effectively evaluated using the Myositis Disease Activity Core Set proposed by IMACS, although MMT score did not sensitively reflect disease activity after treatment.

W19-3

[^{18}F] FDG uptake in proximal muscles assessed by PET/CT reflects both global and local muscular inflammation and provides useful information in the management of patients with polymyositis/dermatomyositis

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Conflict of interest: None

[Objectives] To determine whether [^{18}F] fluoro-deoxy-glucose-positron emission tomography/computed tomography ([^{18}F] FDG-PET/CT) discriminates polymyositis (PM)/dermatomyositis (DM) from non-muscular diseases and also whether the FDG uptake in proximal muscles reflects the activity of PM/DM. [Methods] Twenty treatment-naïve PM/DM patients who underwent [^{18}F] FDG-PET/CT were retrospectively identified. Standardized uptake value (SUV) was calculated for each of the seven proximal muscles. For patient-based assessment, mean proximal muscle SUV was calculated by averaging the SUVs for these proximal muscles bilaterally. [Results] Mean proximal muscle SUVs were significantly greater in PM/DM than those in controls ($P < 0.001$). Mean proximal muscle SUVs significantly correlated with mean proximal manual muscle testing scores ($P = 0.03$), creatine kinase ($P = 0.02$), and aldolase ($P = 0.002$). Furthermore, SUVs in proximal muscles from which biopsy specimens were obtained significantly correlated with the intensity of inflammatory cell infiltration ($P = 0.002$). [Conclusion] [^{18}F] FDG-PET/CT is useful in the diagnosis of PM/DM. The local FDG uptake in a proximal muscle reflects the activity in the same muscle and provides useful information in determining the muscle for tissue biopsy.

W19-4

High prevalence and clustering over time of anti-PL-7 autoantibody-positive inflammatory myopathy

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Conflict of interest: None

[Objectives] Unusually high prevalence of autoantibodies to PL-7 in polymyositis/dermatomyositis (PM/DM) was found in our study 9 years ago. We extended and analyzed a larger population of patients with anti-PL-7 antibodies. [Methods] The diagnosis of PM/DM and amyopathic DM (ADM) was based on the Bohan & Peter criteria and Sontheimer's definition, respectively. Autoantibodies in sera from 97 Japanese patients with PM/DM/ADM were characterized by immunoprecipitation. Antibodies to Jo-1, MDA 5, Mi-2, TIF1a/β/γ and Ro52 also were tested by ELISA. Clinical data was retrospectively collected. [Results] The prevalence of autoantibodies to aminoacyl tRNA synthetases such as Jo-1 (22%), EJ (4%), OJ (1%), and PL-12 (1%), and autoantibodies to Ku (7%), p155/140 (5%), SRP (4%), and Mi-2 (3%) was similar to other studies. However, prevalence of anti-PL-7 was as high as 12% (12 cases) in contrast to other studies (-4%) ($p<0.05$). Notably, disease onset of patients with anti-PL-7 was either before 1993 (3 cases) or after 2002 (9 cases) whereas onset years of patients with anti-Jo-1 were distributed throughout. [Conclusion] Persistently high prevalence of anti-PL-7 is observed, however, there was a ~10 year period when anti-PL-7 was not observed, suggesting roles of environmental factors.

W20-1

Analysis of cytokine profiles in polymyositis/dermatomyositis with or without interstitial lung disease

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Conflict of interest: None

[Objectives] To investigate and compare the cytokine profiles in polymyositis (PM)/dermatomyositis (DM) with interstitial lung disease (ILD) and without ILD. [Methods] Fifty PM/DM patients were enrolled in this study. These patients were divided into two subsets, PM/DM without ILD and PM/DM with ILD, which included 17 and 33 patients, respectively. Moreover, 16 healthy controls (HCs) were enrolled. Serum cytokines were measured by multiplex assay in all subjects. [Results] The levels of IL-6, IL-8, IL-10, IL-12, TNF-α, IFN-α, IFN-γ and IP-10 were significantly higher in the PM/DM without ILD subset than in HCs. No significant differences were found in IL-1β, IL-2, IL-4, IL-13 or IL-17 between these subsets. Moreover, the followings were significantly higher in the PM/DM with ILD subset than the PM/DM without ILD subset: IL-4 ($P = 0.004$), IL-6 ($P = 0.03$), IL-8 ($P = 0.03$), IL-10 ($P = 0.01$), TNF-α ($P = 0.0002$) and IP-10 ($P = 0.011$). A multivariate analysis demonstrated that TNF-α was the cytokine most associated with ILD. [Conclusions] Inflammatory cytokines, including IL-6, IL-8, TNF-α, IFN and IP-10, were involved in the pathophysiology of PM/DM. TNF-α was a key mediator associated with ILD in PM/DM.

W20-2

Serum interferonαand IL-18 concentration in patients with dermatomyositis and rapidly progressive interstitial lung disease

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Conflict of interest: None

[Objectives] It is well known that rapidly progressive interstitial lung disease (RP-ILD) in patients with dermatomyositis (DM) is associated with poor outcomes. Previous findings suggested interferon alfa (IFNα) and interleukin-18 (IL-18) might an important role in pathogenesis of RP-ILD and DM. Therefore, we have examined the association of serum IFNα or IL-18 concentrations to this condition. [Methods] Sera from each 3 patients diagnosed as having DM with or without RP-ILD and normal healthy control (NHC) were examined for serum IFNα and IL-18 level. [Results] Sera from 2 of 3 with DM and RP-ILD showed high IFNα concentration before treatment. All sera from DM without RP-ILD and NHC had no elevation of IFNα concentration before treatment. IFNα level of these two DM and RP-ILD patients decreased down

to below the cut-off level promptly after treatment in parallel with respiratory symptoms. All sera from DM with or without RP-ILD as well as NHC had high IL-18 concentration before treatment. Although serum IL-18 level in DM with RP-ILD group indicated a declining trend, it sustained high level during their course. [Conclusion] These results suggest that serum IFNα concentration might involve in the pathogenesis of RP-ILD in patients with DM and reflect the disease activity.

W20-3

Serum ferritin and liver enzymes correlate with disease activity of interstitial lung disease associated with amyopathic dermatomyositis : three-case series

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Conflict of interest: None

[case1] A 47-year-old man with interstitial lung disease associated with amyopathic dermatomyositis (ADM-associated ILD) was successfully treated with multidrug thrapy including methylprednisolone pulse (mPSL-pulse), cyclosporine, and intravenous cyclophosphamide therapy (IVCY). [case2] A 69-year-old woman with ADM-associated ILD failed to respond steroid, rather her skin and pulmonary lesion worsened. However, she was successfully treated with combination therapy with tacrolimus, IVCY, and intravenous immunoglobulin therapy (IVIG). In both case1 and case2, elevated serum ferritin (2364 ng/ml and 1700 ng/ml, respectively) and liver enzymes decreased with improvement of disease activity. [case3] A 64-year-old woman was admitted with huge skin ulcer and ILD developed despite steroid therapy. She was diagnosed with ADM-associated ILD, and she died from respiratory failure despite multidrug therapy including mPSL-pulse, cyclosporine, IVCY, plasma exchange, and IVIG. Elevated serum ferritin (1599 ng/ml, on admission) and liver enzymes continued to increase (ferritin 10545 ng/ml, at the time of initiating of intensive therapy). [Conclusion] Serum ferritin and liver enzymes can be useful biomarker for activity of ADM-associated ILD and predict the prognosis.

W20-4

Valuable clinical signs for detection early curative malignancies in the clinical course of Polymyositis/Dermatomyositis patients

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Conflict of interest: None

[Purpose] To investigate valuable clinical signs for detection early curative malignancies in the clinical course of Polymyositis/Dermatomyositis(PM/DM) patients. [Methods] We retrospectively examined clinical characteristics of myositis patients who admitted from January, 2006 to October, 2012, and developed some malignancies. [Results] Among all 58 myositis patients including 22 PM and 36 DM, 14 patients had developed malignancies throughout the course. When the myositis developed, 8 of them had not comorbid malignancies, but 5 malignancies were developed within 2 years and another 3 were detected more than 3 years after from the diagnosis of myositis. In 4 of these 8 patients, we could find the prior deterioration of specific dermatitis to DM, but all of 4 were at advanced stage. Only 1 case with hypopharyngeal cancer was at earliest stage, and she had undergone the curative resection, thanks to the incidental computed tomography of her neck. [Conclusion] Deterioration of skin rash can be signs of underlying malignancies, but most of them were already at advanced stage. Before paraneoplastic symptoms appear, we need to detect malignancy for DM patients. We should routinely perform the malignancy screening tests for all myositis patients, and not miss the pharynx cancer.

W20-5

Clinical study of interstitial pneumonia in patients with Polymyositis/Dermatomyositis(PM/DM)

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Conflict of interest: None

Because interstitial pneumonia (IP) is a major prognostic factor in patients with polymyositis/dermatomyositis (PM/DM).We investigated the clinical features of IP in patients with PM/DM.We examined 64 patients with DM/PM who were hospitalized from 2002 to 2011 in our hospital.PM/DM patients with IP were classified into two groups, that with usual interstitial pneumonia (UIP) and that with non-UIP according to results of high resolution computed tomography (HRCT).In the group with IP, KL-7, SP-D and IgG were significantly high and hypoalbuminea and anemia were detected in comparison with that of non-IP group.In the group with IP, steroid pulse therapy and an immunosuppressive therapy were significantly used in comparison with that of non-IP group.HRCT revealed 4 patients with UIP and 22 patients with non-UIP.There was no significant difference between UIP and non-UIP group except for anemia.During the follow up period, 13 patients with IP and 13 patients without IP were died.IP was exacted as a poor prognosis factor in PM/DM patients.Flare and progression was exacted as a poor prognosis factor of the rroup with IP.In the poor prognosis group, some patients were associated with infection, it is important for us to warn an infectious disease when using the immunosuppressive drug.

W20-6

Clinical study of the initial treatment of dermatomyositis and polymyositis in our department

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Conflict of interest: None

[Objectives] Clinical study of the initial treatment of dermatomyositis and polymyositis in our department [Methods] We have analyzed retrospectively 65 patients who were treated in our hospital from 2002 to 2012. [Results] Sixty-five dermatomyositis and polymyositis patients (57.3 ± 17.2 yrs, 67% females) were studied. Sixty-three patients have been treated. Their serum CK value was 1498 ± 1872IU / L. 34 patients (52.3%) have been complicated by interstitial pneumonia. Steroid therapy has been carried out in all of them. 28 of them received Steroid pulse therapy as an add-on treatment, 34 of them received combination therapy of immunosuppressive agents. 13 patients (20%) had a relapse during the course, immunosuppressive agents has not been used in 11 of them. [Conclusion] We concluded that the combination of immunosuppressive agent to be effective in the initial treatment and maintenance therapy in dermatomyositis and polymyositis.

W21-1

Osteoblastogenesis of human mesenchymal stem cells by Nano-fiber scaffold for bone regeneration

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Conflict of interest: None

[Objectives] Previously, we described the enhanced osteoblast differentiation of mesenchymal stem cells (MSCs) in the presence of inflammatory cytokines. We herein utilized electrospun poly-(lactide-co-glycolide) fiber (Nano-fiber) as a scaffold and also as a new delivery system of MSCs for treatment of rheumatoid arthritis (RA) aiming bone repair. [Methods] Human MSCs (hMSCs) seeded on plastic plate or Nano-fiber was cultured in control medium or osteoblast induction medium (OIM) *in vitro*. [Results] hMSCs seeded on Nano-fiber and cultured in OIM differentiated into osteoblasts detected by RUNX2 (day 7), osteocalcin expression (day 7) and mineralization (day 14) which was similar with hMSCs cultured on plastic plate with OIM. Moreover, a osteocyte marker DMP-1 was observed at day 14. Surprisingly, these markers were induced in hMSCs with Nano-fiber culture in media alone (RUNX2; day 7, osteocalcin; day 14, mineralization & DMP-1; day 28). Addition of IL-1β to the culture enhanced and shortened the course of osteoblastogenesis to 14 days. [Conclusions] Nano-fiber is a supportive scaffold for not only osteoblastogenesis but also osteocyte differentiation in vitro. These data suggests the high usability of Nano-fiber as a scaffold for hMSCs aiming bone repair in RA treatment.

W21-2

Quantitative synovial volume in enhanced magnetic resonance imaging was strongly associated with MMP3

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Conflict of interest: Yes

[Objectives] Although software-based image analysis is important for studies of structural changes in rheumatoid arthritis (RA), quantitative software to evaluate the changes has not been established. [Methods] To overcome the problems, we developed a semi-automated software to quantify knee synovial volume on knee magnetic resonance (MR) images. Here, we investigated quantitative synovial volume using this software, association between synovial volume and biochemical examination in clinical study.This clinical study is an open-label study that investigate the effect of ETN+MTX treatment on cartilage deterioration on MR images (3.0-T Philips MR system with a knee coil, Gd enhanced sequence) as compared with MTX alone treatment using our developed semi-automated software for synovial quantification (UMIN000005773). The Inclusion criteria is that RA patient has moderate or severe disease activity, as defined by DAS28 ($3.2 \leq$ DAS28), despite the treatment with DMARDs. [Results] This study is now in progress, however, we obtained interesting knowledge that synovial volume was strongly associated with MMP3 (Pearson correlation coefficient 0.791, 95% confidential interval 0.526-0.916). [Conclusion] Quantitative synovial volume was strongly associated with MMP3

W21-3

Hyaluronan inhibition of mechanical stress-induced cartilage degradation in human chondrocyte cells

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Conflict of interest: None

[Objectives] To investigate the effect of hyaluronan on mechanical stress induced expression of aggrecanases and production of cytokine in human chondrocyte cells. [Methods] Human chondrocyte cells (control samples and HA treated samples) were seeded onto stretch chambers and a cyclic tensile strain (CTS) (0.5 Hz, 10% stretch) was applied for 30 min. After the exposure of the cells to the CTS, RNA was isolated, reverse transcribed, and the expression of ADAMTS-4, -5, -9, MMP-3, -13, RUNX-2 was analyzed by RT-PCR and real-time PCR. The concentration of IL-1β in the supernatant was also measured using ELISA kits. [Results] CTS induced the expression of ADAMTS-4, -5, -9, MMP-3, -13 in control samples. Whereas in HA treated samples, the expression of ADAMTS-4, -9, MMP-3, -13 was reduced. ADAMTS-5 gene expression was biphasic in control samples, and only the second peak (cytokine dependence peak) was reduced in HA treated samples. There was no difference in the expression of RUNX-2 between both samples. The production of IL-1β was enhanced in control samples, but was reduced in HA treated samples. [Conclusion] These data suggest that HA suppresses the expression of aggrecanases through cytokine cascade such as IL-1β, but not through RUNX-2 pathways.

W21-4

Inter-annual change of bone metabolic markers for rheumatoid arthritis

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Conflict of interest: None

[Objectives] We investigated the inter-annual change of bone metabolic markers for RA and volunteers. The predict factor of bone metabolic markers for RA was analyzed. [Methods] We analyzed TOMORROW study, which is a prospective cohort for age and sex matched RA and volunteers. Urinary crosslinked N-telopeptide of type I collagen (ΔNTx) and serum Osteocalcin (ΔOC) were used as bone metabolic marker, and compared 2010 and 2011. We investigated the influence of change of prednisolone (ΔPSL) and disease activity (ΔDAS28) for NTx and OC. [Results] Each 202 RA and volunteers were entry. ΔNTx of RA was -0.51±29.4 nmol and that of volunteers was 7.41±18.7. There was significantly deference ($p=0.0013$). ΔOC of RA was significantly higher than that of volunteers (RA: 0.94±2.47 ng/ml, volunteers: 0.37±1.62, $p=0.0065$). In RA, there was positive correlation between ΔPSL and ΔOC ($r=0.265$, $p=0.02$) and negative correlation between ΔPSL and ΔNTx ($r=-0.153$, $p=0.19$). On the other hand, there was no correlation between ΔDAS28 and ΔOC, ΔNTx. [Conclusion] Bone metabolic makers were improved by decrease PSL. However, there was no correlation between bone metabolic makers and disease activity. If disease activity is controlled well, bone metabolic makers may degenerate. It is important for RA to decrease PSL.

W21-5

Pre-dose of Alendronate to glucocorticoid therapy on change of BMD and bone turnover markers; a longtuidal trial

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Conflict of interest: None

[Objective] To compare the effect of pre-dose of alendronate one day or more before glucocorticoid therapy with co-dose on bone turnover markers and BMD. [Methods] Twenty patients, who were naïve to prednisolone or raise-up at the dose of over 20 mg of prednisolone, were dosed weekly alendronate 35mg one day or several days before the initiation and serum Ca, PTH, bone turnover markers and bone mineral density (BMD) were measured at 7 days, 1, 3 and 6 months after the initiation of glucocorticoid therapy. [Results] Urinary NTx at 7 days after initiation of glucocorticoid therapy did not increase and then significantly decreased after one month when alendronate was pre-dosed before the therapy, otherwise it raised at 7 days after initiation of the therapy with co-dose. Though no significant change was observed in bone formation markers, no significant reduction of BMD in femoral neck was observed in pre-dose group after the initiation of the therapy and the lumber spine BMD significantly increased as well. [Conclusion] Pre-dose of alendronate before glucocorticoid therapy was suggested to be effective for glucocorticoid therapy which was attributed by early suppression of stimulated bone resorption, and this seemed to be effective to prevent glucocorticoid induced osteoporosis..

W21-6

The clinical features of severely suppressed bone turnover detected in X-ray (SSBT-Xp) patients with rheumatic diseases treated under bisphosphonates

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Conflict of interest: None

[Objectives] To clarify the clinical features of severely suppressed bone turnover in X-ray (SSBT-Xp) patients with rheumatic diseases treated under bisphosphonates (BP). [Methods] Ninety-six patients with rheumatic diseases taking BP were included. The X-ray of femurs was examined and those who beaking was detected in lateral cortices were defined as SSBT-Xp. [Results] SSBT-Xp was detected in 9 patients (7.3%) and prodromal pain was detected in 2 patients (1.6%). The mean age, duration of BP therapy and PSL dose in patients with SSBT-Xp(+) showed no significant difference compared to SSBT-Xp(-). Osteogenesis markers showed within normal range or below the lower limit. Bone alkaline phosphatase was significantly different between SSBT-Xp(+) and SSBT-Xp(-) (p=0.043). Bone absorption markers did not show significant difference between two groups. Osteoporosis (T score ≤-2.5SD) was present 14-17% in patients with SSBT-Xp(-), while no patients with SSBT-Xp(+) showed osteoporosis. [Conclusion] The incidence of SSBT-Xp in patients with rheumatic diseases under BP treatment was 7.3%. Most patients showed normal or suppressed bone absorption and osteogenesis regardless of SSBT-Xp. Bone mineral density was better preserved in patients with SSBT-Xp(+).

W22-1

The analysis of reasons of discontinuing biologics in patients with rheumatoid arthritis from NinJa (The national database of rheumatic disease by IR-NET)

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Conflict of interest: None

[Objectives] The use of biologics makes it possible to achieve bio-free remission (BFR). To investigate both the use of biologics and the reason for discontinuing biologics. [Methods] We analyzed both the usage of biologics and the reason for discontinuing biologics comparing among different biologics among RA patients enrolled in the Ninja (National Database of Rheumatic Diseases by iR-net in Japan) during 2008~2011. [Results] Among the 10380 RA patients, 22.1% were on biologics, including IFX; 15.5%, TCZ; 20.1%, ETN; 41.3%, ADA; 11.3%, ABT; 9.0%, and GOL; 2.8%. The reasons for discontinuing biologics were, (1) ineffectiveness, (2) adverse events, (3) remission in many turn. The results showed that IFX, TCZ and ADA might be more effective for inducing BFR than other biologics. ETN had advantage for continuation rate, however, only a few cases of bio-free remission were observed. When we analyzed the BFR, we found no difference in patient characteristics compared with all case of biologic use. [Conclusion] The rate for use of biologics was increasing every year. IFX and TCZ may achieve BFR more effectively compared with other biologics. It was also shown that the bio-free remission can be achieved in patients with long history of RA.

W22-2

Incidence of malignancy from database of patients with rheumatoid arthritis, NinJa 2003-2011

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Conflict of interest: None

[Objectives] Recently the therapy against rheumatoid arthritis (RA) has been changed in some aspects such as increased dose of methotrexate and diffusion of biologic agents, which might raise a risk for malignancy. To disclose incidence of malignancies in RA patients, we analyzed our cohort, database of RA patients `NinJa`. **[Methods]** Data was obtained from NinJa 2003-2011 and stan-

dardized incidence rate (SIR) for malignancies was estimated. **[Results]** In 9 years the cohort consisted of 55164 person-years yielded 311 malignancies in women and 145 in men. Median age at the onset of malignancy and disease duration of RA were 69 years old and 10 years. Most frequent malignancy was lung cancer (n=73) followed by gastric (n=59) and breast (n=55) cancer. SIR for entire malignancies was 0.98 expressing equal incidence in age- and sex- matched general population. SIRs for lung cancer (1.32) and malignant lymphoma (4.17) was significantly higher, whereas several malignancies including colon (0.70) or rectal (0.53) cancer had significantly lower SIR. **[Conclusion]** RA patients had no higher incidence for entire malignancies but should be cared for only such malignancies.

W22-3

Radiographic Outcome of synthetic DMARDs-treated RA patients in daily practice: A large-scale prospective longitudinal cohort study (an interim report of Apple Survey)

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Conflict of interest: None

[Objectives] There have been few epidemiological reports of longitudinal radiographic progression of RA patients captured in daily practice. We have tried to assess the extent of rapid radiographic progression (RRP) in synthetic disease modifying antirheumatic drugs (sDMARDs)-treated RA patients. [Methods] Nine hundred ninety-six patients have been registered to Apple Survey between May 2009 and March 2012. Among these, the RA patients treated by sDMARDs with evaluable data for 1 year have been selected (261 patients at present).We have examined what variables are associated with the development of RRP at 1 year. [Results] RRP was found in 31 out of 261 patients (11.9%). Logistic regression analysis has found that early disease, high time-integrated DAS28-ESR and high mTSS at baseline are independent variables to predict the development of RRP. MTX use tended to inhibit the development of RRP. [Conclusion] Our results have revealed the characteristic of sDMARDs-treated Japanese RA patients who develop RRP. The treat-to-target strategy, especially in early-stage with MTX, is particularly recommended in these patients.

W22-4

Assessment of risks for pulmonary infection in patients receiving immunosuppressive treatment for rheumatic diseases: A report from a large-scale prospective cohort study (PREVENT study)

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Conflict of interest: Yes

[Objectives] To identify risk factors for pulmonary infection (PI) in patients receiving immunosuppressive treatment for rheumatic diseases. [Methods] We prospectively observed 765 inpatients who started immunosuppressive treatment for rheumatic diseases. We collected clinical data, usage of drugs and occurrence of PI for 12 months. [Results] During the observation period, 32 patients (4.2%) died and 66 (8.6%) patients were lost-to-follow up. Patients with PI (n=61, 8%) had a significantly worse accumulated survival rate than patients without. A COX hazard model using baseline data showed that age ≥65 years-old (HR: 3.9 [95%CI 2.2-6.9]), Brinkman index ≥400 (2.7 [1.4-5.3]), serum Cr (1.2 [1.0-1.4] per 1.0mg/dl increase), maximum prednisolone (PSL) dose during the first 2 weeks of treatment (3.2 [1.3-7.8] per 1.0 mg/kg/day increase) were significantly associated with PI. A nested case-control study with logistic regression analysis revealed that maximum PSL dose within 2 weeks before PI (OR: 4.9 [1.4-17.1] per 1.0mg/dl increase) was significantly associated with the events, while immunosuppressants and biologics were not. [Conclusion] Rheumatologists should assess these risk factors before and during immunosuppressive treatment and take appropriate measures to prevent PI.

W22-5

Prevalence of anti-nuclear antibody and impacts of age and sex on the antibody levels in a Japanese population –the Nagahama study

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Conflict of interest: None

[Objectives] To identify distribution of anti-nuclear antibody (ANA) and its fluorescent types according to age and sex in a Japanese population. [Methods] 9,809 volunteers who were aged 30 years or older in Nagahama city, Shiga prefecture were enrolled for this analysis with written consent forms. ANA was quantified using an immunofluorescence assay with Hep-2 cells. Data for ANA, speckled, homogeneous, nucleolar, and discrete speckled patterns was obtained for each participant. Volunteers who told that they have or had autoimmune diseases were excluded from the study. [Results] 9575 subjects were analyzed for ANA distribution. 45.2% and 12.5% showed 1:40 and 1:80 or higher levels of ANA, respectively. We observed higher autoantibody levels in females than in males for ANA and its fluorescent types ($p<1.97x10-6$) except for nucleolar pattern. We also identified dose-dependent increasing effects of age for levels of ANA and fluorescent types ($p<4.2x10-8$) except for nucleolar pattern. [Conclusion] More than 40% of Japanese population showed 1:40 or higher levels of ANA. Aging and female increase the levels and positivity of ANA and its fluorescent patterns. Nucleolar pattern of ANA is the only exception of ANA, not strongly influenced by age and sex.

W23-1

Smoking would influence remission rates of male rheumatoid arthritis patients

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Conflict of interest: None

[Objectives] To investigate the effect of smoking on treatment and remission rates cross-sectionally in rheumatoid arthritis patients [Methods] The subjects were patients who participated in the IORRA survey during April 2011, from whom smoking status, Boolean trials and DAS28 remission rate were available. Never (group N) and current smokers (group C) were selected to compare the differences in serum rheumatoid factor (RF) levels, treatment status, and percentage of patients achieving remission criteria between two groups. [Results] Among 3,343 patients of group N (male; 162, female; 3,181) or group C (male; 209, female; 315), RF levels were significantly higher in group C for both sexes (male (N vs. C, 73.0 vs. 279.9 IU/ml, $p<0.01$), female (105.0 vs. 177.7, $p<0.01$)). No significant difference was observed when doses of methotrexate and corticosteroid, or rates of biologics users were compared. In male, remission rates by the DAS28 (N vs. C, 63.0 vs. 49.8%, $p<0.05$) and Boolean trials (36.4 vs. 25.8, $p<0.05$) were significantly higher those in group N. While no significant difference was found in female groups. [Conclusion] The effects of smoking on remission rates were different between male and female. Male never smokers showed significantly better remission rates than current smokers.

W23-2

The efficacy of A H1N1-pdm vaccination against pandemic influenza in Japanese patients of rheumatoid arthritis: analysis from IORRA cohort

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Conflict of interest: None

[OBJECTIVES] To investigate the efficacy of pandemic A H1N1 influenza (AH1N1pdm) vaccination in Japanese patients with rheumatoid arthritis (RA) by real attack and the factors associated with pandemic attacks in daily practice by using a large observational cohort, IORRA. [METHODS] RA patients who participated in the IORRA survey conducted in April 2010 were analyzed. The AH1N1pdm vaccination status and actual influenza attacks were self-reported to the questionnaire. The factors associated with flu-attack were analyzed with multivariate analysis. [RESULTS] A total of 4,863 patients were analyzed. The attack rates of vaccinated and unvaccinated patients were 2.2% and 3.5%, respectively. The relative risk of vaccination for flu-attack was 0.61 ($p<0.01$), which was significantly reduced in vaccinated patients, thus the efficacy of vaccination was 0.38. The factors associated with influenza attacks were older age (OR 1.03, 95%CI 1.01-1.04, $p<0.001$) and no vaccination (OR 1.28, 95%CI 1.05-1.59, $p<0.05$). Medication (methotrexate, biologics, or corticosteroid), physical dysfunction or disease activity were not the risk factors. [CONCLUSION] The vaccination against AH1N1pdm was effective to be RA patients, thus we should have suggested vaccinations for patients with RA.

W23-3

Prevalence and characteristics of elderly-onset rheumatic diseases

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Conflict of interest: None

[Objectives] We see patients with polymyalgia rheumatica (PMR) or RS3PE syndrome quite often in daily practice, however, they have been considered rare in Japan. Their actual incidence is unclear. The purpose of this study is to clarify their incidence and characteristics. [Methods] We selected all the patients who newly developed RA, PMR or RS3PE after January 2008 to October 2012 from rheumatic clinic, Saitama Medical Center, Jichi Medical Univ. Their age, sex and clinical characteristics were studied. The diagnoses depend on ACR/EULAR 2010 classification criteria for RA, Bird's criteria for PMR, and McCarty's definition for RS3PE. RS3PE is included in PMR for analysis, since it is a subtype of PMR. [Results] During 58 months, there were 127 new RA (92 female) and 42 new PMR (20 female). The average age at onset was 56.6 y.o. in RA and 73.0 y.o. in PMR. The onset ages for RA were in their 60's (32.3%), 70's (17.3%), 40's (16.5%) and 50's (16.5%). The onset ages of PMR were in their 70's (40.5%) and 60's (31.0%). The incidence of PMR was similar in 70's and threefold more in 80's compared with that of RA. Positive anti-CCP was 77.6 % in RA and 9.1% in PMR, and positive RF was 68.3% in RA and 4.9% in PMR. [Conclusion] PMR/RS3PE is much more common than expected especially in elderly.

W23-4

Prevalence of past hepatitis B virus infection in rheumatoid arthritis patients receiving biological and/or immunosuppressive drugs in Kurashiki Medical Center

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Conflict of interest: None

[Objectives] To evaluate the prevalence of past infection with hepatitis B virus (HBV) in patients with rheumatoid arthritis (RA) and the incidence of its reactivation under treatment with biological and/or immunosuppressive drugs. [Methods] 444 past HBV infection patients under immunosuppressive therapy were consecutively enrolled and tested for HBV serology including hepatitis B surface antibody (HBsAb) and hepatitis B core antibody (HBcAb) and HBV-DNA using a real-time polymerase chain reaction assay. [Results] Prevalence of HBsAb-positive and/or HbcAb-positive, HBsAb-positive and HbcAb-positive and HBsAb-positive and/or HbcAb-positive was 77/444(17.3%), 68/444(15.3%), 71/444 (16.0%), 57/444(12.8%). Among these 77 patients, One patient (1.3%) who had been receiving methylprednisolone, methotrexate and tacrolimus experienced reactivation of viral replication (>2.1 log copies/ml) at screening. [Conclusion] The prevalence of past HBV infection patients in our center was low than other reports. Reactivation in most RA patients with past HBVinfection under immunosuppressive therapy was rare, but further studies are required to HBV screening and analysis of the development of clinically de-nove hepatitis under immunosuppressive therapy.

W23-5

Prospective study of Hapatitis B virus reactivation during immunosuppressive therapy in patients with rheumatic diseases in Tohoku area

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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] A total of 95 patients with rheumatic diseases were enrolled and followed up for a year. According to the guideline, titer of HBs antigen, anti-HBc antibody, and anti-HBs antibody were measured before immunosuppressive therapy. HBV-DNA levels were monitored every month in patients with positive anti-HBc antibody and/or anti-HBs antibody. [Results] A total of 21 patients (22%) were HBs antigen negative, anti-HBc antibody positive and/or anti-HBs antibody positive, in whom HBV-DNA were negative before therapy. During immunosuppressive therapy, 3 of 21 patients (14.2%) had positive HBV-DNA and 2 of 3 patients took entecavir. No patients had hepatitis by HBV reactivation. [Conclusion] It is possible to introduce the Japanese guideline for management of HBV reactivation 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.

W24-1

Bone Quality Marker in 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 and bone metabolic markers, BMD and disease activity in patients with rheumatoid arthritis (RA) [Methods] Sixty-two RA patients were included in this study. Thirty-two of 62 patients received biologics. The plasma concentrations of 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 with biologics (B group) and those with other agents (N group). The relationships between disease activity and bone quality markers were examined. [Results] The CDAI, SDAI, CRP, and MMP-3 were significantly lower in the B group than the N group. The BMD, intact P1NP and TRACP-5b levels showed no significant differences between the two groups. However, the levels of pentosidine were significantly lower in the B group than the N group. The pentosidine level was significantly correlated with ESR, DAS28-ESR, CDAI, and SDAI, and the homocysteine level was significantly correlated with DAS28-CRP. [Conclusion] These results suggest that biologics can improve not only the disease activity, but also the bone quality in RA patients.

W24-2

GWAS analysis for the prediction of anti-TNF effectiveness in RA

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Conflict of interest: Yes

[Objectives]30% of RA patients treated with anti-TNF show little or no response. Our aim was to identify genetic marker(s) associated with anti-TNF response in order to predict effectivenss. [Methods] DNA samples from RA patients treated with TNF inhibitors (infliximab, etanercept and adalimumab) were genotyped using the Illumina Omni1 genome-wide SNP panel. A multivariate linear regression of DAS28 scores at 6 months was performed and was adjusted for baseline values of the DAS28, age, RA duration, methotrexate used and rheumatoid factors, gender and smoking history. Using EULAR response criteria as the outcome variables (good response, or combining good and moderate response), multivariate logistic regression analyses were utilized after adjustment for the same covariates as in the linear regression. [Results] 744863 SNPs were selected for the association analyses. Five SNPs (rs1866924, rs9324794, rs9348738, rs12212740 and rs9929620) were selected with moderate level of association ($p < 1x10^{-4}$) with anti-TNF response, although they did not reach GWAS significance. [Conclusion] In the present study population, 5 SNPs were found to have possible association with anti-TNF effectiveness at 6 months. To raise association level, more patients need to be recruited in Japan.

W24-3

The omparison of subcutaneous anti TNF antibody agents from Tsurumai Biologics Communications registry (TBCR)

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Conflict of interest: None

[Objectives] The aim of this study is to investigate the comparison of drug survival rate with golimumab (GLM) and adalimumab (ADA) as both of them are similar characteristics and subcutaneous TNF blocker. [Methods] 69 cases treated with GLM and 61 cases treated with ADA were extracted from TBCR. Kaplan-Meier analysis was used to estimate drug survival rates of ADA group and GLM group (50mg & 100mg) and the difference in retention curves was examined by means of a log-rank test. [Results] 8 of 61 patients were discontinued within the ADA group (3; lack of effect, 5; adverse event) and 17 of 69 patients were discontinued (10; lack of effect, 5; adverse event, 2; others). 52 patients started 50mg and 17 patients started 100mg. ADA group showed higher results than GLM (50mg) but there is any difference between ADA and GLM (100mg) group. MTX concomitant rate was 91.8% in ADA group and 63.8% in GLM group respectively. Biological naïve patients were 85.2% in ADA group and 43.5% in GLM group. There is any statistical difference among three groups with adverse events. [Conclusion] Our data have shown that drug survival rate with ADA is higher than GLM and improvement of ADA administration after launch and good efficacy of 100mg of GLM.

W24-4

Development of a novel algorithm to predict RA patient response to infliximab treatment using clinical data before infliximab treatment

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Conflict of interest: Yes

[Introduction] Predicting the response prior to treatment is important for patients, doctors and health insurance systems. Several methods for predicting the response to anti-rheumatic biologics in RA patients have been under development and have not been covered by insurance. **[Methods]** About 50 components of the clinical data were obtained from 99 patients with RA before infliximab (IFX) treatment at the Saitama Medical University Hospital. Patients at 12 weeks after the 1st infusion of IFX were classified as responders (good or moderate) or non-responders according to the EULAR response criteria. The prediction algorithm to classify responders or non-responders was developed by using machine learning algorithm. **[Results]** The prediction algorithm lacked versatility because the learning process above alone was insufficient. Therefore, we improved the learning technique and could develop the high-versatility prediction algorithm showing over 90 percent accuracy. Next, we verified this algorithm by applying other hospital data and could predict 85 percent accuracy using it. **[Conclusions]** Our algorithm has an advantage over the other methods from both cost-effectiveness and accuracy. Applying more patients' data from other hospitals is necessary to verify the accuracy of our algorithm.

W24-5

Gelatin-coated film zymographic analysis of extracellular matrix-degrading activity in synovial fluid of RA patients before and after treatment with etanercept

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Conflict of interest: Yes

[Objectives] In this study, to reveal the effect of etanercept (ETN) therapy on the amount of extracellular matrix-degrading enzymes in synovial fluids of RA patients, zymographic analysis was performed. [Methods] Synovial fluids from RA patients were pretreated with hyaluronidase and p-Aminophenylmercuric acetate (APMA). Two-fold serial dilutions of synovial fluid samples were reacted with gelatin-coated film overnight at 37°C. Gelatin remaining on film was staind by Ponceau S. [Results] Eight of nineteen patients showed reduction in gelatin-degrading activity by ETN therapy. These patients indicated more remarkable reduction of CRP and DAS28 than other patients. Furthermore there were different patterns of change of MMP3 between these groups. [Conclusion] These results suggest that the decrease in the extracellular matrix-degrading activity in synovial fluid may be correlated with the clinical efficacy of ETN. This simple zymographic analysis may be a useful method for prognosis prediction of RA patients.

W24-6

Analysis on Results of Japanese Clinical Trials with Golimumab (Simponi®) in Patients with Rheumatoid Arthritis (3) : Evaluation of Remission using the new ACR/EULAR Criteria

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Conflict of interest: Yes

[Objectives] To assess the remission rates from Japanese clinical trials with Golimumab (GLM), using the new ACR/EULAR rheumatoid arthritis (RA) remission criteria. [Methods] RA remission rates in GO-FORTH study (with MTX) and GO-MONO study (without MTX) were prospectively assessed using the new ACR/EULAR remission criteria (SDAI and Boolean) through 104 weeks. At 24w for GO-FORTH or 16w for GO-MONO, all patients in placebo groups crossed over to receive GLM 50mg. [Results] At 14w (primary endpoint), the SDAI and Boolean remission rates (%) in GO-FORTH were 20.5/19.3 in GLM50mg and 18.1/12.0 in GLM100mg, and were higher than placebo (1.2/0.0). Likewise, the remission rates in GO-MONO were 7.2/8.2 in GLM50mg and 8.0/7.0 in GLM100mg, and were higher than placebo (1.1/0.0). After long GLM dosing term (104w), the SDAI and Boolean remission rates (%) in GO-FORTH were 38.6/30.0 in placebo, 44.8/31.3 in GLM50mg and 39.4/29.6 in GLM100mg, in GO-MONO were 24.4/19.2 in placebo, 31.1/24.3 in GLM50mg and 27.8/23.3 in GLM100mg respectively. These remission rates were increased after long dosing term. [Conclusion] Although the new ACR/EULAR remission criteria were more stringent than previous criteria, these data suggested high remission rates were achieved by GLM treatment.

W25-1

Golimumab (GLM), a Human Anti-TNFα Monoclonal Antibody Administered Subcutaneously Every Four Weeks in Patients with Active Rheumatoid Arthritis (RA) Despite Methotrexate Therapy: Long-term Results of Clinical and Safety Assessments

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Conflict of interest: Yes

[Objectives] To assess long-term efficacy and safety of GLM in Japanese patients (pts) with active RA despite MTX therapy. [Methods] Pts were randomized to SC PBO, GLM 50 mg, or GLM 100 mg q4 wks. All pts received MTX 6-8 mg orally/wk. The numbers of pts treated with GLM continued to wk104 were 67 in GLM 50mg and 71 in GLM 100mg. [Results] Clinical remission defined as DAS28 (ESR)<2.6 and HAQ remission defined as HAQ <0.5 were maintained to wk104. The proportions of pts with DAS28 (ESR)<2.6 and HAQ <0.5 in GLM 50mg were 49.3% (33/67) and 65.7% (44/67) respectively. Likewise in GLM 100mg were 39.4% (28/71) and 66.2% (47/71) respectively. Median changes from baseline to wk104 in TSS were zero in two treatment groups. The proportions of pts with no progression (change in TSS≤0) were also maintained from baseline to wk 104 in GLM 50mg 65.7% (44/67) and in GLM 100mg 64.8% (46/71). The rates of SAE in two treatment groups were similar. [Conclusion] Treatment with GLM 50 mg and GLM 100 mg plus MTX sustained the efficacy of signs/symptoms and prevention of structural damage during 104 wks, and were well-tolerated.

W25-2

Golimumab (GLM), a Human Anti-TNFα Monoclonal Antibody Administered Subcutaneously Every Four Weeks as Monotherapy in Patients with Active Rheumatoid Arthritis (RA) Despite DMARD Therapy: Long-term Results of Clinical and Safety Assessments

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Conflict of interest: Yes

[Objectives] To assess the long-term efficacy and safety of Golimumab (GLM) as monotherapy in Japanese patients (pts) with active rheumatoid arthritis (RA) despite DMARD therapy. [Methods] Pts were randomized to SC PBO, GLM 50 mg, or GLM 100 mg q4 wks as monotherapy. The numbers of pts treated with GLM continued to wk104 were 73 in GLM 50mg and 90 in GLM 100mg. [Results] Clinical remission defined as DAS28 (ESR)<2.6 and HAQ remission defined as HAQ<0.5 were maintained to wk104. The proportions of pts with DAS28 (ESR)<2.6 and HAQ<0.5 in GLM 50mg were 39.2% (29/74) and 62.2% (46/74) respectively. Likewise in GLM 100mg were 35.6% (32/90) and 58.9% (53/90) respectively. Median changes from baseline to wk104 in TSS were 1.00 in two treatment groups. The proportion of pts with no progression (change in TSS≤0) were slightly decreased from wk52 to wk104 in both of GLM 50 mg (30.6%, 22/72) and GLM 100 mg (44.9%, 40/89). The rate of SAE in GLM 50mg was higher than in GLM 100mg. [Conclusion] Treatment with GLM 50 mg and GLM 100 mg monotherapy sustained the efficacy of signs/symptoms during wk104. Inhibition of structural damage in GLM 100 mg was relatively greater than GLM 50mg. However the progression went on slowly during 104wks in both of the GLM groups.

W25-3

Prospective study on the efficacy of etanercept therapy in RA patients with moderate disease activity - ENCOURAGE Study (ENBREL Outcome in RA patients for Growing Evidence): Results of Period-I (1 year treatment) -

Hisashi Yamanaka[1], Yohei Seto[1], Shohei Nagaoka[2], Yuichi Nishioka[3], Hitomi Haraoka[4], Tsuyoshi Kasama[5], Kazuyoshi Saito[6], Kei Ikeda[7], Yukitaka Ueki[8], Yasuhiko Munakata[9], Makoto Nishinarita[10], Koichi Amano[11], Ryuji Nagamine[12], Yasushi Nawata[13], Naoto Tamura[14], Toshihisa Kanamono[15], Taio Naniwa[16], Tetsuya Tomita[17], Yoshiya Tanaka[6], Tsutomu Takeuchi[18], Encourage study group
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Conflict of interest: Yes

【Objectives】 This is an interim report on the prospective, multi-center,study in 40 centers (38 from Japan; 2 from Korea) to investigate the therapeutic strategy in MTX-resistant RA patients with relatively shorter RA history (< 5 Y) and moderate disease activity.【Methods】 The total of 178 RA patients was randomly allocated to either etanercept (ETN) +MTX (Group E) or MTX+ DMARD (Group M) arm. The primary endpoint (EP) is remission rate; secondary EPs are EULAR/ACR improvement rates etc.【Results】 For this interim report the data in 111 patients (E: 92, M:19, mean aged of 55.1y) were analyzed. The clinical remission rates were significantly higher in E-group than in M-group at both 6 and 12m. (E: 58.6; M: 10.2% and E: 71.3; M: 22.2%), whereas no difference in structural remission rates (E: 59.6; M: 62.5%). Functional remission rates at 6 and 12 m. were E: 47.7; M: 15.8% (P< 0.05) and E: 48.1; M: 22.2%, respectively. In secondary EPs E-group was also superior to M-group. Patients in Group-E who achieved clinical remission are to enter into the Period-II (ongoing in 97 patients at present) where patients are randomly allocated either to ETN+MTX or MTX alone arm.【Conclusion】 Thus higher remission rate was achieved in Group-E than in Group-M in this study population.

W25-4

Long-Term Safety, Efficacy, and Patient-Reported Outcomes of Certolizumab Pegol in Japanese Rheumatoid Arthritis Patients in Whom Methotrexate Could Not Be Administered: 52 Week Results from Open Label Extension of the HIKARI study

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Conflict of interest: Yes

Objective: To evaluate the long-term safety, efficacy, and patient-reported outcomes of certolizumab pegol (CZP) in Japanese Rheumatoid arthritis patients (pts) in whom MTX could not be administered due to efficacy or safety reasons. **Methods:** During the open label extension (OLE) study, pts withdrawn at 16wk of double-blind (DB) due to lack of efficacy (Group I, n=110) and completers without an ACR20 response at DB 24wk (Group II, n=12) received CZP 200mg Q2W. DB completers with an ACR20 response were randomized to CZP 200mg Q2W (Group III, n=43) or CZP 400mg Q4W (Group IV, n=43). **Results:** DB completers (Group II+III+IV) maintained their ACR20 responses (82.7% and 83.7%) and their DAS28-ESR remission rates (23.5% and 35.7%) at OLE entry and at 52wk, respectively. Improvements of HAQ-DI, Pain VAS, and SF-36 scores were also sustained. Efficacies of Groups III and IV were comparable. Serious adverse events were observed in 13.9% of all patients; no TB or death was reported. **Conclusion:** Paients in whom MTX could not be administered showed long-term response to CZP 200mg Q2W and 400mg Q4W at similar efficacy and safety. CZP without concomitant MTX was well-tolerated with no new safety signals.

W25-5

High Rate of improvement in serum matrix metalloproteinase-3 levels at 4 weeks predict for remission at 52 weeks in patients with rheumatoid arthritis by using anti-TNFα treatment

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Conflict of interest: None

[Objectives] Serum MMP-3 is a specific inflammatory marker of the synovium in patients with rheumatoid arthritis (RA).Our aim in this study was to investigate whether serum MMP-3 is the predictor for remission in treatment for RA patients with biologics. [Methods] All RA patients (n=175) who underwent adalimumub (ADA) treatment in TBC registry were enrolled in this study. We analyzed 107 patients in continuation with ADA therapy at 52 weeks.They were divided into 2 groups: high rate of improvement (HR group) and low rate of improvement (LR group) in serum MMP-3 levels at 4 weeks. We evaluated the rate of remission at 4, 12, 24, and 52 weeks in HR group and LR group. ROC analysis was performed to determine the cut-off rate of improvement in serum MMP-3 value for remission at 52 weeks. [Results] The rate of remission at 4, 12, 24 and 52 weeks in HR group is significantly higher than in LR group($p<0.05$).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%(sensitivity: 60%, specificity: 80%, accuracy: 66%). [Conclusion] We considered that rate of improvement in serum MMP-3 can be useful for estimating the remission at 52 weeks in RA patients with ADA therapy.

W25-6

The usefulness of Golimumab in RA patients of our hospital

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Conflict of interest: None

[Objective] To examine the usefulness of golimumab (GLM) in RA patients who went through 24 weeks of GLM treatment. [Method] 33 RA patients (59 years old of mean age, all women, mean disease duration 10.8 year) who GLM was commenced by April 2012 were evaluated. The change of DAS28-CRP, SDAI, HAQ and the drug survival rate were evaluated retrospectively using the medical record. [Result] After GLM treatment, and DAS28-CRP was declined from 4.1 to 2.7, SDAI from 21.1 to 9.6, HAQ from1.2 to 0.9, significantly. AT the 24-week, clinical remission rate was 18% in SDAI and 42% in DAS28-CRP. At 24-week, GLM survival rate is 88%, and the discontinuation due to adverse event was not seen. Moreover, DAS28-CRP in biologics naïve cases (n=16) declined significantly from 4.4 to 2.3, SDAI from 24.4 to 6.7, HAQ from 0.7 to 0.5, and DAS28-CRP remission rate was 63% and SDAI remission rate was 31%. Although DAS28-CRP (from 4.1 to 2.7) and SDAI (from 17.3 to 13.0) of a switch case (n=17) improved significantly, the clinical remission rate was only 24% in DAS28-CRP and 6% in SDAI, and, as for HAQ, the significant difference was not seen (from 1.6 to 1.4). [Conclusion] The biologics naïve group showed high clinical remission rate and HAQ improvement after GLM medication, as compared with the switch group.

W26-1

Induction of regulatory B cells (Bregs) in normal subjects and RA patients

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Conflict of interest: None

[Objectives] B-cell depletion therapy highlights a role of B cells in the pathogenesis of rheumatoid arthritis (RA). Recent evidence shows that B cell subpopulations exert regulatory functions via IL-10 production and are termed regulatory B cells (Bregs). In this study, we compared Breg induction in normal subjects and RA

patients. [Methods] IL-10 expression in B cells was assessed using quantitative PCR and ELISA. Bregs were co-cultured with T cells, and proliferation and IFNg production of T cells were assessed. [Results] CpG strongly induced IL-10 expression in normal B cells, and IgM memory subsets expressed the highest levels of IL-10. Bregs inhibited proliferation and IFNg production of T cells in an IL-10-dependent manner. Intriguingly, CpG-induced IL-10 production was remarkably abrogated in B cell subsets of RA patients. Accordingly, the regulatory function of Bregs towards T cells was significantly impaired in RA patients. We are currently elucidating the underlying mechanisms of defective Breg function in RA patients. [Conclusion] These findings provide not only a better understanding of a role of human Bregs in the pathogenesis of RA, but also a novel clue to manipulating the generation of Bregs for the treatment of RA.

W26-2

Identification of citrullinated cellular fibronectin in synovial fluids from patients with rheumatoid arthritis

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Conflict of interest: None

[Objectives] Citrullinated peptides are major autoantigens in rheumatoid arthritis (RA). Fibronectin consists of plasma fibronectin and cellular fibronectin (cFn). As for plasma fibronectin, citrullinated form is reported to be present in RA plasma. Previous studies demonstrated the presence of cFn in RA synovial fluids (RASF). The aim of the present study is to demonstrate the presence of citrullinated cFn (Cit-cFn) in RA. [Methods] Synovial fluids obtained from 25 RA patients and 7 controls were used. Paired sera obtained from 9 RA patients were also used. Cit-cFn was examined by ELISA and IP-Western blotting, using commercially available ELISA kit and agarose-conjugated anti-cFn mAb. [Results] Cit-cFn was detected in synovial fluids of RA patients at higher levels than those of controls. Cit-cFn was also identified by IP-Western blotting in RASF. The level of Cit-cFn was significantly higher in synovial fluids than that in serum. No correlation was found between Cit-cFn and total cFn or anti-citrullinated peptide antibody level. [Conclusion] Cit-cFn was detected at higher level in RA synovial fluids than in serum. It was suggested that citrullination of cFn might be intraarticular phenomenon observed in RA.

W26-3

Autoantigen BiP-specific regulatory T cells in rheumatoid arthritis and thier therapeutic application

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Conflict of interest: None

<Objectives> BiP is a rheumatoid arthritis (RA) autoantigen and we reported BiP-derived epitopes which were recognized by Th17 cells in RA. However, some reports described that BiP-responsible T cells had regulatory activities. <Methods> PBMCs from RA patients were cultured with BiP-derived peptides, and IL-10 secretion was measured by ELISA. $CD4^+$ T cells in RA were stained by BiP-derived peptide-HLA-DRB1*0405 tetramer and other surface markers, and analyzed by FACS. BiP-derived peptide was orally administrated to collagen-induced arthritis (CIA) mice, and measured clinical scores. IL-10 secretion from cultured CD4+ T cells was measured by ELISA. <Results> Some BiP-derived peptides induced IL-10 from PBMCs. The strongest IL-10-inducing peptide (BiPreg)-conjugated HLA-DRB1*0405 tetramer-positive CD4+ T cells showed CD25-CD127- Tr1-like phenotype and increased expression of IL-10. Oral administration of BiPreg peptide ameliorated CIA. $CD4^+$ T cells from BiPreg-treated mice secreted significantly higher amounts of IL-10 in response to BiP. <Conclusion> Imbalance between BiP-specific effecor and regulatory T cells could be associated with the breaking of self tolerance in RA. Restoring the balance by inducing BiP-specific Tr1 cells could be an antigen-specific therapy for RA.

W26-4

IL-33 synergistically enhances immune complex-induced TNF-α production in human synovial mast cells

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Conflict of interest: None

Objectives: Substantial evidence suggests that human synovial mast cells (syMCs) are involved in the pathogenesis of rheumatoid arthritis (RA). IL-33 is believed to play an important role in the pathogenesis of RA. We recently reported that FcγRI is responsible for producing abundant TNF-α from cultured synovium-derived MCs in response to aggregated IgG. However, whether IL-33 affects immune complexes (IC)-induced syMC activation remains unknown. The present study sought to evaluate the effect of IL-33 on IC-induced syMC activation. ***Methods:*** Cultured syMCs were generated by culturing synovial cells with stem cell factor. ST2 expression was analyzed using FACS and immunohistochemical techniques. Mediators released from the MCs were measured using EIAs or ELISAs. ***Results:*** SyMCs obtained from patients with RA or osteoarthritis (OA) expressed ST2 on their surfaces. We confirmed the expression of ST2 in MCs using immunofluorescence staining in joint tissue obtained from RA patients. IC-triggered histamine release was not enhanced by IL-33. However, IL-33 synergistically enhanced IC-induced TNF-α production in SyMCs. ***Conclusions:*** ICs and IL-33 may exacerbate inflammation associated with RA by abundantly producing TNF-α from syMCs.

W26-5

Analysis for the expression of IL-12B p40 induced by DcR3 in rheumatoid synovial fibroblasts

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Conflict of interest: None

[Objectives] Decoy receptor 3 (DcR3), a secreted decoy tumor necrosis factor receptor, competitively binds and 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. In this study, by using comprehensive genetic analysis, we revealed DcR3 induced IL-12B expression in RA-FLS. Further, we analysed IL-12B expression in RA-FLS stimulated with DcR3 in

detail. [Methods] Gene expressions in RA-FLS stimulated with DcR3-Fc or control IgG1 were detected by microarray assay. IL-12B mRNA and IL-12B p40 protein expression in RA-FLS were analysed by real-time PCR and western blotting, respectively. [Results] Microarray data analysis revealed DcR3 up-regulates IL-12B expression in RA-FLS. Real-time PCR showed DcR3 significantly increased IL-12B mRNA in a dose dependent manner. Western blotting confirmed that DcR3 increased IL-12B p40. [Conclusion] IL-12, consisted with IL-12A p35 and IL-12B p40, and IL-23, consisted with IL-12B p40 and IL-23A p19, are linked with autoimmune diseases via Th1 and Th17 immune responses, respectively. DcR3 may affect the pathogenesis of RA by regulating IL-12B expression in RA-FLS.

W26-6

Analysis of the expression of TNFAIP3 and TNFAIP9 in patients with rheumatoid arthritis

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Conflict of interest: None

[Backgroud] TNFAIP3 or 9 deficient mice spontaneously develop polyarthritis, suggesting regulatory function to arthritis. [Objectives] To clarify their expression on peripheral blood mononuclear cells (PBMC) and the pathogenicity in the regulation of rheumatoid arthritis (RA). [Methods] 1) TNFAIP3 and 9 mRNA expression in PBMC from 40 patients with RA, 17 healthy subjects (HS) and 16 patients with Sjögren syndrome (SS) were examined. 2) The fluctuated mRNA expression of them at baseline and 6 months after administration of infliximab (IFX) was also compared. 3) The dominant expressing cells of TNFAIP9 was analyzed using FACS and their expression after stimulation with TNFα was examined. [Results] 1) TNFAIP3 mRNA expression in RA was significantly lower than HS, and TNFAIP9 was higher than HS and SS.2) TNFAIP3 expression was increased after IFX treatment, and the difference was more significant in good-responders. The difference in TNFAIP9 was not found, whereas baseline expression level was clearly higher in good-responders compared to non-responders.3) TNFAIP9 was expressed in $CD14^+$cells, and upregulation by TNFα was observed 24h after stimulation. [Conclusion] The different expression pattern of them indicates that they might play different roles in the regulation of RA.

W27-1

Lysophosphatidic acid receptor 1 (LPA_1) is essential for the development of arthritis

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Conflict of interest: None

[Objectives] Lysophosphatidic acid (LPA) is a bioactive lipid. In the previous JCR meeting, we showed lysophosphatidic acid receptor 1 (LPA_1) is highly expressed in rheumatoid arthritis (RA) synovium, LPA_1 antagonist inhibited murine collagen-induced arthritis (CIA), and macrophage migration into the synovium. In addition, LPA_1 antagonist inhibited osteoclast formation and Th17 differentiation. In this study, we analyzed the effects of LPA_1 on arthritis using LPA_1-deficient mice. [Methods] CIA was induced in $LPA_1^{-/-}$ or wild-type (WT) mice. Migrated fluorescence labeled-$CD11b^+$ splenocytes, which were transferred into CIA, into the synovium were counted. Bone marrow cells were incubated with RANKL+M-CSF, and osteoclast formation was analyzed by TRAP staining. $CD4^+$ naïve T cells were incubated with Th1-, Th2-, or Th17-polarizing condition and Th differentiation was analyzed by FACS. [Results] LPA_1 KO mice did not develop arthritis by the collagen immunization. Infiltration of $LPA_1^{-/-}$ $CD11b^+$ cells was suppressed compared with WT. Osteoclast formation and Th17 differentiation, but not Th1 and Th2, was also inhibited in $LPA_1^{-/-}$ cells. [Conclusion] LPA-LPA_1 signaling contributes to the development of arthritis by cellular infiltration, Th17 differentiation and osteoclastogenesis.

W27-2

Role of periodontitis for the initiation of chronic inflammatory arthritis

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Conflict of interest: Yes

[Objectives] To study the role of periodontitis for the initiation of chronic inflammatory arthritis. [Methods] Patients with arthralgia without prior use of corticosteroids or DMARDs who first visit the department for the rheumatic diseases in our hospital were examined for periodontitis status and quantified for *Porphyromonas gingivalis* (*P.G.*) DNA of plaque samples. Correlation between periodontitis and the diagnosis, disease activity, anti-CCP antibody status of arthritis were analyzed. Patients were observed for the introduction of methotrexate treatment. [Results] Among 82 enrolled patients, 29 were initially diagnosed as RA, 12 as osteoarthritis, while 42 were followed as undifferentiated arthritis. *P.G.* quantity well correlated with the clinical evaluation of periodontitis (plaque depth≦3mm vs plaque depth≧4mm). The severity of arthritis (SJC, VAS, SDAI, or CDAI) was higher in periodontitis patients compared with periodontal healthy patients. Periodontitis status had no specific correlation with RA diagnosis or anti-CCP antibody. Patients with periodontitis tended to be introduced for methotrexate treatment within 8 months. [Conclusion] Patients with arthralgia who have periodontitis tend to develop into chronic inflammatory arthritis that requires methotrexate.

W27-3

Rheumatoid Arthritis Patients have High Risk of Cardiovascular Disease instead of Lower Energy and Nutrient Intake -TOMORROW Study-

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Conflict of interest: None

[Objectives] There are few reports about relationship between risk status of cardiovascular disease and nutrient intake in RA patients. We investigated food and nutrient intake status in RA patients compared to volunteers. [Methods] We started age and sex

matched cohort study from 2010. The cohort consists of 202 volunteers (C group) (age: 57.9 ± 13.2, BMI: 22.6 ± 3.2kg/m^2) and 202 RA patients (RA group) (age: 59.1 ± 12.7, BMI: 22.6 ± 3.6kg/m^2). Food and nutrient intake status was obtained by using BDHQ (brief-type self-administered diet history questionnaire) at the spring of 2011. Furthermore, we analyzed relationship between clinical data and food and nutrient intake status. [Results] Energy and other nutrient intake in RA group were low. However, RA group showed higher blood pressure and HOMA-R (homeostasis model assessment insulin resistance). There was significant relationship between blood pressure, HOMA-R and nutrient intake such as saturated fatty acids. Also there was significant relationship between DAS28 score and nutrient intake such as n-3 fatty acids. Gender difference was observed on this relationship between clinical data and food and nutrient showed. [Conclusion] Total management including food and nutrient intake status is required for the treatment of RA patients.

W27-4

Plasticity and pathogenicity of T follicular helper cells in rheumatoid arthritis

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Conflict of interest: None

[Objectives/Methods] 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 the role in the pathogenesis of rheumatoid arthritis (RA) remain unclear. We studied the molecular mechanisms of Tfh cell differentiation and document the relevance of Tfh cells to pathological processes in RA. [Results] Among various cytokines, IL-12 induced IL-21 and Bcl6 via STAT4-activation, generating cells with features of both Tfh and Th1 cells. Using ChIP-seq, we found that STAT4 directly bound to multiple genes involved in Tfh and Th1 cell development, regulating gene expression and active histone modifications. The proportion of CD4$^+$CXCR5$^+$Tfh cells and CD4$^+$CXCR3$^+$Th1 cells has characteristically increased in peripheral T cell subsets in patients with RA compared to normal individuals. Those cells expressed active surface markers such as CD38 as well. The proportion of Tfh cells has increased in APCA-positive patients, whereas that of Th1 cells was closely correlated with disease activity. [Conclusion] These findings argue that phenotypic plasticity between Tfh and Th1 cells underlies the pathogenesis of RA, i.e., active involvement of Tfh cells in autoantibody production and Th1 cells in inflammation in RA.

W27-5

Alteration of DNA methylation by pro-inflammatory cytokines in Rheumatoid Arthritis synovium

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Conflict of interest: None

[Objectives] RA FLS exhibit a unique aggressive phenotype that contributes to the cytokine milieu and joint destruction. DNMTs are critical enzymes involved in establishing proper control of DNA methylation (DNAme). We evaluated if pro-inflammatory cytokines might contribute to differential DNAme previously described in RA FLS through altered DNMT expression. [Methods] FLS were obtained from RA and OA synovium at total joint replacement. DNMT expression was determined by qPCR and Western blot analysis. DNMT activity and DNAme status was determined by an ELISA-based assay. [Results] Unstimulated RA and OA FLS expressed DNMTs similarly. DNMT1 and -3a mRNA expression were decreased by IL-1ß, LPS, or TNF. IL-1 decreased DNMTs mRNA in a dose-dependent manner, which was regulated transcriptionally. DNMT activity and global DNAme were also decreased when FLS were cultured continuously for 14 days with IL-1ß. Removal of IL-1ß recovered DNAme levels. Chronic IL-1 exposure also mimicked the effect of a DNMT inhibitor on FLS gene expression. [Conclusion] Exposure to pro-inflammatory mediators alters DNAme in FLS by decreasing DNMT expression, indicating that the rheumatoid synovium can imprint FLS by altering DNAme and potentially inducing a more aggressive phenotype.

W27-6

Altered Histone methylation is associated with IL-6 dependent MMPs gene transcriptional activation in rheumatoid arthritis synovial fibroblasts

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Conflict of interest: None

[Objectives] Rheumatoid arthritis (RA) is a chronic inflammatory autoimmune disease that is hardly cured and causes progressive joint destruction. RA synovial fibroblasts (SFs) produce matrix-degrading enzymes and promote bone and cartilage destruction. Epigenetic mechanisms are considered to be important regulators in gene transcription. We hypothesized that aberrant epigenetic regulations might lead to synovitis in RA. [Methods] We measured MMPs gene expression and histone methylation in their loci in RASFs and osteoarthritis (OA) SFs. Because serum IL-6 is elevated in RA, we stimulated SFs with IL-6 and/or soluble IL-6 receptor alpha (sIL-6Ra). We measured cell surface expressions of IL-6 receptor and the phosphorylation of STAT3. [Results] MMP1, 3, 9 and 13 mRNA levels were high in RASFs. H3K4me3 was high whereas H3K27me3 was low in the MMP1, 3, 9 and 13 loci in RASFs. MMP1, 3 and 13 mRNA levels increased after stimulation with IL-6 and sIL6Ra in RASFs. Cell surface expressions of gp130 and IL-6Ra were comparable and STAT3 was similarly phosphorylated after stimulation with IL-6 and sIL-6Ra in RASFs and OASFs. [Conclusion] Characteristic histone methylation is associated with IL-6 dependent MMPs gene transcriptional activation and possibly arthritogenic properties of RASFs.

W28-1

Remodeling of the glomerular lesions by bystander IgM antibodies of experimental lupus nephritis : Induction of E-selectin on the endothelial cells *in situ*

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Conflict of interest: None

Lupus nephritis (LN) frequently shows various histopathological types of glomerular lesions, associated with the glomerular deposition of various subtypes of immunoglobulins, in transitional forms. However, the mechanism of remodeling of glomerular lesions in LN is unclear. We previously showed that the combination of nephritogenic IgG3-producing hybridoma clone, 7B6.8, from a MRL/lpr lupus mouse, which induced a wire loop-like type of glomerular lesions, with the non-nephritogenic IgM-producing hybridoma, Sp6, remodeled the wire-loop type to the cell-proliferative type of glomerular lesions, when injected into SCID mice. We herein investigated the association of E-selectin expressions with these remodelings of glomerular lesions in LN of this lupus model mouse. The degree of these remodellings was significantly associated with increased levels of glomerular E-selectin. In addition, these remodellings of glomerular lesions in this lupus model mouse were significantly suppressed by overproductions of soluble E-selectin proteins in the plasma of SCID mice. We conclude that these remodeling of glomerular lesions in the concomitant presence of non-nephritogenic bystander IgM antibodies is initiated by the glomerular expressions of E-selectin *in situ*.

W28-2

Influence on podocyte function of Calcium/calmodulin dependent kinase protein type IV in lupus nephritis

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Conflict of interest: None

[Objectives] It has been reported that expression of Calcium/calmodulin-dependent protein Kinase Type IV (CaMKIV) increases in T cell of systemic lupus erythematosus patients. We examined the influence on the glomerulus epithelial cells (podocyte) function of CaMKIV in lupus nephritis using human kidney biopsy specimens and podocyte cell line (AB8/13). [Methods] We examined the expression level of nephrin and CaMKIV in normal control and LN by immunofluorescence staining. We stimulated podocytes with IgG purified from normal controls and LN patients for 24-48 hr and analyzed mRNA levels of CaMKIV by real time PCR. We also performed microarray analysis related CaMKIV gene. [Results] The expression level of nephrin decreased, and CaMKIV expression increased inversely in LN. The mRNA levels of CaMKIV expression in podocyte cell line significantly increased by LN IgG stimulation. Additionally, we found the expression level of CaMKIV in podocyte stimulated with LN IgG increased 1.65349 times compared with normal IgG by microarray analysis. In gene ontology analysis showed that the gene related with cell activation including CaMKIV changed significantly in LN IgG stimulated podocytes ($P<0.04711$). [Conclusion] These data indicate that CaMKIV may alter the function of podocytes in LN.

W28-3

Time of initial appearance of renal symptoms in the course of systemic lupus erythematosus and combined therapy with prednisolone and other immunosuppressant as a prognostic factor for lupus nephritis

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Conflict of interest: None

[Objectives] We reported that the prognosis of lupus nephritis (LN) is different between two LN categories, LN manifested initially at systemic lupus erythematosus (SLE) onset (e-LN)) and LN of delayed manifestation after SLE onset (l-LN). This time we report 113 cases of LN patients(mean period: 21.4 ± 10.1 years). [Methods] We extracted patients who have been infected with SLE for more than 5years and diagnosed with LN. We divided renal function into 3phases to compare e-LN with l-LN.We analyzed correlation between renal function and combination therapy. [Results] At last observation,the probability that patients are classified to irreversible renal failure phase is lower in e-LN(23.4%) than in l-LN(45.5%)($p=0.04$).The probability 5,15years later is similar.The probability that patients becomes hemodialysis patients is 4/48 in e-LN and 10/59 in l-LN.The probability of patients classified to irreversible renal function group 10,15years later is 3/23,12/22 in PSL only group and 9/15,7/13 in combination therapy group. [Conclusion] The prognosis of LN patients classified to e-LN is better than l-LN.The combined therapy with prednisolone and other immunosuppressant may improve kidney convalescence.

W28-4

Relationship between clinical manifestations and autoantibodies in ISN/RPS classV lupus nephritis

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Conflict of interest: None

[Objectives] To clarify the relationship between clinical manifestations and autoantibodies positivity in classV lupus nephritis (LN). [Methods] 31 patients with classIII/IV LN and 22 patients with classV LN were enrolled. Clinical manifestations, autoantibodies positivity were compared between two subsets. Next, we analyzed the relationship between clinical manifestation and each autoantibody in classV LN subset only. [Results] Anti-dsDNA Ab positivity was tend to be higher in classIII/IV (87.1% vs 63.6%, $P = 0.05$) and anti-Sm Ab positivity was tend to be higher in classV (19.3% vs 42.9%, $P = 0.12$). Anti-dsDNA Ab(+)/anti-U1snRNP Ab(-) was significantly higher in classIII/IV (54.1% vs 19.1%, $P = 0.03$). Anti-dsDNA Ab(-)/anti-U1snRNP Ab(+) was significantly higher in classV (0% vs 33.3%, $P < 0.01$). In classV LN, low complementemia was significantly higher ($P < 0.01$) in anti-dsDNA positive subset. SLEDAI score was significantly higher ($P = 0.02$) in anti-Sm positive subset. Rash and anti-dsDNA Ab positivity were significantly higher ($P < 0.01$ and $P = 0.04$, respectively) and arthritis was tend to be higher ($P = 0.05$) in Anti-Ribosomal P Ab positive subset. [Conclusions] We showed the relationship between clinical manifestations and autoantibody positivity in ISN/RPS classV LN patients.

W28-5

Association between endocapillarychange and IgG3 in lupus nephritis

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Conflict of interest: None

[Objectives] the role of immunoe complex is important for developping lupus nephritis. Immunoglobulin g (IgG) 3 has the strongest activity for immune complex and the shortest half life in all IgG subclasses. However, the role of IgG3 in the progression of lupus nephritis, especially endocapillary change is still unknown. [Methods] Biopsy proven lupus nephritis between October 2001 to October 2011 were analyzed. We performed IgG subclass staining for all cases and classified them according to the ISN/RPS 2003 classification. the relationships between positivity and strength of IgG1 and 3 according to the classification were analyzed. [Results] The positivity of IgG3 vs IgG1 in each class were as follows; class I or II (n=7), 29% vs 71%; class III (n=7), 14% vs 86%; class IV(S) (n=4), 50% vs 75%; class IV(G) (n=14), 86% vs 100%; class V (n=6), 50% vs 83%, respectively. [Conclusion] There is a consistant association between endocapillary change and positivity and strength of IgG3. These findings imply the importance of IgG3 in the endocapillary change in lupus nephritis.

W28-6

The Influence of Thrombotic Microangiopathy on Patients with Diffuse Proliferative Lupus Nephritis

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Conflict of interest: None

[Objectives] Examined the influence of Thrombotic Microangiopathy (TMA) on the renal outcome of patients with diffuse proliferative lupus nephritis (LN). [Methods] We screened 71 SLE patients who were suspected of having LN and underwent renal biopsy in our department from 2000 to 2010. We conducted a retrospective analysis of 27 patients of them diagnosed with type IV on clinical information such as clinical picture, treatment history, treatment response, and presence or absence of exacerbation. The average observation period was 5.0 years. [Results] 27 patients including 5 ones associated with type V were classified into type IV, and 4 cases (15%) were associated with TMA. We compared clinical characteristics of cases associated with TMA and ones which were not. Tendencies such as short period before the development, many cases associated with hyperpiesia, and high value in proteinuria were observed in the TMA group, and cases associated with TMA had higher serum creatinine values with a significant difference than ones which were not. [Conclusion] TMA is a serious complication of diffuse proliferative LN. We therefore consider that it is necessary to maintain renal function by providing prompt immunosuppressive treatment in addition to the early detection of TMA.

W29-1

Lack of association between juvenile dermatomyositis and HLA-DRB1 alleles, *STAT4*, and *BLK* polymorphisms in Japanese

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Conflict of interest: None

[Objectives] Genetic factors in juvenile dermatomyositis (JDM) have not fully investigated because of the rarity of the disease.The aim of the present study was to investigate the involvement of the HLA-DR alleles as well as non-HLA genes in the susceptibility of JDM in Japanese. [Methods] We recruited 63 patients with JDM, and typed the HLA-DRB1 alleles. As for the non-HLA genes, *STAT4* (signal transducer and activator of transcription 4) and *BLK* (B lymphocyte kinase) polymorphisms were investigated because these genes were recently associated with adult-onset dermatomyositis (DM) in Japanese. We also typed 72 patients with adult-onset DM as wells as 265 control subjects. [Results] There was no specific HLA-DRB1 alleles associated with development of JDM, as was the case with DM. Furthermore, neither STAT4 (rs7574865) nor BLK (rs13277113) polymorphisms was associated with susceptibility to JDM. [Conclusion] Although JDM and DM share some clinical, histological and immunogenic features, the age of disease onset is not overlapping. The present study did not detect any common genetical factors between both the diseases.

W29-2

Investigation about the dose of mycophenolate mofetil in pediatric patients with systemic lupus erythematosus

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Conflict of interest: None

[Objectives] To evaluate the dose of MMF, we investigated safety and clinical efficacy of MMF to pediatric patients with SLE. [Methods] It was retrospectively evaluated to use clinical records. Thirty-one patients were investigated. [Results] The age of disease onset was 10.2 ± 3.1 years old. The daily dose of MMF was from less than 1000mg to 2000mg. In evaluation per body weight, the number of the patients who were prescribed 20 mg/kg of MMF was two. The number of 30 mg/kg was 17, and 40mg/kg was 12. The daily dose of PSL was 5mg, 7.1mg and 7.8mg in the patients who had the dose of MMF 20, 30 and 40 mg/kg respectively. About the adverse events, diarrhea was frequently observed. Severe diarrhea occurred in one patient who had been prescribed 1500mg of MMF (30mg/kg/day). As other serious adverse events, the infection that required hospitalization was seen in three patients. One patient with herpes zoster had been prescribed 2000mg of MMF (40mg/kg/day). [Conclusion] By the using of MMF to 40mg/kg for pediatric patients with SLE, the dose of PSL could have decreased to less than 10mg in many patients. In this study, the correlation between adverse effects and dose of MMF was not seen. However, it is necessary to increase the number of cases and to investigate over a long period.

W29-3

Clinical efficacy and safety of tocilizumab as a first-line biologic therapy for adolescent patients with rheumatic disease showing an inadequate response to methotrexate

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Conflict of interest: None

Objective: We evaluated the efficacy and safety of tocilizumab (TCZ) as a first-line biologic therapy for adolescent patients with rheumatic disease showing an inadequate response to methotrexate (MTX). ***Methods:*** We investigated 5 patients (2 males, 3 females) under 19 years of age (mean age 16.6±1.8 yr, disease duration 1.3±0.9 yr) with rheumatic disease (2 patients with juvenile idiopathic arthritis [JIA], 2 with adult-onset Still's disease, and 1 with rheumatoid arthritis [RA]) who had been treated with TCZ (mean period 83.3±44.6 wk). X-ray examination showed joint space narrowing in 3 patients and erosion in 1. We determined disease activity in terms of the active joint count, patient global assessment, CRP, and ESR at the baseline and during treatment. Four patients had a high titer of MMP-3, and 3 (JIA, RA) had a high titer of anti-CCP antibody. ***Results:*** Rapid improvements in disease activity were observed within 8 weeks. Although most of the adverse events were mild viral infections, TCZ was discontinued in 1 patient due to hemophagocytic syndrome caused by acute Epstein-Barr virus (EBV) infection. ***Conclusion:*** TCZ is a rapidly effective treatment for rheumatic disease in adolescents. However, the possibility of acute EBV infection must be borne in mind.

W29-4

Reversible Vasogenic Oedema of Basal Ganglia Lesions in Central Nervous Systemic Lupus

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Conflict of interest: None

[Objectives] Neuropsychiatric (NP) involvement is a serious manifestation of Systemic Lupus Erythematosus (SLE). The American College of Rheumatology (ACR) has established the standardized 19 symptoms to diagnose of NPSLE. Magnetic resonance imaging (MRI) is useful with NPSLE. We herein report three cases of Japanese girls with NPSLE. [Case report] They had a fever and severe headache. T2-weighted brain MRI showed high intensity lesions around of basal ganglia. Both Diffusion-weighted MRI (DWI) and ADC mapping were high. Marked elevation of the cerebrospinal fluid (CSF) interleukin (IL)-6 were noted. And IgG anti-NR2 glutamate receptor antibody was elevated. We diagnosed them with Vasogenic Oedema resulting from NPSLE. They were treated with immunomodulatory and anticoagulation medications. Their clinical symptoms improved, and her CSF IL-6 and autoantibodies levels were decreased. After treatment, T2WI and DWI showed normal intensity. [Conclusion] The etiology of NPSLE remains unclear. There have been few reported pediatric cases of NPSLE. Our cases indicate that brain MRI including DWI and ADC mapping might be useful in not only in the diagnosis of NPSLE, but also in assessing the type of vasculopathy.

W29-5

Examination of the non-remitted cases of the initial therapy for systemic juvenile idiopathic arthritis

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Conflict of interest: None

[Objectives] As "Proposal for juvenile idiopathic arthritis (JIA) guidance" was published in 2007, the need of the standard treatment was indicated. However, it is also true that JIA is diverse and the optimal medical treatment is needed for each case. So,we were examined with the validity of our initial therapy according to "Proposal for JIA guidance". [Methods] A total of ten patients suffering from systemic JIA at our hospital during the period from 2007 to 2012, were performed with the initial therapy. Examples of complications of macrophage activation syndrome were excluded from the study. The patients received two cycles of methylprednisolone pulse therapy followed by the basic dose of 0.7 - 1.0mg/kg of PSL (up to maximum of 30mg/day) as after-treatment. The minimal dosage of PSL was determined 15 mg per day in our study.We extracted data such as age, duration of fever, laboratory data (CRP, ferritin) and examined the risk factors. [Results] Six out of ten patients did not achieve a complete remission and needed to intensify the treatment. It was found out CRP and ferritin were relatively high in the non-remitted cases. [Conclusion] It was suggested that a dosage of 1.0mg/kg of PSL may not be sufficient for the lower age group in post-steroid treatment.

W30-1

Diversity of anticardiolipin/β_2-glycoprotein I antibody: A study using patient-derived IgG-type monoclonal antibody

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Conflict of interest: None

[Background and objectives] Antiphospholipid syndrome (APS) is a thrombosis or/and pregnancy complication with the presence of antiphospholipid antibody (APL). Anticardiolipin/β_2-glycoprotein I antibody (aCL/β_2-GPI) is a representative APL. In this study, the diversity of aCL/β_2-GPI was examined with IgG monoclonal aCL/β_2-GPI from APS patient. [Methods] B cells from APS patients were immortalized with EBV infection to clone aCL antibody-producing cells using limiting dilution and sorting techniques. A stable cell line containing an IgG-monoclonal antibody (EV35102:EV) was established by introducing genes in the IgG variable region into CHO-K1 cells. The presence of a homologous antigen of EV was examined by ELISA. The coagulation function of EV was evaluated in monocytes from healthy controls using quantification of induced tissue factor (TF) mRNA by real-time PCR. [Results] EV interacted with cardiolipin in a β_2-GPI-dependent manner. EV did not bind to full-length β_2-GPI under any conditions, but interacted with β_2-GPI domain I. EV significantly induced monocyte TF mRNA expression compared with the IgG3 control (9.23±2.79 vs. 2.18±0.32, $p<0.05$, t-test). [Conclusion] EV is a new thrombus-evoked aCL/β_2-GPI with anti-β_2-GPI-negtive patterns, but with an epitope in β_2-GPI domain I.

W30-2

Role of Ribophorin II and phosphatidylserine-dependent antiprothrombin antibody in the tissue factor expression on monocytes

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Conflict of interest: None

[Objectives] To investigate the membrane protein involved in the binding of Prothrombin (PT) and antiprothrombin antibody to cell surface and the induction of TF expression on monocytes. [Methods] 1) RAW 264.7 cells with FLAG-tagged PT were incubated and applied for affinity chromatography with anti-FLAG antibody-conjugated Sepharose beads. The purified fraction was subjected to SDS-PAGE and detected with CBB staining. Immunopurified proteins were analyzed by an online-nano LC-

MS/MS. 2) The binding between PT and Ribophorin II (RPN2) was analyzed by co-transfection assay, ELISA, Surface Plasmon Resonance (SPR). 3) To elucidate the role of RPN2 in TF mRNA expression, RAW 264.7 cells treated with RPN2 small interfering RNA (siRNA) expression and TF mRNA was determined by real-time PCR. [Results]1) RPN2 was identified as the candidate molecule to be the membrane protein involved in the PT binding to cell surface. 2) The binding between PT and His-RPN2 was confirmed by co-transfection assay, ELISA and SPR. 3) Treated cells with RPN2 siRNA showed significantly reduction of the TF expression mediated by PT and antiprothrombin antibody. [Conclusion] RPN2 was detected as the PT binding protein. RPN2 may be involved in the pathophysiology of thrombosis in patients with APS.

W30-3

Study of patients positive for lupus anticoagulant despite of normal APTT

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Conflict of interest: None

[Objectives] Antiphospholipd antibody syndrome, APS, is a potentially severe sickness that can lead to abortus habitualis, fetal death, cerebral infarction, retinal embolism, myocardial infarction or pulmonary embolism. APS is often associated with systematic lupus erythematosus, SLE. The detection of lupus anticoagulant, LA, and anticardiolipin antibody, and clinical criteria is important for diagnosis of APS. LA is generally tested in patients with prolonged activated partial thromboplastin time, APTT. However, the feature of patients with normal APTT and the presence of LA remains to be determined. [Methods] We analyzed 403 cases that underwent testing of both APTT and LA from August 2010 to July 2012. LA was determined using dilute Russell's viper venom time. [Results] APTT was found prolonged in 176 of all the patients. LA was positive in 25 of all the 403 patients, 21 of the 176 patients with prolonged APTT, and 4 of 227 patients with normal APTT. All 4 patients with normal APTT and positive LA were thrombocytopenic. Two patients were diagnosed to have SLE, one idiopathic thrombocytopenic purpura, and one Evans syndrome. [Conclusion] When APS was suspected in patients with thrombocytopenia, LA should be tested regardless of normal APTT.

W30-4

Analysis of patients with connective tissue disease using medication against pulmonary hypertension in our department

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Conflict of interest: None

[Objectives] To examine connective tissue disease (CTD) patients who received medication against pulmonary hypertension (PH). [Methods] Data were extracted from patients who had CTD by prescription of these medicine; beraprost, bosentan, ambrisentan, sildenafil, and tadarafil and were compared with the relevant CTD patients data. [Results] The group who might have PH includes MCTD (43 patients), SLE (267 patients), and Scleroderma (158 patients). The age of onset was 39.5±2.4, 32.8±1.0, 55.1±1.0, respectively. Gender ratio was 12:31, 36:231, 16:142, respectively. In this group, patients who received anti-PH drug was 2.3% (MCTD), 3.4% (SLE), and 13.9% (SSc), respectively. The age of onset was 59.3±2.5 years old (M/F;1/31). Average level of BNP was 275.8±110.8pg/ml, estimated RVP was 40.0±2.5mmHg, the level of LDH was 222.0±8.8IU/L, and KL-6was 634.7±67.4U/ml. The 1st option was mainly PGI2 derivative (62.5%) and ET receptor inhibitor and PDE5 blocker were prescribed as 2nd or 3rd. Death rate increased with the increasing number of medicine. [Conclusion] In patients who took medication against PH, MCTD was slightly rare. The proportion of CTD was not different between single and multiple medicines. Medicated patients had high level of KL-6 and were suggested to have pulmonary involvement.

W30-5

Long-term outcomes after the patients is diagnosis mixed connective tissue Disease (MCTD) at initial visit

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Conflict of interest: None

[Objectives] To clarify the disease evolution and clinical entity of the patients with MCTD by prolonged observation. [Patients and Methods] MCTD patients who diagnosed from 1974 to 2012 and recorded in our database were evaluated retrospectively. We defined a disease evolution and death as an event, and Kaplan-Meier method were used to analyze event-free survival in patients with MCTD [Results] One hundred eighty-four MCTD patients (Female 166) who diagnosed at initial visit were included. The average age was 40.4±14.2 (mean±SD), and follow-up period 10.3±8.5 years. One hundred thirty-three MCTD patients remain the same diagnosis, and 51 evolved into anther connective tissue disease (SLE 31, SSc 8, Overlap syndrome 7, RA 2, Vasculitis 2, and polymyositis 1). The event-free survival rates were 97.3%, 92.3%, and 87.4% at 1, 3, and 5 years, respectively. In 133 MCTD patients monitored without disease evolution, total mortality was 13 (4 CPA, 3 malignancy, 2 subarachnoid hemorrhage, 1 pulmonary hypertention, and 4 other) and the median survival time was 33.1 years (95%CI: 32.1-37.3). The survival rates in this group were 91.8%, 84.3%, and 77.4% at 10, 20, and 30 years, respectively. [Conclusion] MCTD is a district clinical entity, and the patients with stable MCTD had a good prognosis.

W31-1

Analysis of the factors that contribute to the differences between DAS28-ESR and DAS28-CRP (Importance of paying attention to the background of patients for the evaluation of DAS28-CRP)

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Conflict of interest: None

[Objectives] To analyze the factors that have an influence on the differences between DAS28-ESR and DAS28-CRP (=DAS-28DIF). [Methods] We analyzed the data from 5987 patients with rheumatoid arthritis (RA) registered in NinJa 2011. The mean DA28-ESR and DAS28-CRP was 3.24±1.28 and 2.58±1.10, respectively. [Results] A univatiate analysis showed that gender, age,

disease duration, stage, class, mHAQ, ESR, PtPainVAS, PtGVAS, DrVAS, artificial joint, and TJC28 were associated with DAS-28DIF with p<0.01. A multivariate linear regression analysis demonstrated that ESR (standard partial regression coefficient :0.631), female gender (0.195), age (0.122), class (-0.100), and BMI (-0.034) were associated with DAS28DIF. Category analysis also revealed that value of DA28DIF was higher with increasing ESR, age, disease duration, class, and with decreasing BMI. There was significant difference in DAS28DIF between male (0.41) and female (0.72). Mean DAS28DIF was -0.002 in patients whose ESR was 11 mm/hr or less. [Conclusion] This study showed that DAS-28DIF can be affected by many kinds of valuables. We should pay attention to the background of the patients when analyzing the data by using DAS28-CRP and evaluating the cut-off value of remission for DAS28-CRP based on that of DAS28-ESR.

W31-2

The Epidemiologic Analysis of Remission maintenance-A repot from NinJa Cohort-

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Conflict of interest: None

[Objectives] Although remission induction is emphasized in Target to Teat strategy, remission maintenance is relatively ignored. There is little information about remission maintenance in clinical practice. [Methods] We extracted the newly inducted remission cases in 2004 and 2009. Seventy cases and 296 cases were extracted.The duration of remission, the remission rate three years later, and background factors were evaluated. We attempted to examine the factors which affect the remission maintenance using Logistic regression analysis. [Results] Remission lost rates were 52.6% in 2004 group and 44.3% in 2009 group three years later. The change of treatment strategy has no impact on the incidence of remission maintenance. (p=0.194) Biologics usage was more frequent in the remission lost cases. Regarding the 2009 group, the shorter disease duration, the lower mHAQ, Phy's VAS, DAS-28ESR and corticosteroid dosage were found in the remission maintenance cases than in the remission lost cases. The lower Phy's VAS(Odds ratio 0.7), the lower mHAQ (Odds ratio 0.4), and remission induction without biologics(Odds ratio 0.5) were extracted as statistically significant factors by Logistic regression analysis. [Conclusion] The half of remission cases lost remission status three years later.

W31-3

Does satisfying patient global assessment criterion in the four Boolean criteria make a difference in prognosis of rheumatoid arthritis?

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Conflict of interest: None

【Objectives】To investigate the importance of patient global assessment (PGA) criterion in the four Boolean remission of rheumatoid arthritis in daily clinical practice.【Method】We defined patients fulfilling just three but not PGA of the four Boolean criteria as "near Boolean". Twenty-nine "Boolean" (Group B) and 31 "near Boolean" patients (Group N) were enrolled into this study. CRP, ESR, serum MMP-3, DAS28-CRP, SDAI, CDAI, and mHAQ at the baseline were compared between two groups. In addition, 56 patients with follow-up period greater than 1 year were compared above-described data, remission rate with Boolean or near Boolean, ΔmHAQ, and ΔmTSS at 1 year point.【Results】In Group B, DAS28/SDAI/CDAI at baseline, and SDAI/CDAI at 1 year point were lower compared to Group N significantly. The remission rate of Group B/N at 1 year point with Boolean criteria was 70%/41%, and with near Boolean criteria was 81%/93%, respectively. There were little differences in the ΔmHAQ and ΔmTSS between Groups B and N.【Conclusion】Based on a comparison of two groups, there were few differences in PGA-independence indices, such as inflammatory markers, mHAQ, and mTSS. The current study suggests that "near Boolean" is available for assessment of clinical remission in daily clinical practice.

W31-4

Analysis of factors impact on patient global assessment in daily practice based on observational cohort IORRA

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Conflict of interest: None

[Objectives] The purpose of this study is to reveal what factors are significantly associated with high scores of patient global assessment (PtGA) in rheumatoid arthritis (RA) patients of our cohort. [Methods] The subjects in this study were RA patients who participated in the IORRA survey during April 2011 and from whom all 4 components of Boolean trials (TJC, SJC, CRP and PtGA) were available. Univariate and multivariate models were used to evaluate the effect of clinical parameters including pain VAS, J-HAQ, TJC and SJC on PtGA scores of >1 compared to PtGA scores of ≦1. [Results] Of the 5,276 patients (female 84.3%, mean age of 60.1 years, duration of 13.5 years and PtGA scores of 2.9 cm), 31.3% of them fulfilled PtGA scores of ≦1, while about 75% of them satisfied TJC, SJC, or CRP of ≦1. PtGA scores were highly correlated with pain scores (r=0.86) and J-HAQ scores (r=0.54). In multivariate analysis, PtGA scores of >1 were associated with degree of pain (OR: 1.25, 95%CI: 1.23-1.27, p<0.01), physical dysfunction (OR: 1.82, 95%CI: 1.49-2.23, p<0.01) and no use of biologics (OR: 0.69, 95%CI: 0.69-0.90, p<0.01). [Conclusions] In clinical practice, pain, physical dysfunction and biologics use were the important determinant factors that associated with PtGA scores of >1.

W31-5

High Patient Global Assessment Scores Associate with the Residual Disease Activity Unidentified by a 28-joint Examination in Rheumatoid Arthritis Patients with Near Remission

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Conflict of interest: None

[Objectives] To reveal the difference of patients with patient global assessment (PtGA) ≦1 from patients with 1<PtGA≦2

among rheumatoid arthritis patients with tender joint count (TJC), swollen joint count (SJC) and C-reactive protein (CRP) ≦1 [Methods] The subjects in this study were patients who participated in the IORRA survey during April 2011, and fulfilled 3 of 4 components of Boolean trials (TJC, SJC, CRP ≦1). Univaliate and multivariate logistic regression analyses were performed to evaluate factors associated with PtGA in patients with PtGA ≦1 (group A) compared to those with 1<PtGA ≦2 (group B). Swollen and tender joint counts were recorded by examination of 45 joints. [Results] Between group A (n=1,272) and group B (n=538), no significant difference was observed when gender, mean age and duration were compared. In multivariate analysis, high PtGA scores (1<PtGA≦2) were associated with pain scores (OR: 1.26, 95%CI: 1.23-1.29, p<0.01), physical dysfunction (OR: 1.89, 95%CI: 1.40-2.55, p<0.01) and swollen joint counts not counted by 28-joint scoring system (OR: 1.44, 95%CI: 1.03-2.02, p<0.05). [Conclusions] In clinical practice, a rheumatologist must pay attention to the other joint involvements unidentified by a 28-joint scoring system to the patients near remission.

W31-6

Validation of remission criteria in rheumatoid arthritis: KURAMA cohort study

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Conflict of interest: Yes

[Objectives] The Boolean based ACR/EULAR remission criterion is stricter than indexes based criteria. This study is aimed to validate these criteria in clinical practice. [Methods] We chose the 371 of RA patients in our clinical cohort and assessed swollen joint count, tender joint count, CRP, ESR, patient global health assessment, physician global health assessment, stage, class, duration of RA, and mHAQ. The frequency of remission was evaluated by SDAI, CDAI, DAS28 and the Boolean based criteria. [Results] SDAS, CDAI, DAS28 and the Boolean based remission are achieved in 29.1 %, 28.8%, 50.4%, and 21.3% of patients, respectively. Functional remission was more often achieved in Boolean based remission than in indexes based remission. Two hundreds and four patients had SJC ≤ 1, TJC ≤ 1 and CRP ≤ 1, and 79 patients of them had PtGA ≤ 1. On the other hand, 125 patients of them had PtGA > 1 and tended to have higher class and longer RA duration in comparison with the Boolean based remission group (rs=0.493, p<0.01). [Conclusion] Our results showed that the Boolean based remission criterion is most strict. PtGA of long RA duration appeared hard to be decreased.

W32-1

Treatment of collagen-induced arthritis with $CD4^+CD25^-LAG3^+$ regulatory T cells and tofacitinib-induced $CD4^+Egr2^+PD\text{-}L1^+$ cells

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Conflict of interest: None

[Objectives] We have recently identified a novel $CD4^+CD25^-Foxp3^-$ regulatory T cells (Treg) population that expresses both lymphocyte activation gene-3 (LAG3) and early growth response gene-2 (Egr2). IL-10 producing $CD4^+CD25^-LAG3^+$ Treg ($LAG3^+$Treg) suppress the development of murine colitis in an IL-10 dependent manner. We have also found that Tofacitinib, a JAK inhibitor, induces $LAG3^+$Treg-like $CD4^+Egr2^+PDL1^+$ T cells (Tofa-T cells) *in vitro.* The purpose of this study was to examine the effects of $LAG3^+$Treg and Tofa-T cells on collagen induced arthritis (CIA) in DBA1J mice. [Methods] The percentage of $LAG3^+$Treg was examined in the spleen of young to aged DBA1J mice. $LAG3^+$Treg or Tofa-T cells were transferred to type II collagen-immunized DBA1J mice just before the onset of arthritis. [Results] Young DBA1J mice had fewer $LAG3^+$Treg in the spleen compared with C57/BL6(B6) mice, although the frequency of $CD4^+CD25^+$Treg showed no difference between DBA1J and B6 mice. $LAG3^+$Treg and Tofa-T cells significantly suppressed the progression of CIA in DBA1J mice. [Conclusion] Decrease in $LAG3^+$Treg may be associated with the susceptibility to CIA in young DBA1J mice.

W32-2

The functional analysis of human $CD4^+CD25^-LAG3^+$ T cells and their association with autoimmune diseases

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Conflict of interest: None

[Objectives] We identified human counterpart of murine $CD4^+CD25^-LAG3^+$ T cells that were reported as new regulatory T cells. We analyzed their function and association with autoimmune regulatory T cells. [Methods] We identified $CD4^+CD25^-LAG3^+$ T cells in human Tonsil and PBMC using FACS analysis, and analyzed their gene expression, cytokine production and effect on either T cells or B cells *in vitro*. For *in vivo* analysis, we made humanized mice with human cells transfer into severe immunodeficient mice (NOG mice), and observed the effect on GVHD. We also analyzed $CD4^+CD25^-LAG3^+$ T cells in autoimmune disease patients, and compared with healthy control. [Results] There were $CD4^+CD25^-LAG3^+$ T cells in human Tonsil and PBMC, and they produced high amount of IL-10. They suppressed B cell activation *in vitro*, and suppressed GVHD of NOG mice *in vivo*. There were fewer $CD4^+CD25^-LAG3^+$ T cells in autoimmune disease patients compared with healthy control. [Conclusion] There were human counterpart of murine $CD4^+CD25^-LAG3^+$ T cells, and their character was similar to murine $CD4^+CD25^-LAG3^+$ regulatory T cells. Because of the reduction of this cell group in autoimmune disease patients, human $CD4^+CD25^-LAG3^+$ T cells might have association with disease induction or maintenance.

W32-3

Innovation of novel upstream therapy for rheumatoid arthritis, targeting T cell costimulation molecule CD26

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Conflict of interest: None

T cell costimulatory molecule, CD26 is preferentially ex-

pressed on human $CD4^+CD45RO^+$ memory T cells, and is upregulated following $CD4^+$ T cell activation. These T cells respond maximally to recall antigens, and exert the transendothelial migratory capacity. In fact, patients with autoimmune diseases such as rheumatoid arthritis (RA) have been found to have increased numbers of $CD26^+$ T cells in inflamed synovium. Moreover, $CD26^{high}CD8^+$ T cells in humans belong to effector memory T cells, and exert the cytotoxic effect with CD26-mediated costimulation. Therefore, it is conceivable that $CD26^{high}$ T cells plays an important role in the inflammatory process. In the present study, after peritoneal injection of human peripheral blood mononuclear cells into NOD/SCID/$g_c^{-/-}$ mice, mice showed onset of inflammatory symptoms such as dermatitis and arthritis with $CD26^{high}$ human lymphocytes emerging. Administration of anti-human CD26 monoclonal antibody resulted in decreasing the severity of these symptoms and prolonged survival in hu-PBL-NOG mice without loss of engraftment of human T cells, while increasing doses of CTLA4-Ig treatment diminished engraftment of human lymphocytes. Our data point to CD26 as a novel target for therapeutic intervention in human immune mediated diseases such as RA.

W32-4

Comprehensive microRNA analysis identifies miR-24, miR-26a, and miR-125a-5p as plasma biomarkers for rheumatoid arthritis

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Conflict of interest: None

[Objectives] We investigated whether plasma miRNAs could be specific biomarkers for rheumatoid arthritis (RA) by a comprehensive array approach. [Methods] We performed a systematic, array-based miRNA analysis on plasma samples from three RA patients and three healthy controls (HCs). Plasma miRNAs with significant change in expression were confirmed with plasma from eight RA patients and eight HCs using real-time PCR. Consistently detectable miRNAs with significantly different expression were chosen for further validation with 102 RA patients and 104 HCs. Specificity was confirmed with 24 patients with osteoarthritis (OA), and 11 patients with systemic lupus erythematosus (SLE). [Results] The array analysis and the subsequent confirmation in larger patient cohort identified significant alterations in plasma levels of miR-24, miR-26a and miR-125a-5p. The area under curve (AUC) of each miRNA was 0.80, 0.80 and 0.83 respectively. The levels of miR-24, miR-26a, and miR-125a-5p in OA and SLE patients were as low as in HC. Combination of miR-24, miR-30a-5p and miR-125a-5p, termed *E*stimated *P*robability of *RA* by plasma *Mi*RNA (ePRAM), increased diagnostic accuracy (AUC: 0.89). [Conclusion] Plasma miR-24, miR-26a, miR-125a-5p and ePRAM are diagnostic biomarkers for RA.

W32-5

Downregulation of miR-193b in systemic sclerosis regulates the proliferative vasculopathy by urokinase-type plasminogen activator (uPA) expression

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Conflict of interest: None

Objectives To investigate the association of miRNA with SSc. Methods To investigate differentially expressed miRNAs in SSc and normal healthy (NH) skin fibroblasts, we performed miRNA array analysis. MiR-193b in SSc skin fibroblasts and SSc skin sections were analyzed by Real-time PCR.Transfection of miR-193b precursor/inhibitor were used to identify target of miR-193b. Expression and localisation of uPA were examined by Real-time PCR, WB and IHC. Human pulmonary artery smooth muscle cells (HPASMC) were treated with uPA and proliferative effect was determined by WST-1 assay and annexin V staining. Results 31 miRNAs showed differentially expression. MiR-193b was significantly down regulated in SSc fibroblasts. MiR-193b was also reduced in SSc skin sections. Induction of miR-193b in SSc and NH fibroblasts suppressed the expression of uPA. Conversely, the knockdown of miR-193b increased the level of uPA. The basal expression of uPA was up regulated in SSc. uPA expressed almost all in vessel in SSc skin section. Interestingly, uPA induced cell proliferation and inhibited apoptosis on HPASMC. Conclusion In SSc, down regulation of miR-193b induces the expression of uPA, which leads to proliferation of vascular smooth muscle cells and thereby contributes to the proliferative vasculopathy.

W32-6

A hyaluronan synthesis inhibitor suppresses inflammatory response and joint destruction in murine collagen-induced arthritis

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Conflict of interest: None

[Objectives] The aims of this study were to clarify the roles of hyaluronan (HA) in joint inflammation and the process of joint destruction using 4-methylumbelliferone (MU), an inhibitor of HA synthesis, in a collagen-induced arthritis (CIA) mouse model, and in a monolayer culture of fibroblast-like synoviocytes (FLS) derived from patients with rheumatoid arthritis. [Methods] Mice were immunized with type II collagen. Effects of 4-MU were evaluated with the physiological arthritis score, paw swelling, histological arthritis score, and expression of MMP-3 and MMP-13 in chondrocytes and synovial tissues. In vitro, the effects of 4-MU on mRNA and protein expression of MMP-1 and MMP-3 were determined. [Results] Treatment with 4-MU in CIA mice dramatically decreased the severity of arthritis, based on the arthritis score, paw thickness and histopathological findings. Expression of MMP-3 and -13 in chondrocytes and synovial cells was significantly inhibited by 4-MU in vivo, as were tumor necrosis factor-α-stimulated FLSs in a dose-dependent manner. [Conclusion] Reduced disease activity induced by 4-MU in CIA mice revealed HA to be a crucial regulator in the course of arthritis. 4-MU is a potential therapeutic agent in arthritis, possibly mediated by suppression of HA synthesis.

W33-1

JAK inhibitor, tofacitinib suppresses lipopolysaccharide induced activation and induces dendritic cells with a tolerogenic phenotype

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Conflict of interest: None

Objects: Tofacitinib (tofa), a Janus Kinase (JAK) inhibitor has shown clinical benefit in rheumatoid arthritis and is considered to act on lymphocytes. We herein investigated the effect of tofa on dendritic cells (DCs). Methods: Maturation of human monocyte derived DCs and T-cell stimulatory capacity were assessed. Results: Cell toxicity was not observed with tofa. Tofa reduced LPS induced CD80 and CD86 expression but not HLA-DR. Additionally, production of TNF-α, IL-6 and IL-1β were suppressed. Notably, tofacitinib increased indoleamine 2, 3-dioxygenase (IDO) expression an enzyme involved in tolerance. Co-culture of tofacitinib-treated DCs resulted in reduction of T cell proliferation and IFN-γ production. Among the transcription factors involved in regulation of co-stimulatory molecule expression, IRF7 known as a factor activated by type I IFN was suppressed. Pretreatment with cyclohexamide or blockade of type1 IFN-receptor resulted in suppression of CD80 and CD86 expression. Conclusion: Tofa inhibited the activation of IRF7 induced by type I IFN resulting in attenuated CD80 and CD86 expression and cytokine production with enhanced IDO expression and reduced T-cell stimulatory capacity. Our results suggest that tofa induce tolerogenic DCs and JAK play an important role in DCs.

W33-2

Tofacitinib reduces IL-17 production from CD4+ T cells resulting in inhibition of bone destruction in patients with rheumatoid arthritis

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Conflict of interest: None

Objective: Tofacitinib (tofa) targeting JAK has gathered attention in treatment of rheumatoid arthritis (RA). We collected $CD4^+$ T cells from RA patients treated with tofa, and investigated IFN-γ and IL-17 production and its relevance to clinical efficacy. Methods: Patients who participated tofa clinical trial were eligible. $CD4^+$ T cells were collected at 0, 1 and 2 year and cultured for 4 days. IFN-γ and IL-17 concentration in supernatants were measured. Joint damage was assessed by modified total Sharp score (mTSS). Results: 1) Background: 32 patients were assigned, mean age 53.9 years, disease duration 80.5 months, MTX use 71.3%, PSL use 25.0%, SDAI 37.9, HAQ 1.4, mTSS 64.6, ⊿mTSS 15.7, CRP 2.3, ESR 51.0, MMP-3 293.0, RF 184.3. 2) SDAI, HAQ, ⊿mTSS, CRP, ESR, MMP-3, and RF at 1 year were significantly lower than that at baseline. These tendencies continued at 2 year. 3) Production of IL-17 was reduced significantly at 1 year and 2 year (58.7→27.1→22.9 pg/ml), although IFN-γ production did not change (20.7→29.5→150.4 pg/ml). 4) There was correlation between the concentration of IL-17 at 1 year and ⊿mTSS at 1 and 2 year. Conclusion: Tofa acted on T cells and suppressed IL-17 production in correlation with bone destruction, suggesting one of the major mode of action.

W33-3

Efficacy and positioning and of Igulatimode in rheumatoid arthritis patients at the author's institution

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Conflict of interest: None

【Objective】We report the results of the clinical phase 3 study conducted at this institution, and the actual clinical experience of IGU after its launch are reported.【Methods】The subjects were RA patients responding poorly to MTX treatment that were enrolled in the above clinical study and patients in this institution that had received IGU treatment after its launch.【Results】The 17 patients treated with IGU at this institution had a mean age of 67 years, and mean duration of illness was 6 years. All most all the patients received MTX concomitantly. In actual clinical practice, IGU has been administered to patients responding poorly to MTX and those in which it is difficult to increase the MTX dose, and to date, effective treatment has been achieved. There has been no case of treatment discontinuation due to adverse event or non-response to the treatment.【Conclusion】When used concomitantly with MTX, IGU was found to be a highly effective drug. The speed at which that effect manifested was not inferior compared to that of other DMARDs and its tolerance was also high. In future RA treatment, IGU is suggested as an effective treatment drug for patients that respond poorly to MTX and those in whom, for some reason, raising the dose of MTX is difficult.

W33-4

New therapeutic strategy of rheumatoid arthritis ; combination therapy of cell cycle regulation and cytokine inhibition

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Conflict of interest: None

[Objectives] The pathogenesis of rheumatoid arthritis (RA) is characterized by immune cell infiltration and synovial hyperplasia. Biologic agents down-regulate immune reactions and show clinically high efficacy, however, they may cause serious infections. We reported cyclin-dependent kinase 4/6 inhibitor (CDKI) ameliorated animal models of RA by suppressing synovial cell proliferation, however, excessive CDKI caused transient myelosuppression. The aim of this study is to clarify the synergic efficacy of combination therapy with less adverse effects. [Methods] Type II collagen (CII)-induced arthritis (CIA) of mice were treated with CDKI and/or anti Interleukin-6 receptor antibody (IL-6R-Ab), and were assessed by arthritis score and peripheral blood counts. The titer of anti-CII antibody and CII-specific cell proliferation were assessed after those treatments. [Results] Combination therapy with low-dose CDKI and IL-6R-Ab showed higher efficacy than each monotherapy. By contrast, high-dose CDKI monotherapy also showed high efficacy with myelosuppression. No CII-specific immune responses were observed under these treatments. [Conclusion] This is the first report demonstrating the advantage of dual targeting therapies, which showed synergistic efficacy with less adverse effects.

W33-5

A novel peptide from TCTA protein inhibits proliferation of fibloblast-like synoviocyte (FLS) from RA patients

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Conflict of interest: None

Objective: We have demonstrated that a novel peptide from T cell leukemia translocation-associated gene (TCTA) protein inhibits human osteoclastogenesis (JCR2008, Kotake et al. Bone, 2009)

and that monkey osteoclastogenesis is inhibited by the peptide (JCR2009). The peptide inhibits the total and mean area of human osteoclasts (JCR2010). Methods: 5 RA FLS were cultured with or without the peptide. Results: The peptide inhibited the proliferation of RA FLS. Conclusions: The peptide may be used for the therapy of both osteoporosis and RA.

W33-6

Regulation of IL-6-type cytokine-mediated signaling by JAK inhibitors in rheumatoid synoviocytes

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Conflict of interest: None

[Objectives] JAKs inhibitors have been developed as anti-inflammatory and immunosuppressive agents and currently undergoing clinical trials. However the mechanisms that mediate the beneficial effects in RA are not clear. [Methods] In vitro studies were performed using synovial fibroblasts isolated from patients with RA. Levels of activation of JAKs and STATs proteins were detected by western blot. [Results] Rheumatoid synovial fibroblasts highly expressed phospho-JAK3 in histologicallay. IL-6 type cytokine, oncostain-M (OSM) induced JAK1,2,3/ STAT1,3,5 phosphoylation, and IL-6 mRNA expression in rheumatoid synoviocytes, OSM-induced JAKs/STATs phosphorylatioon and IL-6 induction were blocked by CP-690,550. In contrast, OSM-induced JAK2/ STAT3 phosphoylation and IL-6 mRNA expression was not blocked by a JAK3-specific inhibitor related to CP-690,550 in structure, PF-956980. Whereas PF-956980 blocked OSM-induced JAK3/STAT1 phosphoylation and matrix metalloproteinase-3 (MMP-3) mRNA expression in rheumatoid synoviocytes [Conclusion] Our findings suggest that each JAKs differentially regulate the cytokines / MMPs induction and JAK inhibitors attenuate these JAKs/STATs signaling and proinflammatory mediator induction contributing to the therapeutic efficacy against rheumatoid synovitis.

W34-1

Clinical characteristics and treatment of 109 patients with Psoriatic Arthritis (PsA) in St. Luke's International Hospital

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Conflict of interest: None

[Objectives] PsA describes various subgroups in terms of types of psoriasis and arthritis with or without enthesitis which mimics rheumatoid arthritis. This study aims to demonstrate the epidemiology, clinical manifestations and treatment of PsA in our hospital. [Methods] PsA patients between January 1, 2003 and September 30, 2012 were reviewed retrospectively. We analysed age, sex, psoriasis patterns, distribution of arthritis, soft tissue inflammation (such as enthesitis, tenosynovitis and dactylitis), rheumatoid factor (RF) and anti-CCP antibody positivity, and complications. Positivity of CASPAR(ClASsification criteria for Psoriatic Arthritis) criteria and ASAS(Assesment in Ankylosing Spondylitis) criteria was calculated. [Results] A total of 109 (52 male, 57 female) patients were diagnosed with PsA: mean age 47.3-year old. Dermatological prevalence was 84.4% for plaque psoriasis and 13.8% for pustular psoriasis. At diagnosis, 38.5%, 41.3%, and 19.3% of patients had asymmetric oligoarthritis, systemic polyarthritis, and DIP arthritis, respectively. 44.0% of them had axial joint involvement. Positivity of CASPAR criteria was 91.7% and100% in ASAS criteria (peripheral joint involved type). [Conclusion] This information would help to further understand RA mimicking disease.

W34-2

Gender differences of axial involvement in patients with psoriatic arthritis

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Conflict of interest: None

Psoriatic arthritis (PsA) is an inflammatory arthritis associated with psoriasis. It has been reported in 15-40% of patients with psoriasis. Some of the patients with PsA suffer from spondylitis. PsA has been reported to affect men and women equally. However, gender differences in PsA have seldom been studied in Japanese patients with PsA. [Objectives] The aim of this study was to analyze gender differences of axial involvement in PsA by using skeletal radiographs. [Methods] Radiographs of cervical, thoracic, lumbar spine and sacroiliac joints were obtained. We compared the radiographic features of psoriatic spondylitis between men and women. [Results] The patients in this study consisted of 49 men and 27 women. The mean age/ disease duration of men and women at radiographic evaluation were 50.7/ 55.6 years, 7.3/ 9.3 years, respectively. The prevalence of axial involvement of men was higher than women (55.1%/ 38.4%). While syndesmophyte was the most frequently observed finding in both man and women, marginal type of syndesmophyte was observed only by men. Sacroiliitis was observed more frequently in men than in women. The grade of sacroliitis was higher in men than women. [Conclusion] These results suggested that in PsA men were more likely to develop axial involvement rather than women.

W34-3

Clinical outcome of psoriatic arthritis(PsA) treated with methotrexate(MTX) and Tumor Necrosis Factor-α(TNF-α) inhibitors with MTX

Koei Oh[1,2], Osamu Namiki[3], Yoichi Toyoshima[3], Tsuyoshi Odai[2], Yusuke Oshita[1], Hitoshi Mikumo[1], Masanori Nakamura[1], Katsunori Inagaki[3]
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Conflict of interest: None

[Objectives] To investigate the efficiency of MTX and TNF-α inhibitors with MTX for the treatment of PsA. All of the patients were treated with ciclosporin or UVB phototherapy before, but those therapeutic effects were insufficient. [Methods] The PsA patients in this study diagnosed by the CASPAR Criteria. There were 7 patients (5 men and 2 women) with a mean age of 40.8 years. Effectiveness was assessed using the Psoriasis Area and Severity Index (PASI), PASI-75 and ACR-70 response criteria, Patient Global Assessment (PGA), DAS28(ESR),CRP,mHAQ at the time of before administration,4 weeks,12 weeks, and 24weeks after treatment. [Results] From before administration to 4 weeks after treatment, the PASI decreased from 15.1±7.98(mean±SD) to 9.13±5.1, DAS28(ESR) decreased from 5.91±1.1 to 3.8±2.4, PGA decreased

from 84±4.62 to 24.2±25.1, CRP decreased from 4.84±2.16 to 1.53±1.35, mHAQ decreased from 2.5±1.3 to 2.4±1.65. The early therapeutic effect was remarkable. At 24 weeks after treatment, PASI-75 was 71.4%, ACR-70 was 85.7%. [Conclusion] Treatment with MTX for PsA, which is golden standard therapy in Europe and any other countries, is not covered by insurance in Japan. In this study, treatment with MTX and TNF-α inhibitors with MTX decreased in disease activity and improved function of PsA.

W34-4

The comorbidities of Crowned dens syndrome (CDS) in polymyalgia rheumatica (PMR) patients in our department

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Conflict of interest: None

[Objectives] PMR is rheumatic disease presented as stiffening of the neck, fever, and proximal muscle ache. On the other hand, CDS is a radioclinical entitiy defined by the radiological calcification of the cruciform ligament around the odontoid, and has symptom of cervical pains with fever, and marked inflammatory response. There are many cases that we are difficult to distinguish with PMR and CDS, because of clinical common points. [Methods] Cervical CT scan examined 14 patients diagnosed as PMR by Bird's criteria since 2009 to 2012 in our department. [Results and Conclusion] In 14 patients diagnosed as PMR by Bird's criteria since 2009 to 2012 in our department, 6 patients are CDS positive by cervical CT scan. There is clinical tendency that CDS positive PMR patients are tapered off steroids, but there are no significantly differences between CDS positive PMR and CDS negative PMR at average of age onset (75.5 yr VS 76.3 yr) and gender.

W34-5

RS3PE syndrome was improved by colonoscopic polypectomy without steroid administration ;A case report

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Conflict of interest: None

An 86-year-old-woman has suffered from cough. She began to complain of pitting edema of her extremities and fatiguability. She was admitted to the hospital because of fever and joint pain and difficulty sitting up. Chest radiography showed pleural effusion. Antibiotics and diuretic drug were administrated. Her temperature returned to normal, but she was still suffering from the other symptoms. She was transferred to our hospital. Laboratory data showed CRP 5.73 mg/dl. ANA, RF and CCP antibody were negative. There was no infection and malignancy in the pleural effusion. Ultrasonography showed subcutaneous edema and tenosynovitis. The symptoms and the laboratory data established diagnosis of RS3PE syndrome. Colonoscopy was performed and revealed a polyp which was removed by polypectomy. It was diagnosed carcinoma in adenoma pathologically. From the next day of the polypectomy, pitting edema and arthritis were immediately improved and pleural effusion was gradually decreased. This case is rare that RS3PE was improved by polypectomy without steroid administration. There are some reports that the pathogenic mechanism of RS3PE is associated withVEGF. In this case, VEGF was positive on the polyp by immunostaining. VEGF produced from the polyp might develop RS3PE and pleural effusion.

W34-6

A case of SAPHO syndrome complicated with lower limb paresis due to large arachnoid cyst and improved by cyst peritoneal shunt

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Conflict of interest: None

The patient was a 70 year-old woman who had low back pain from age of 33, and diagnosed lumber disc herniation. At the age of 56, the low back pain got worse and leg pain appeared, she diagnosed ankylosing spondylitis and treated with NSAIDs. On Decenber 2011, severe pain of the lower limbs, numbness were appeared, then she was admitted to our hospital due to paresis of the lower limbs and frequent urination appeared from april 2012. X-ray showed bamboo spine and sternocostoclavicular hyperostosis. We diagnosed her SAPHO syndrome because of her history of palmoplantar pustulosis. In MRI, cauda equina syndrome due to large arachnoid cyst was observed. We considered laminectomy or administration of infliximab, but laminectomy was not performed because of the risk of cerebrospinal fluid leakage, and we gave up the administration of infliximab because non-tuberculous maycobacterial infection was suspected in chest CT. Finally cyst peritoneal shunt was performed. Frequent urination and severe pain were improved after surgery, paresis became better and lead possible to walk. We report this case and the characteristics of arachnoid cyst together with the previous reports of arachnoid cyst with spondyloarthritis.

W35-1

Clinical analysis of pregnancy complicated with connective tissue disease in our institution

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Conflict of interest: None

【Background】 Pregnancy complicated with connective tissue disease (CTD) is high risk, and causes the exacerbation of underlying disease. 【Objective】 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. 【Method】 We investigated 59 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. 【Result】 9 cases among all were exacerbated underlying diseases, and 6 needed corticosteroid pulse therapies. Positive anti SS-A antibody was found in 23 cases, but there was no complication related with its antibody. Positive antiphospholipid antibody revealed 17 cases, and one had a preterm birth associated with its antibody. There was no relationship between preterm birth (9 cases), LFD (5cases) or perinatal complication (23 cases) and dose of corticosteroid. 【Conclusion】 In pregnancy complicated with CTD, preterm birth, LFD, perinatal complication is associated with the disease activity strongly. Therefore, we need to treat underlying disease strictly with corticosteroid for safer pregnancy and delivery.

W35-2

Two cases of the success of eltrombopag tratment of refractory thrombocytopenia with autoimmune diseases

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Conflict of interest: None

Eltrombopag (EP) is a thrombopoietin receptor agonist and approved for refractory idiopathic thrombocytopenic purpura (ITP). Effectiveness of EP in thrombocytopenia with autoimmune disease has been reported a few. We report two cases of refractory thrombocytopenia accompanied with autoimmune disease where EP was given to treat. Case 1: A 67-year-old female patient with Sjogren syndrome associated with severe thrombocytopenia. She received high-dose steroid therapy and recovered. But due to recurrence of thrombocytopenia with tapering of steroid dose, she needed to receive 10mg/day prednisone for maintenance dose. Then EP treatment made her platelet count recover and her steroid dose tapered down to a complete stop. Case 2: A 29-year-old female patient with lupus nephritis. She was associated with refractory thrombocytopenia and received high-dose steroid therapy many times. EP treatment made her platelet counts recover to normal levels. Then her dose of prednisone was tapered from 12.5mg/day to 5mg/day. Generally the second line therapy was splenectomy for refractory ITP. However patients with autoimmune disease will require lifelong immunosuppression therapy and also splenectomy increases susceptibility to infection. EP has the potential to become more safety therapy.

W35-3

Clinical investigation of bone sarcoidosis in hand

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Conflict of interest: None

We investigated clinical features and outcomes of seven cases of bone sarcoidosis in hand from 2006 to 2011. All of cases had the progressed other sarcoidois lesions before bone affection. Bone lesions appeared in middle and proximal phalanx and metacarpal bone. X-ray pictures indicated radiolucent bone lesions in all of cases. MR imaging and bone scintigram were very useful for the diagnosis. Pathological studies were performed in two cases, epithelioid cell granuloma without necrotic lesions appeared. As treatment, six cases were treated with glucocorticoid, another case was treated with low dose glucocorticoid and minocycline. All cases were successfully treated. For prevention of the pathological fracture and following deformity, glucocorticoid treatment should be required for bone sarcoidosis cases.

W35-4

The autoimmune manifestations associated with myelodysplastic syndrome: a report on three cases

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Conflict of interest: None

[Case1] A 78-year-old male was diagnosed as entro-Bechet's disease and myelodysplastic syndrome (MDS) coincidentally in 2010. Although he was treated with PSL, SASP, AZP, IFX, and ETN, his abdominal symptoms were not controlled, and the small intestinal perforation was developed. After the surgical treatment, 5-azacytidine was started, and the laboratory data improved. [Case2] The second case was a 58-year–old man who was diagnosed as polyarteritis nodosa and organizing pneumonia (OP) in 2008. Since OP was refractory to PSL, CPA and CsA were added. In 2012, thoracic CT revealed the recurrence of OP. He was admitted to our hospital and diagnosed as MDS. He died from the concomitant pneumonia. [Case3] A 58-year–old man was presented with fever and chest X-ray abnormality. VATS revealed OP, and MDS was also diagnosed by the BM examination. His symptoms were successfully treated with 35mg/day of PSL. [Discussion] Approximately 10-20% of MDS are associated with an autoimmune disease. Whereas this association was reported to be attributable to the overexpression of IRF-1 or the dysfunction of T cells, the precise mechanism still remains controversial. We would like to review the cases concomitant of MDS and autoimmune diseases in our department and clarify its clinical characteristics.

W35-5

The assessment of synovitis activity with ultrasound in a patient with multicentric reticulohistiocytosis – a case report

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Conflict of interest: None

A 69 year-old woman was referred to our hospital for multiple skin nodules in the dorsal aspects of bilateral hands which gradually increased in number over eight months. The biopsy specimen of the skin revealed proliferation of histiocytes. The patient had marked joint swelling in the fingers, wrists, and knees. Blood tests revealed normal levels of acute inflammatory responses, negative rheumatoid factor, negative anti-CCP antibody, and an elevated level of MMP-3. Plain radiograph of hands showed joint space narrowing in the PIP joints and erosions in the MCP and CMC joints. Ultrasound demonstrated synovial hypertrophy accompanied by increased Doppler signals. [^{18}F] FDG-PET/CT showed increased FDG uptake in multiple joints with no abnormal uptake suggesting malignancy. The patient was diagnosed with multicentric reticulohistiocytosis based on the histopathological finding of skin biopsy and the presence of polyarthritis. As the arthritis was refractory to the treatment with 16 mg/week of methotrexate with the persistent activity of synovitis on ultrasound and the progression of joint destruction on radiograph, the patient received infliximab. This is the first report in which ultrasound is performed for the assessment of arthritis in multicentric reticulohistiocytosis.

W35-6

A case of Multicentric Castleman's disease presented with lesions closely mimicking IgG4 related disease

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Conflict of interest: None

Castleman's disease presenting with lesions closely mimicking IgG4 related disease is rare. We herein report a case for discussion. The patient was a 61-year-old housewife presented with an 8-month history of weight loss (52 kg to 45 kg) and a 3-month his-

tory of fever and night sweat. Her blood test revealed anemia, low serum albumin, high level of C-reactive protein (CRP), hypergammaglobulinemia with M-proteinemia, and high level of serum IL-6. Computed tomographic scanning showed remarkable enlarged lymph nodes in left supraclavicular area and paraaortic to paracommon iliac artery region, thickening soft tissues around aorta, left hydronephrosis, and abnormal soft tissue in anterior region of sacral bone resembling retroperitoneal fibrosis. Renal biopsy revealed well localized interstitial nephritis mimicking IgG4 related kidney disease. Bone marrow biopsy shows no evidence of neoplasms. Biopsy of left supraclavicular lymph node showed hyperplasia of germinal center with IL-6 positive matured plasma cells among follicles. She was diagnosed Multicentric Castleman's disease and was started on 30 mg per day of oral prednisolone. However, CRP levels had been still high after one month later. Administration of tocilizumab 360 mg per 4 weeks was initiated.

W36-1

The rise of ACPA advances bone destruction

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Conflict of interest: None

Background ACPA being not only deeply related to the onset of rheumatoid arthritis, but activating of an osteoclast directly and promoting bone resorption is known. It was examined clinical relationship between ACPA rate of change and bone destruction. Method The 120 RA patients, the dulation is less than 3 years, 4.5 or more ACPA, measured ACPA in my hospital were selected. ACPA, RF, CRP, MMP-3, DAS28-CRP, CDAI, and the joint Xp, and found correlation with each parameter and an ACPA rate of change. (this abstract is 81 patients interim analysis) Result ACPA decreased intentionally after treatment ($p<0.0001$). The ACPA rate of change correrated with ⊿DAS28-CRP and ⊿CDAI weakly ($p= 0.0225$, $p= 0.0183$ respectively), and correrated with RF rate of change strongly ($p<0.0001$) A cese with bone destruction, ACPA and RF rate of change go up intentionally ($p= 0.0072$, $p= 0.0090$ respectively).correlation was seen in neither ⊿DAS28-CRP nor ⊿CDAI. The tendency for an ACPA rate of change to be connected with aggravation of a bone change independently by logistic regression analysis was seen ($p= 0.0832$). Conclusion Increase ACPA is not only used by the diagnostic purpose of RA, but suggested that bone destruction advances. It is thought that intermittent measurement of ACPA is useful.

W36-2

Factors undetectable by 28-joints count scoring system lead to worse functional outcome in patients with rheumatoid arthritis

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Conflict of interest: None

[Objectives] To evaluate factors affected the progression of functional disability in RA patients without tender and swollen joints evaluated 28-joints count scoring system. [Methods] RA patients who participated consecutive 5 IORRA cohort surveys from October 2009 to October 2011 (2 years) were analyzed. Tender (TJC28) and swollen joints (SJC28) were assessed by 28-joint counts scoring system. The proportion of patients with progressed physical dysfunction evaluated by J-HAQ score was analyzed for each group stratified according to the number of observations in which the patient achieved TJC28=0 and SJC28=0. The factors associated to physical dysfunction were analyzed. [Results] A total of 1,399 patients were recruited (females 82.0%, age 60.2 years, disease duration 12.7 years, DAS28 2.3, and J-HAQ 0.4). The proportion of patients with progressed physical dysfunction was decreased from 38.0% to 16.7% according the number 1 to 5 in which fulfilled TJC28=0 and SJC28=0. The mean CRP was 0.39 mg/dl in the patients who progressed dysfunction among who constantly fulfilled TJC=0 and SJC=0. The factors related to progression of dysfunction were age, NSAID and CRP. [Conclusion] Factors undetectable by 28-joints count scoring system lead to worse functional outcome in IORRA cohort study.

W36-3

Predictors at baseline of good prognosis after three-year treatment obtained through ARIGATO Registry

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Conflict of interest: None

[Objectives] To search for predictors of good prognosis of RA. [Methods] We established ARIGATO Registry of RA patients for the study of functional and life prognosis. Through this registry, predictors for good response to treatment defined by SDAI was searched for using age, BW, BMI, gender, parity, smoking history, family history for RA, disease-duration, tender joint counts, swollen joint counts, CRP, provider global VAS, and patient global VAS as variables. Clinical remission (CR) and low disease activity (LDA) were dependent variables and multivariate logistic regression analysis was performed. [Results] In 217 patients, 15 (6.9%), 93 (42.9%), 89 (41%), and 20 (9.2%) were in CR, LDA, moderate disease activity (MDA), and high disease activity (HDA), respectively, at baseline. These figures were 76 (35%), 106 (48.8%), 30 (13.8%), and 5 (2.3%), respectively, in 3 years. Comparing variables at baseline of the patients became LDA after 3 years with those of MDA and HDA, tender joint counts and disease-duration were selected as significant predictors. As for CR, patient global VAS and disease-duration were significant predictors. [Conclusion] Shorter disease-duration, less swollen joint counts and better patient global VAS at baseline were predictors of good treatment response.

W36-4

Clinical features and short-term prognosis of patients who developed rheumatoid arthritis with large joints arthritis

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Conflict of interest: None

[Objectives] To investigate the clinical features and the short-term prognosis of patients who developed rheumatoid arthritis (RA) with large joints arthritis. [Methods] Sixty-six RA patients who diagnosed by 2010 ACR/EULAR classification criteria within 1 year of onset enrolled into this study. Based on the criteria, we defined shoulder, elbow, hip, knee, and ankle as "large joint". The participants were divided into 3 groups according to the number and location of involved joints; Patients with two or more large

joints (group A), single large joint (group B), and small joints only (group C). Laboratory data (CRP, ESR, rheumatoid factor, ACPA, serum MMP-3), DAS28-CRP, and mHAQ were compared at the time of diagnosis. In addition, 47 patients who followed for 1 year were compared above-described data and Boolean remission rate at 1 year after diagnosis. [Results] At the time of diagnosis, CRP, ESR, MMP-3, DAS28, and mHAQ were highest in group A, and statistical significant compared to group C. At 1 year after diagnosis, DAS28 and mHAQ in group A were significantly high compared to in group C. Remission rates was 18.2%, 50.0%, and 47.4% in group A, B, and C, respectively. [Conclusion] The short-term prognosis was poor in patients who developed RA with large joints arthritis.

W36-5

Evaluation of Disease Activity in Very Elderly Patients with Rheumatoid Arthritis

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Conflict of interest: None

[Objectives] Increase of elderly patients is an important problem in RA clinic in Japan. This study is to investigate the characteristics of patients over 70s, who are older than patients over 60s, defined as "elderly RA". [Methods] 642 patients with RA in out-patient clinic were studied. We compared DAS28, CRP, JHAQ and EQ5D score among groups of patients under 60 years (A), patients in 60s (B) and older than 70 years (C). [Results] In group A, B and C, there were 192, 220 and 230 patients. Average of DAS28 is increased in elder group than in younger one, 2.87, 3.13 and 3.39 in group A, B and C. JHAQ and EQ5D score were significantly deteriorated in group C compared with other two groups. About the components of DAS28, ESR and patients' GVAS were significantly increased in group C, but tender and swollen joints count revealed no difference. [Conclusion] (1) Patients older than 70 years were 35.8% of all patients of out-patient RA clinic. (2) RA patients over 70s showed higher disease activity, worse functional ability and quality of life (QOL) than younger patients, but their impaired joint score didn't show any difference. (3) Functional disability and lower QOL due to aging may increase patients' GVAS can disturb scoring of disease activity in RA patients over 70s.

W36-6

The multi-biomarker disease activity (MBDA) score is the most predictive disease activity index for structural remission in patients with rheumatoid arthritis treated with TNF inhibitors

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Conflict of interest: None

[Objectives] To validate the multi-biomarker disease activity (MBDA) as a predictor for radiographic progression (RP) in RA patients with a TNF inhibitor (TNFi). [Methods] In 147 RA patients treated with TNFi (IFX 49, ETN 49, ADA 49), disease activity and radiography at 0 and 52 weeks were evaluated, with measuring 12 serum biomarkers (VCAM-1, EGF, VEGF-A, IL-6, TNF-RI, YKL-40, MMP-1, MMP-3, leptin, resistin, SAA, CRP) to input into the algorithm to generate the MBDA score (1-100) and modified total Sharp score (mTSS). [Results] Baseline characters (median) were; age 60y, duration 60m, DAS28-ESR 5.74, SDAI 28.1, CDAI 25.4, MBDA 64, mTSS 17 (8.4/y). MBDA was correlated to DAS28-ESR, -CRP, CDAI, SDAI ($p<.0001$ in all). TNFi improved MBDA which changes were correlated with those of DAS28, CDAI and SDAI and 70.9% fulfilled $DmTSS_{0\text{-}52w} \leqq 0.5$ at year 1. By ROC analysis between $\Delta mTSS_{0\text{-}52w} \leqq 0.5$ and disease activity indices, AUROC were .622, .618, .579, .604, .604 at week 0, and .664, .637, .645, .654, .680 at week 52, in DAS28-ESR, -CRP, CDAI, SDAI, MBDA, respectively, indicating MBDA as the highest at both points. [Conclusion] MBDA was confirmed as the most predictive index for structural remission in RA patients with TNFi.

W37-1

Inhibition of osteoclastogenesis by a low molecular weight DMARD, Bucillamine

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Conflict of interest: None

[Objectives] Recent studies revealed that bone-resorbing osteoclasts are essential for bone destruction in RA. It has been demonstrated that the combination of Bucillamine (BUC) and MTX resulted in significantly less progression of bone destruction than MTX alone. The current study examined the effect of BUC and its intramolecular disulfide metabolite SA981 on osteoclastogenesis from murine monocytic cell line RAW 264.7. [Methods] RAW 264.7 cells were cultured with RANKL in the presence of various concentrations of BUC and SA981 with or without MTX (2 nM). After incubation for 5 days, TRAP-positive multinucleated cells were evaluated. [Results] BUC and SA981 inhibited osteoclastogenesis in a dose-response manner. BUC and SA 981 displayed significant inhibition of osteoclastogenesis at pharmacologically attainable concentration as little as 0.3 μM. The suppressive effect of 0.3 μM of BUC or SA 981 was equivalent to that of 2 nM of MTX. Furthermore, 0.3 μM of BUC or SA 981 and 2 nM of MTX synergistically inhibited osteoclast formation. [Conclusion] These results indicate that BUC and SA981 have bone protective effects at pharmacologically attainable concentrations. The data also suggest that BUC and SA981 might inhibit osteoclast formation in a different mechanism from that of MTX.

W37-2

Addition of tacrolimus in patients with rheumatoid arthritis refractory to tocilizumab treatment

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Conflict of interest: None

[Objectives] To evaluate addition of tacrolimus (TAC) in patients with rheumatoid arthritis (RA) refactory to tocilizumab (TCZ) treatment. [Methods] 5cases in 29 cases who began TCZ in our institute were included in this study. 3 female and 2 male. Patients characteristics, efficacy and safety were investigated. [Results] Age was 47-70 yo, RA duration was 2-14y and RF and ACPA were double positive in all 5 cases. MTX was difficult to use in 5 cases dure to pasthistory of MTX pneumonia, liver desfunction, bone marrow disorder, renal desfunction and shadow of

lung, respectively. TCZ+TAC was effective in 3 cases. Time course of CDAI (introduction of TCZ, addition of TCZ, last observation) were (39.8, 28.5, 4.0), (33.1, 9.8, 6.3) and (13.7, 18.9, 9.3), respectively. These 3 cases continue TCZ+TAC over one year. TAC was started at dose of 1mg/d in all cases and dose escalation was performed in 3 cases. 5 adverse events were observed and 3 events among them were infection. 2 cases stopped TCZ+TAC due to ineffectivenes and adverse event (renal desfunction). [Conclusion] Addition of TAC in RA patients refractory to TCZ is one of promisong option. Infection was most frequentry occurred. Addition of TAC should be started at dose of 1mg/d in patients with RA treated with TCZ for safety.

W37-3

How to use intraarticular steroid injection to achieve the Boolean or SDAI remission

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Conflict of interest: None

[Objectives] Now, in the RA treatment, remission criteria such as Boolean index or CDAI<3.3 rather DAS remission had been a realistic target by MTX and biologics. But we commonly encountered RA patients who achieve DAS remission or low disease activity (LDA) but not met the strict remission criteria. The aim of this study was reassessment of intraarticular steroid injection as a tool to clear strict remission criteria. [Methods] 16cases of RA patients achieved DAS remission or LDA with less than 3 persisted swollen joints were recruited. After intraarticular injection of triamcinolone acetonide and lidocaine to Power Doppler (PD) positive swollen joint, durability of effect were evaluated by US, DAS and biochemical markers. [Results] Mean observation period was 8.3 months. DAS, CRP and ESR were significantly decreased. Gray scale grading and PD signal were significantly improved and preserved during observation period. In 2cases, PD signal were relapsed at 4 month after injection, but stayed in Grade1. [Conclusion] Frequent intraarticular steroid injection should be avoided because of its harmful effect on joint. But for the RA patients achieved clinical remission or LDA, this double edged sword might be a useful application to achieve and maintain strict remission.

W37-4

Efficacy of tramadol/acetaminophen combination tablets for rheumatoid arthritis patients with chronic pain

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Conflict of interest: None

[Objectives] It is reported that opioids and pregabalin are effective for chronic musculoskeletal pain which was poorly controlled by NSAID. We investigated the clinical efficacy of tramadol/acetaminophen combination tablets (TRAM/APAP) in rheumatoid arthritis (RA) patients with chronic pain which were inadequately controlled by DMARD, biologics and/or NSAID. [Methods] 14 RA patients (female, n=11; male, n=3) with an average age of 70 years (range 55-86 years) were administered TRAM/APAP (2 -4 tablets) in our hospital. The mean disease duration was 10 years. The clinical response was assessed by a 100-mm visual analog scale (VAS) and the Health Assessment Questionnaire disability index (HAQ-DI). [Results] The mean VAS score decreased from 64.0 mm to 39.3 mm. The mean HAQ-DI score improved from 1.58 to 1.07. Adverse events were drowsiness and nausea. [Conclusion] TRAM/APAP was highly effective for RA patients with chronic pain and improved ADL of RA patients. It is necessary for administration from low dose of TRAM/APAP and pretreatment of anti-emetic drugs to prevent adverse effects. Use of TRAM/APAP is valuable treatment option for RA patients with chronic pain.

W37-5

The combination therapy with biologics and tacrolimus for the patients with rheumatoid arthritis

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Conflict of interest: None

[Objectives] The combination therapies of biologics (Bio) and tacrolimus (TAC) for the patients with rheumatoid arthritis (RA) are increasing in recent years. We investigated the condition of the combined therapies in our outpatient clinic, and examined the effect of those therapies. [Methods] We targeted at 28 RA patients (6 men, 22 women) who were using Bio and TAC together. It was 60.8 ±12.6 years old of age, and 10.8 ±6.9 years disease duration. The rate of MTX usage was 75% and the average dose was 7.6 mg/week, 69% of PSL usage, and the average dose was 3.5mg/day. [Results] The biologics used together were 13 IFX, 4 ETN, 7 ADA, 7 TCZ and 2 GLM. We used TAC before the initiation of Bio for 14 cases, and for the other 19 cases, TAC were added under biological therapies for the reduction of disease activity of RA. SDAI at the time of the combination therapies was 20.7±14.7, and the dose of TAC 1.88±0.77 mg/day. The SDAI was not significantly different between those two groups; the reason for the combination therapy. SDAI at the time of the last observation was 10.9±11.8, the dose of TAC 2.10±0.63 mg/day, and TAC blood concentration 4.3±2.70 ng/ml. [Conclusion] The combination therapies of Bio and TAC were considered to be one of the effective methods in the treatment of RA.

W37-6

Clinical experience of igulatimode (IGU) at the author's institution

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Conflict of interest: None

【Objective】 Igulatimode (IGU), is a novel anti-rheumatoid drug that is classed pharmacologically as an immunoregulator. We present the results of the phase III clinical study conducted at this institution that involved concomitant use of IGU + MTX, and we hereby report the usefulness of the treatment. 【Methods】 The subjects were 9 patients that were enrolled in the IGU + MTX concomitant use study on RA patients responding poorly to MTX. Safety and efficacy of the treatment were assessed in the double-blind phase of up to 28 weeks, and the continued treatment phase from 29 to 52 weeks. 【Results】 There were 15 onsets of adverse events in 6 of the 9 patients, however, all were not serious and the outcome was recovery.Changes in DAS28-CRP in the IGU group showed remission for 1 patient, slightly effective for 2 patients, and ineffective for 2 patients at 24 weeks; and effective for 1 patient, slightly effective for 3 patients and ineffective for 1 patient at 52 weeks. 【Conclusion】 The usefulness is considered high for pa-

tients that respond poorly to MTX and those that cannot use MTX. The results on the postmarketing clinical experience are also reported.

W38-1

Comparison between triple DMARDs combination therapy (Methotrexate, Sulfasalazine, and Bucillamine) and anti-TNF treatment for early rheumatoid arthritis (a JaSTAR study)

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Conflict of interest: None

[Objectives] Aggressive treatment in the first phase of rheumatoid arthritis is essential for disease control. However, some patients cannot be treated with biologics. Therefore, Japan Association of Rheumatologists in Private Practice conducted a multicenter study to compare the efficacy and safety of triple combination therapy with methotrexate, sulfasalazine, and bucillamine (TriD) with those of treatment with TNF inhibitors (TNFI). [Methods] We recruited 119 patients who had inadequate responses to a single disease-modifying antirheumatic drug (DMARD) or 2 DMARDs from 32 institutions. The intervention, TriD or TNFI, was chosen by the patients. The primary endpoint was the average disease activity score (DAS)28 at 6 and 12 months. [Results] TriD and TNFI were administered to 60 and 46 patients, respectively, for 6 months. In the TriD and TNFI groups, the average baseline DAS28 scores were 4.91 ± 1.06 and 5.12 ± 1.21, respectively, and the corresponding scores at 6 months were 3.34 ± 1.40 and 3.15 ± 1.47 ($p = 0.470$). Intergroup differences in the European League Against Rheumatism (EULAR) responses at 3 and 6 months were not statistically different. [Conclusion] Results of 6-month TriD therapy suggest that it may be an option to anti-TNF treatment.

W38-2

Analysis of the efficacy of LCAP from "Kyusyu LCAP study group" during 2011 and 2012

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Conflict of interest: Yes

【Purpose】Treatment of RA makes remarkable advance with biologics and MTX. We have examined the indication of LCAP and evaluate the efficacy and safety by analyzing RA patients treated with LCAP from 2011 and 2012.【Method】We analyzed 19 RA patients treated with LCAP from 2011 and 2012 in the participating hospital of our conference. We evaluated their background, the reasons for selection of LCAP, and the efficacy and safety of LCAP therapy.【Result】The mean age of patients was 64 years old, and the mean disease duration at entry was 11 years. Seventy percent of patients received glucocorcicoids (mean 3mg), and two patients treated with glucocorticoid only. Thirty percent of patients received methotrexate. Sixty percent of patients were complicated with pulmonary disorders, including atypical mycobacteriosis and interstitial pneumonia. DAS28-CRP significantly decreased at 4 weeks after LCAP and 40% achieved in more moderate or good response. No serious adverse events were observed except temporary anemia.【Conclusion】In our study, LCAP therapy was mainly performed toward the RA patients who are not able to be treated with biologics or MTX because of their complications, especially pulmonary complications, and LCAP therapy is suspected to be useful and safe for such patients.

W38-3

Annual serious adverse event in patients with RA medicated high dose MTX monotherapy registrated NinJa cohort

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Conflict of interest: Yes

[Objectives] The purpose is to research annual serious adverse event by MTX dose in patients with RA. [Methods] n 10368 Japanese RA patients registered with NinJa2011, 3,264 medicated MTX monotherapy without biological DMARDs or combination synthetic DMARDs were divided four groups by MTX dose. ; 1-5mg/week n=560 average age 67.4, mean duration of illness 14.2years, 6-7.5mg/week n=961, 63.1, 12.1, 8mg/week n=963, 62.3,10.9,over 8mg/week n=780 57.2, 9.8. We defined hospitalization for various infectious disease (including opportunistic infections), interstitial pulmonary disease, pancytopenia, malignant lymphoma as serious adverse event and research annual hospitalization and compare for 4 groups by Odds ratio. [Results] The annual hospitalization number were 21 patients (3.8%) in 1-5mg group, 23 (2.4%) in 6-7.5mg group, 18(1.9%) in 8mg group, 15 (1.9%) in over 8mg group. Serious adverse events were infectious disease, interstitial pulmonary disease, malignant lymphoma, and no pancytopenia. The incidence of the NinJa 2011 cohort was 326 (3.1%), and the OR with each group were 1.06, 0.73, 0.55, 0.55 respectively. [Conclusion] MTX monotherapy within 16mg/week is safe because Japanese doctors pay attention to age, a renal function, existing pulmonary disease and perform dose setting of MTX.

W38-4

***HLA-A*31:01* and Methotrexate-Induced Interstitial Lung Disease in Japanese Rheumatoid Arthritis Patients**

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Conflict of interest: Yes

Background: Methotrexate-induced Interstitial Lung Disease (MI-ILD) can occur in RA patients and represents a potentially life-threatening drug hypersensitivity reaction. It is believed that Japanese RA patients are more susceptible to MI-ILD. We investigated the association of *HLA* with MI-ILD in RA. *Methods:* A study of associations between the frequencies of *HLA class I* alleles and occurrence of MI-ILD in RA was conducted. *Results:* We found a highly significant association of the *A*31:01* allele with MI-ILD. The RA-ILD Study Consortium; Beppu Medical Center, Saiseikai Narashino Hospital, Himeji Medical Center, Hokkaido Medical Center, Hyogo College of Medicine, Kin-ikyo Chuo Hospital, Kitami Hospital, Kitasato University, Komagome Hospital, Kumamoto Saishunso Hospital, Kumamoto Shinto General Hospital, Kurashiki Medical Center, Kurume University, Kyoto Daiichi Hospital, Kyushu Medical Center, Matsuta Clinic, Miyakonojo Hospital, Morioka Hospital, Nagasaki Medical Center, Nagoya

Medical Center, Niigata Rheumatic Center, Shimokitazawa Hospital, Shimoshizu Hospital, Takasaki General Medical Center, Tama Medical Center, Teikyo University, Tenri Hospital, Ureshino Medical Center, Yokohama City University Medical Center, Yokohama Minami Kyosai Hospital.

W38-5

Is the conventional MTX treatment for RA the best? : A report from an unique experience of extra-low-dose MTX treatment in Japan

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Conflict of interest: None

[Objectives] To compare the efficacy of extra-low-dose MTX treatment (ExLD-MTX) and the conventional MTX treatment (C-MTX) [Methods] RA cases treated with ExLD-MTX (n=133) were retrospectively investigated. After 12 months of the treatment, the efficacy was evaluated. Next, the concentrations of MTX in the serum and MTXGlu1–7 in RBC lysates were quantitated (HPLC method). [Results] After 12M of ExLD-MTX (6. 7 mg/wk), 72.2% of cases were still maintained with the same treatment. The DAS remission was achieved 31.4% of patients, which is comparable to those of MTX monotherapy arm (16.9mg/wk) in PREMIER. The rate of withdrawal because of AE was much lower in ExLD-MTX. In the comparison with the C-MTX (17mg, once a wk), the AUC and Cmax of the ExLD-MTX (6mg, 3 times a wk) were 62% and 31%. The analysis of intracellular MTX-PG after ExLD-MTX revealed 88.2% of MTX-PG was MTX-PG6-7, whereas the rate of MTX-PG6-7 was reported to be less than 1% after C-MTX. The percentages of low MTX-PG concentration were 7.7% in the DAS<2.6 group vs 44.8% in the DAS>3.2 group after ExLD-MTX. [Conclusion] Although it seems to be beneficial to escalate the MTX dosage for some of patients with ExLD-MTX, our findings prompt researches for the most favorable dose initiation and escalation method of MTX.

W38-6

Leukocytapheresis (LCAP) contributed to maintain remission or low disease activity with 3 rheumatoid arthritis cases for a long term

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Conflict of interest: None

[Background] As for the recent RA treatment, early intervention of MTX and biological (Bio) agents are standard, but some cases are difficult. We show RA cases with LCAP first because of large amount of medical expenses burden for Bio agents. After that, disease activity has maintained remission or low disease activity for 2-5 years. [Case 1] A 50s female, 4mg/w of MTX was not enough for control, and LCAP was chosen. DAS28CRP of before, 1 month, 6months, and 1.5 years after LCAP were 4.78, 5.70, 2.54, and 1.65, respectively. SDAI was 25.5, 34.0, 3.75, and 0.58, respectively. [Case 2] A 50s female, 6mg/w of MTX was not enough, and LCAP was chosen. DAS28CRP of before, 1 month, 6months, and 1.5 years after LCAP were 5.84, 3.99, 3.69, and 3.22, respectively. SDAI was 39.0, 19.5, 14.4, and 10.2, respectively. [Case 3] A 60s female, 6mg/w of MTX was not enough, and LCAP was chosen. DAS28CRP of before, 1 month, and 6months after LCAP were 5.51, 3.61, and 1.99, respectively. SDAI was 32.3, 17.4, and 4.7, respectively. [Summary] LCAP may induce remission or low disease activity. LCAP is much cheaper than medical expenses burden of the Bio agents for over years. When induction of Bio agents is limited for some reason, LCAP might contribute to medical economy.

W39-1

A prospective study of the influence of methotrexate (MTX) on the standardized incidence ratio (SIR) of tuberculosis (TB) in patients with RA by *NinJa* for 9 years

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Conflict of interest: None

[Objectives] To evaluate the incidence of methotrexate (MTX) 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 9 years. [Results] Among 53,952 RA patients registered from 2003 to 2011, 46 patients developed TB. 17 patients (37%) were treated with MTX. The SIR of TB in RA patients treated with MTX was 4.46, and the SIR of TB in patients treated without MTX was 3.67. [Conclusion] The incidence of TB in RA patients treated with MTX was higher than that in RA patients treated without MTX.

W39-2

Reduction of plasma IL-6 by methotrexate in patients with early rheumatoid arthritis: a potential biomarker for radiographic progression

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Conflict of interest: None

[Objective] To determine the effect of methotrexate (MTX) on plasma cytokines and to investigate their associations with radiographic responses in patients with early rheumatoid arthritis (RA) [Patients] RA patients in prospective cohort of newly diagnosed RA of our hospital and treated only with MTX. [Method] Plasma level of TNFα and IL-6 was measured before the treatment and 1 year later. Patients who used biological agents were excluded. [Result] Forty-two patients were included in this study. The median age was 56 years and 35 (83%) patients were female. The median disease duration was 3.5 months. Thirty-one (74%) patients were anti-CCP antibody-positive. DAS28-ESR and plasma IL-6 decreased significantly ($p<0.01$ and $p<0.05$, respectively) after MTX treatment, but plasma TNF-α did not. Radiographic progression was significantly correlated with DAS28-ESR and plasma IL-6 levels but not with TNF-α after MTX treatment. Patients with plasma IL-6 level above 4.03 pg/ml showed clinically relevant radiographic progression with a sensitivity of 89% and a specificity of 88%. [Discussion] In this early RA cohort, we demonstrated a significant reduction of plasma IL-6, but not TNF-α, during MTX treatment. The post-treatment IL-6 level was a strong indicator of

radiographic progression.

W39-3

Dosage of MTX per body weight in adult patients with rheumatoid arthritis

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Conflict of interest: None

[Objectives] To evaluate and compare the dosage of MTX per body weight (BW) with other parameters including gender in adults patients with rheumatoid arthritis (RA). [Methods] Among patients registered in NinJa 2011, 1110 adult RA patients (905 female and 205 male) treated with MTX alone without steroid was selected for this study. Their mean age was 60.8 yrs, disease duration 9.7 yrs, and BW 51.7 kg in female and 64.2 kg, respectively. [Results] There was no correlation between BW and dosage of MTX. Mean dosage of MTX (mg/w) was not different between in female (7.3) and in male (7.4). Dosage of MTX per BW (MTX/BW mg/w/kg) was correlated with SDAI, TJC, SJC, VAS, mHAQ, and inversely correlated with BW, BMI, and age. Mean MTX/BW in female (0.143) was significantly more than in male (0.119), however, there was no differences in mean SDAI between female and male. Among 421 patients with SDAI remission, mean dosage [upper 95 percentile] of MTX in female (6.9 [12]) was also not different from that in male (6.8 [10]). Also, in patients with remission, BW was not correlated with dosage of MTX, and MTX/BW was larger as BW lower. [Conclusion] Regardless of BW or gender, fixed dosage of MTX was needed for achievement of remission. A dosage of MTX per BW may be needed more as BW lower.

W39-4

Comparison of corticosteroid reduction or stoppage by increase of MTX dose and BIO introduction in rheumatoid arthritis patients

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Conflict of interest: None

Objection) RA patient has difficulty in steroid decrease for recurrence risk and depression of adrenal function. We compared steroid reduction and stoppage by increased MTX dose or BIO introduction. Methods) We used 43 cases that steroid therapy did not change the dose more than three months. Patients were categorized as follows: MTX (group A:20 cases) and BIO (group B:24 cases). We observed both groups for disease activity and adrenal function. Target of steroid dose were less than PSL 3mg. Result) Patients background did not differ in both groups. Mean PSL dose had been reduced in both groups. In two years, there was no significant difference in the reduction and stoppage rate. The mean period to steroid reduction was 464 days in group A and 528 days in group B. Time to steroid stoppage was shorter in group A. The correlation between steroid decrease and DAS28, SDAI were not seen in both groups, and the rise of disease activity by steroid reduction was not seen. The mean period to normalized ACTH was 293 days in group A, 211 days in group B. So it was significantly shorter in group B ($p < 0.05$). Conclusion) As for recovery of the adrenal function, BIO introduction was better than increase of MTX. BIO could reduce steroid more safely.

W39-5

A study on safety and tolerability of MTX therapy in MTX naïve RA patients-2nd Report-

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Conflict of interest: None

[Objectives] We have reported the safety and tolerability of MTX in patients with MTX naïve at this meeting the last time. In this report we have investigated the safety and tolerability at 6 months and 12 months. [Methods] 73 MTX naïve RA patients within 2 year after disease onset were started MTX therapy at 6 or 8mg/w. 2mg/w of MTX were increased every two weeks until DAS28 remission and the maximum dose of MTX was 16mg/w. 6 months after, we investigated the safety and the tolerability. [Results] MTX dose at 6 months was 1 case of 4mg, 7 cases of 6mg, 14 cases of 8mg, 11 case of 10mg, 8 cases of 12mg, 3 cases of 14mg and 12 cases of 16mg. 3 cases were discontinued by GI symptom. 18% cases of 12mg/w reduced MTX dose by liver dysfunction and this frequency significantly higher compared to 8mg (3%), 10mg (2%), 14mg (0%) and 16mg (7%). 47 patients were administered with MTX for up to 12 months and the adverse event in only two patients after 6 months. One case was liver dysfunction in 8mg, one case was GI symptom at 16mg. [Conclusion] The adverse events ware significantly increased at 12mg ($p = 0.0006$). In cases there were no adverse events at 12mg, MTX dose could be increased up to 16mg. Our results showed safety and tolerability of the dose up to 16mg.

W39-6

Study of MTX usage in older patients with rheumatoid arthritis since 2011

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Conflict of interest: None

[Objectives] To describe the propblems of MTX in older patients with rheumatoid arthritis (RA) since February, 2011. [Methods] Data were collected retrospectively from RA patients who were more than 65 years old in our hospital. We examined the difference of MTX dose, PSL, CRP, ESR,DAS28-CRP(4), DAS28-ESR(4), CDAI, and SDAI between group A:79 patients(65-74 years old) and group B:54 patients (more than 75 years old.) [Results] There was not significant difference between group A and B in PSL(3.20mg:3.49mg), CRP(0.90mg/dl:1.02mg/dl), ESR(20.7mm/h:24.9mm/h), DAS28-CRP(4)(2.42:2.50), DAS28-ESR(4)(2.88:3.07), CDAI(7.31:7.45) and SDAI(7.91:8.51), but there was significant difference in MTX dose(6.9mg/week:5.7mg/week). [Conclusion] Since 2011,we could prescribe much more MTX up to 16mg/week, but there is difficulty in the usage of MTX in older patients with RA.

W40-1

Study of Dose Reduction and Background Factors in Patients on Long-Term Treatment with Etanercept

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Minami Osaka Conference of Rheumatology

Conflict of interest: None

[Objectives] We conducted a survey on actual doses administered to patients on long-term treatment with etanercept (ETN) to evaluate situations resulting in dose reduction and background factors for the increased likelihood of such dose reduction. [Methods] We investigated data such as actual doses and patient characteristics from rheumatoid arthritis patients receiving ETN for more than 2 years at Minami Osaka Conference of Rheumatology member institutions. [Results] Twenty institutions contributed to this survey, reporting on 82 patients. Major patient characteristics: mean administration period 47.1 ± 17.1 months (max 91 months); mean age 57.3 ± 13.1 years; and mean disease duration 10.6 ± 9.0 years. Of the 82 patients, 27 (32.9%) had ETN dose reduction to 25 mg/w, 25 mg/10 days, 25 mg/2 wks, 25 mg/3 wks and 25 mg/4 wks. Comparison of background factors between ETN dose reduction and maintenance groups showed a significant difference in disease duration, proportion of Class 1+2 and presence/absence of previous treatment with other biologicals, but no difference in age, Stage and pre-dose disease activity. [Conclusion] Initiation of ETN treatment in the early time point of disease duration increase possibility of dose reduction in patients that have to be on long-term treatment.

W40-2

Factors affecting discontinuation of Adalimumab treatment after introducing clinical remission state

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Conflict of interest: Yes

[Objectives] We investigated the factors affecting discontinuation of Adalimumab (ADA) in patients with the rheumatoid arthritis (RA) after introducing clinical remission. [Methods] Fifty-five patients (10 males and 45 females, mean age ; 55 ys) treated with ADA were examined. When patients who were administered ADA for at least 1 year sustained remission for ≧6 months and desired to discontinue ADA, ADA was discontinued. We compared the patient backgrounds between the group of sustained remission (group A) and that of non-sustained remission (B group). [Results] Ten of 55patients (18%) discontinued ADA after due to remission. Nine patients (16%) sustained discontinuation of ADA without flare, but ADA was re-administered to 1 patient due to flare. Compared with group B, mean disease duration at the initiation of ADA (A; 61.8 months vs. B; 103.6 months, p=0.03) was short and concomitant rate of salazosulfapyridine was low (non-concomitant: A; 0/9 vs. B: 25/46, p=0.0099) significantly in group A. ROC analysis was conducted. A cut-off value of disease duration at the initiation of ADA was 9.0 months. [Conclusion] Not only discontinuation of ADA due to sustained remission but also biologically-free remission are achievable by early introduction of ADA.

W40-3

Investigation of cases of infliximab (IFX) discontinuation in the AORA database

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Conflict of interest: None

[Objectives] To investigate cases of infliximab (IFX) discontinuation in the AORA database. [Methods] A total of 125 registered patients with a history of IFX use were retrospectively investigated. [Results] At initiation of IFX therapy, patients had a mean age of 58.2 years and a mean disease duration of 10.6 years. The mean matrix metalloproteinase 3 was 260.5 ng/mL, and 55% of the 69 patients whose disease activity could be assessed at initiation exhibited high disease activity. IFX was discontinued in 65 patients, and the cumulative continuation rate at one year was 82.9%. The main reasons for discontinuation were lack of efficacy, complications, and malignancy, and only three patients discontinued the drug due to remission. While IFX therapy was continued in 85.7% of patients who exhibited low disease activity at initiation, the continuation rate was only 36.8% among patients who exhibited high disease activity. No significant differences were observed for rate of improvement on the Disease Activity Score 28 at five months after therapy initiation between cases of continuation and discontinuation. [Conclusion] We report the present study in comparison to previous cohorts while including the detailed course of patients discontinuing IFX.

W40-4

The length of remission and rate of relapse after withdrawal of biologics in rheumatoid arthritis patients

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Conflict of interest: Yes

[Objectives] To assess the length of remission in rheumatoid arthritis (RA) patients after withdrawal of biologics. [Methods] Patients who received biologics for treating active RA despite treatment with methotrexate or leflunomide and discontinued biologics after achieving remission were analyzed. [Results] Forty-four patients could be analyzed, 73% females with a mean age of 54 yrs. Mean symptom duration at the onset of biologics was 1.4 years. Rheumatoid factor and anti-CCP antibodies were positive in 91% of patients. Thirty-seven patients reached remission without switching biologics in our clinic, including 20 with infliximab (IFX group), 14 with etanercept (ETN group). Seven patients reached remission after switching biologics in our clinic (SW group). At the time of submitting abstract, 28 patients were eligible for the analysis of 1-year of follow-up, 14 (50%) patients, including 9 of 13 in IFX group, 4 of 9 in ETN group, 1 of 5 in SW group. Kaplan-Meier analysis revealed tendency toward longer length of remission in the order of IFX, ETN, and SW groups. [Conclusion] Long-term remission is possible in a substantial number of recent-onset RA patients after suspension of biologics. The length of remission after withdrawal of biologics might be different among biologics used.

W40-5

Influence of concomitant Methotrexate and Prednisolone on drug inefficacy of Etanercept and Adalimumab in patients with rheumatoid arthritis

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Conflict of interest: None

[Objectives] In treating RA patients with ETN or ADA, influence of concomitant Methotrexate or Prednisolone on biologic inefficacy remains unknown. [Methods] 284 RA patients who were followed-up more than 6 months after starting ETN (184 patients; 1stBio 148;2nd or later Bio 36) or ADA (100 patients; 1stBio 60;2nd or later Bio 40) were enrolled. [Results] Drug inefficacy was monitored in 20.7% of ETN (1stBio 16.9%; 2nd or later Bio 36.1%) and 28.0% of ADA (1stBio 21.7%; 2nd or later Bio 37.5%) (ETN vs. ADA; P=0.16). In ETN, inefficacy group showed higher dose of pre-treated PSL (7.0 vs. 4.4 mg/day; P<0.001) compared to efficacy group. In ADA, inefficacy group showed lower dose of MTX (4.6 vs. 7.0 mg/week; P<0.01) compared to efficacy group. As for MTX, when less than 6mg/week, inefficacy rate was significantly higher in ADA (36.5%) compared to ETN (21.0%) (P<0.05), while treated more than 8mg/week, inefficacy rate was similar (ETN 19.0% vs. ADA 18.8%). On the other hand, in ETN, inefficacy rate was 8.2% when pre-treated PSL was≦4mg/day, whereas it was significantly higher (28.8%) in those pre-treated≧5mg/day (P<0.001). [Conclusion] When choosing ETN or ADA, concomitant MTX ≧8mg/week or pre-treated PSL dose≧5mg/day may be taken into consideration to avoid drug inefficacy.

W40-6

Switching biologics agents in patients with rheumatoid arthritis: an observational study of 128 patients about efficacy, ADL, QOL and depression

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Conflict of interest: Yes

[Objectives] The objective of this study is to analyze biologic agents in terms of their efficacy and their effects on the ADL, the health-related quality of life (HRQoL) and depression in patients who have switched between biologic agents for the treatment of rheumatoid arthritis (RA). [Methods] Eighty-eight RA patients were assessed prior to treatment and 30 weeks after initiating the first biologic therapy (Group 1). The DAS28, the ADL (mHAQ), the HRQoL questionnaire (SF-36) and the depression scale (HAM-D) were administered to the patients. Thirty-three patients were assessed following the initiation of a second biologic therapy (Group 2), and 7 patients were assessed following a third therapy (Group 3), each using similar assessments. [Results] After 30 weeks of administration, the DAS28, mHAQ and HAM-D scores changed in all Groups respectively (p<0.05). Although all of the categories of SF-36 showed significant improvements (p<0.001) in Group 1, some categories were not improved in Group 2 and 3. [Conclusion] In this study, the first biologic agent treatment had high efficacy and improved the ADL, HRQoL and depression scores. Although the second and third biologic treatments showed significant improvements in the efficacy, ADL and depression, improvement of the HRQoL was limited.

W41-1

Efficacy of golimumab in patients with rheumatoid arthritis in clinical setting

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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 41 RA patients being treated with GLM; 26 patients were bio-naïve patients and 31 were receiving concomitant MTX. At baseline, after 1, 3 and 6 months, the following parameters were investigated: CRP, ESR, MMP-3, DAS28-ESR, DAS28-CRP, CDAI, SDAI, drug survival rate of GLM and adverse events. [Results] After 1, 3 and 6 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 6 months was 88%. No differences were found between the groups in adverse events. [Conclusion] These results suggest that patients who receive GLM can achieve improvement in disease activity soon.

W41-2

The decrease in disease activity of rheumatoid arthritis during treatment with adalimumab depends on the dose of methotrexate

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Conflict of interest: Yes

[Objectives] Analyze the efficacy of adalimumab (ADA) by the presence/absence of methotrexate (MTX) and its dose. [Methods] Enrolled were 46 patients who started ADA from Jul 2008 to Feb 2012 and were followed for 24 wks. Pearson's product-moment correlation coefficient was used to assess the correlations between improvement in DAS28-ESR and MTX dose in patients without MTX and those receiving MTX at <8, 8 and >8 mg/wk. [Results] Mean duration of illness was 9.9 ± 9.1 yrs in 38 patients with MTX (mean dose 8.6 ± 2.1 mg/wk) and 16.7±14.5 yrs in 8 patients without MTX. Mean DAS28-ESR at baseline and week 24 were, respectively, 4.7±1.3 and 2.8±1.2 in patients with MTX and 4.5±1.0 and 4.2±1.5 in patients without MTX, and 53% and 25% of them achieved clinical remission by week 24. Patients who continued ADA by week 24 accounted for 84.2% and 50.0% in patients with and without MTX. In 14 patients receiving MTX at >8 mg/week, DAS28-ESR decreased quickly from 4.5±1.1 at baseline

to 3.3±1.0 and 2.4±1.0 at weeks 4 and 24. Clinical remission was achieved in 71% and 40% of those receiving MTX at >8 and £8 mg/week. A significant correlation was noted between the improvement in DAS-ESR and MTX dose. [Conclusion] Combination with a sufficient dose of MTX enhances the clinical efficacy of ADA.

W41-3

The efficacy and safety of titration of Infliximab(IFX) treatment on a long-term basis

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Conflict of interest: None

[Objectives] It has been more than 3 years since IFX dose adjustment has approved in Japan, however there is still few information about the effectiveness and safety in the long term which was investigated in this retrospective study. [Method] We have examined 23 cases with titration of IFX therapy for at least 24 weeks without dose-iincrease of MTX and prednisolone up to March 2012. We have analyzed the clinical indexes such as DAS28(4) ESR, CRP, MMP-3, RF and the continuance at 24, 48, 72 and 96 weeks. [Result] Comparison with the clinical indexes just before the dose adjustment, they tend to decrease at each point. Just before the titration, at 48 weeks and 96 weeks DAS28(4) ESR were 3.4±1.1, 3.3±1.0, 2.8±0.9. During follow-up period, 3 cases considered ineffective and 2 cases because of adverse events (pneumonia and gastric carcinoma) discontinued the treatment. There are 1 case which stopped the therapy with clinical remission and 2 cases have maintained it at other hospitals. The persistancy rates by Kaplan-Meier method at each point were 91.3, 69.6, 58.9, 58.9% respectively (95% CI: 0.73-1.0, 0.51-0.88, 0.38-0.80, 0.38-0.80). [Conclusion] Titration of IFX treatment has been considered effective with clinical safety in the long-run as well.

W41-4

Results of golimumab (GLM) treatment of rheumatoid arthritis (RA)

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Conflict of interest: None

[Objectives] Unlike other agents, GLM is a fully human anti-TNF transgenic antibody. Injected subcutaneously, characterized by few anti-GLM antibodies and injection reactions. We retrospectively evaluated GLM-treated patients followable for ≥24 wk. [Methods] From Sep. 2011, GLM administered to 40 RA patients (7 male, 33 female; mean age: 60; mean disease duration: 14.4 yr). Doses: 50 and 100 mg with 17 and 23 subjects. MTX also administered to 92.5% (mean dose: 6.7 mg). 14 bio-naïve, including 2 trial-transfer subjects, 26 switched from other biologics (IFX, ETA, ADA and ABT: 18, 5, 1 and 2). Findings evaluated with DAS28 (CRP). [Results] Low-activity and remission subjects [DAS28 (CRP) < 2.7] were 7.5% pre-admin., but 75% and 68% after 24 wk in 50- and 100-mg groups; and 66% and 75% in bio-naïve and switched subjects. With 6 subjects, 50 increased to 100 mg within 24 wk, due to insufficient efficacy. 1, 6 and 1 subjects were discontinued, due to adverse reactions, insufficient efficacy, and hospital change. [Conclusion] With both bio-naïve and switched subjects, GLM and other anti-TNF agents showed similar efficacy. For initial dose, research with more subjects needed. Advantage of GLM: with monthly admin., hospital visit number and hospital time are less than with other agents.

W41-5

Efficacy of Golimumab on Rheumatoid Arthritis Patients with Biologics Naïve or Switch from other Biologics

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Conflict of interest: None

[Objectives] We evaluated the efficacy of Golimumab (GLM) on naïve and switch RA patients in our clinic. **[Methods]** 21 naïve patients and 22 switch patients were evaluated on DAS28, CDAI, SADI, ACR20, ACR50, ACR70, swollen joint count and tender joint count over 24 weeks. The continuation rate of GLM was compared with other biologics using previous our hospital data. **[Results]** The mean age for naïve patients were 52.5 and switch patients were 67.8 years old, and the mean disease duration were 10.2 and 15.7 years, respectively. Previous biologics use in switch patients were infliximab 2, etanercept 9, adalimumab 6, tocilizumab 3 and abatacept 2. Remission rate of DAS28 and SDAI at week 24 were approximately 20% and 10% in naïve patients, which seemed to be higher than switch patients. CDAI remission, ACR70 and ACR50 on naïve and switch patients were similar. **[Conclusion]** The remission on naïve patients achieved by GLM treatment was higher than switch patients as well as other biologics. Although the efficacy onset of GLM on switch patients was later than naïve patients, the efficacy on switch patients was induced in 3 months. The continuation rate of GLM on naïve and switch patients were excellent comparing with other biologics in our hospital data.

W41-6

A case study about decreasing efficacy of etanercept & SNPs analysis

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Conflict of interest: None

(Objectives) Etanercept (ETN) has high retention rates, but there've been patients who switched medication due to decreased efficacy. We believe it significant identifying patients on whom ETN has attenuated efficacy before treatment. Clinical and SNPs analysis were done to identify on whom ETN would have decreased efficacy. (Method) As subjects, 272 outpatients using ETN were split into 3 groups; those who didn't attain moderate response were defined as non-responders (NR), those who successfully responded responders (R), and those with decreased efficacy (NR2). Clinical comparisons and SNP analysis were made between the R and NR2 group to study genetic backgrounds. (Results) Twenty-seven patients (9.9%) were NR, 157 (57.7%) were R, and 37 (13.6%) were NR2. Backgrounds of the R and NR groups didn't show significant differences in age, duration or CRP, but disease activity was higher in NR2. SNP analysis among 118 patients in the NR and NR2 groups showed a significant difference of $P<0.05$

among genes for signal transduction and other pathways. (Conclusion) Clinical indexes before treatment don't suggest particular differences between the R group and the NR2 group. However SNP analysis is thought to have greater potential to identify patients before using ETN.

W42-1

The survival predictor of anti-tumor necrosis factor therapy in patients with rheumatoid arthritis

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Conflict of interest: None

OBJECTIVE: To investigate the survival of tumour necrosis factor (TNF) α antagonists in patients with rheumatoid arthritis (RA). **METHOD:** This study included 296 RA patients who started infliximab (IFX), etanercept (ETN), or adalimumab (ADA) as the first biological therapy. Patients were prospectively analyzed to compare drug survival rates and the baseline factors that may predict adherence to therapy. **RESULTS:** One hundred eight-nine patients started treatment with IFX, 91 with ETN and 16 with ADA. They were followed up over 4.4, 3.0 and 2.0 years, respectively. According to Kaplan-Meier methods, the retention rate of anti-TNF-α therapy was 82% (IFX survival 83%, ETN 86%) at one year. Using Cox proportional hazards models, predictors from multivariable analysis (age, sex, BMI and disease duration) of continuation included low disease activity score (DAS) 28 at the first 14 week (Hazard rate (HR): 1.30. p=0.004), 22 week (HR: 1.45, p<0.001) and improvement of DAS 28 during the first 22 weeks (HR: 0.81, p=0.012). **Conclusion:** Low DAS28 scores measured at first 14, 22 week and rapid improvement after receiving TNF antagonists were found to predict subsequent continuation.

W42-2

Interleukin-6-Based Evaluation on Patients Achieving Sustained Remission via Etanercept Dose Tapering and Becoming Biological-free

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Conflict of interest: None

Objective: Using IL-6 levels, we evaluated patients responding to etanercept (ETN) and achieving sustained remission and becoming biological-free through ETN dose tapering. **Methods:** Patients who started at 50 mg/w ETN and had DAS improvement and no radiographic joint destruction progression had their doses tapered. Those without DAS measured relapse being on a dose of 25 mg/4 wks were considered as ETN-free. This dose reduction group was evaluated using new remission criteria including SDAI, CDAI, and IL-6; those having slight relapse were treated with MTX dose increase in accordance to IL-6 concentrations as indices. **Results:** ETN could be tapered in 15 of 21 patients, of whom 2 could discontinue biologicals. Among 15 patients in the dose reduction group, 13 had IL-6 levels of 4 pg/ml or lower, exhibiting their dose reduction procedures raised no concerns. In 2 patients with slight relapse, MTX dose increase resulted their elevated IL-6 levels to decrease and no ETN dose increase was required. **Conclusion:** These data suggest that ETN responders can have dose reduction and even become biological-free; of these responders, those with slight relapse can be treated with MTX increase instead of ETN increase and IL-6 may be useful in evaluating relapses.

W42-3

Review of discontinuation of adalimumab in rheumatoid arthritis with clinical remission

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Conflict of interest: None

[Objectives] To investigate whether adalimumab (ADA) might be discontinued and maintain remissin (bio-free remission) after achievement of clinical remission in patients with rheumatoid arthritis (RA). [Methods] We examined enhanced MRI and power Doppler to find residual synovitis in patients with bio-naïve RA who were in clinical remission (DAS28-ESR<2.6) in 2 year after treatment with ADA plus methotrexate (MTX). If synovitis is none or little in the images, ADA was discontinued (bio-free). We studied the possibility of the bio-free remission in these patients. [Results] Among 56 patients with RA who had received ADA treatment, 44 patients continued ADA, 4 patients discontinued ADA by adverse events, and 8 patients stopped and changed biologics by lack of efficacy. Seven patients (38.9%) who had clinical remission and little inflammation in the image, discontinued ADA (bio-free) in 18 patients treated by ADA beyond two years. Bio-free period were 2-13 months (mean 6.9 months). The changes of the values from baseline to final observation after the discontinuation of ADA were from 2.2 to 2.11 for DAS28-ESR, from 3.1 to 2.3 for CDAI. These data showed bio-free remission was possible in ADA treated RA patients. [Conclusion] Bio-free remission was possible in ADA treated RA patients.

W42-4

Continued effectiveness after tapering of etanercept in rheumatoid arthritis

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Conflict of interest: None

[Objectives] To investigate whether standard dose (50 mg/w) of etanercept (ETN) could be reduced to ≦ 25 mg/w for the treatment of RA. [Methods] All the patients (n = 244) introduced with ETN between Jun/2005 and Mar/2011 were reviewed in Mar/2012. Continuity rate, disease activity, dose of ETN, MTX, and PSL before and after treatment were evaluated. [Results] The number of patients started with 50 mg/w of ETN were 153 (59.4%). Clinical parameters before and at the last observation, respectively, were as follows: median DAS28-CRP, 5.01 and 2.05; concomitant MTX, 62.1 and 68.4%; mean MTX dose, 7.2 and 6.9 mg/w; and mean PSL dose, 4.6 and 1.5 mg/day. Continuity rate was 51.6% (79/153) and median observation period was 49.6 months. At the last observation, median CDAI was 4.1. Patients maintained on ≦ 25 mg/w were 44.3% (35/79). The median interval from the start of ETN to the time reduced to ≦ 25 mg/w was 20.7 months. Among patients maintained on 50 mg/w and those on ≦ 25 mg/w, median DAS28-CRP before treatment was 4.68 and 4.8, and median DAS28-CRP and CDAI, at the last observation, were 2.03 and 2.10, and 4.2 and 4.1, respectively. [Conclusion] About half of the patients started with 50 mg/w were maintained on 25 mg/w without apparent loss of effectiveness.

W42-5

Is it possible to de-escalate or stop infliximab in dose escalation therapy in patients with rheumatoid arthritis?

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Conflict of interest: Yes

[Objectives] We reported the efficacy of dose escalation of infliximab (IFX) therapy in patients with rheumatoid arthritis (RA). However, the clinical course after escalation of IFX is unknown. This time, we report whether de-escalation of IFX is possible or not. [Methods] Fifty patients (4 males and 46 females) treated with high dose of IFX were examined. If the patient still remain in state of moderate disease activity, dose escalation of IFX is performed (3→6→10mg/kg). If the patient maintain the remission state, the dose de-escalation of IFX is performed (10→6→3mg/kg). Moreover, when patients sustained remission for ≧6 months at the dose of 3mg/kg of IFX and desired to discontinue IFX, IFX was discontinued. [Results] The dose of IFX was increased up to 6mg/kg in 12% and 10mg/kg in 88% of patients. At the time of the last observation, 26% of patients were given in dose of 10mg/kg, 12% in 6mg/kg and 28% in 3mg/kg of IFX. Three patients (6%) sustained discontinuation of IFX. Twenty-six percent of patients were discontinued IFX in mid-course, because of some reasons (adverse effects; 8%, insufficiency; 8%, discontinuation of MTX; 6%, changing hospital; 4%, patient's risk; 2%). [Conclusion] The doses of IFX could be de-escalated in dose escalation of IFX therapy in patients with RA.

W42-6

The strategy after discontinuation of infliximab after attaining remission in patients with rheumatoid arthritis

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Conflict of interest: None

BACKGROUND: After achieving remission, discontinuation of Infliximab may become an important issue from Japanese study such as RRR in patients with established rheumatoid arthritis (RA). But, the therapeutic system is not established. OBJECTIVE: To analyse disease activity, joint destruction and another serological factors during the discontinuation and to built the therapeutic system after discontinuation of infliximab. METHOD: 100 patients with RA who had received IFX treatment, and whose Disease Activity Score, including a 28-joint count (DAS28) was <2.6 (remission) for at least 24 weeks, were studied. RESULTS: 69.3% attained bio-free remission and 30.7% do not attained at 1 year after discontinuing infliximab, and there were significant difference between delta mTSS and the rate of structural remission. RF and delta mTSS increased significantly at 2 year after discontinuing infliximab. Delta RF (2y-BL) correlated with delta RF (1y-BL) significantly. Delta RF (1y-BL) decreased significantly at bio-free remission group. BL-RF negative group or BL-RF positive group of lower delta RF attained lower disease activity and higher rate of remission. CONCLUSION: RF and mTSS are important factors after discontinuation of infliximab.

W43-1

Evaluation for histological features of synovium in patients with rheumatoid arthritis treated with tocillizumab

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Conflict of interest: None

[Objectives] The study aims to clarify the effect of TCZ by comparing pathological findings in synovium before and after TCZ treatment in the same patients. [Methods] Subjects were 10 RA patients treated with TCZ from 2009 to 2012 and had surgeries in our department. Pathological findings in synovium collected during surgeries were reviewed using Rooney score and inflammation score obtained by excluding Fibrosis from the Rooney score. Clinical evaluation was conducted by CDAI. [Results] Average age and disease duration were 55.9 and 13.8 years. Low, moderate and high disease activities were observed in three (30%), five (50%) and two (20%) joints. CDAI was significantly improved from 28.3 to 16.0 before and after TCZ administration. Rooney scores for lymphocytes numbers in synovial lining cells and perivascular area, lymph follicle and lymphocytic infiltration were significantly reduced after TCZ treatment. Fibrosis increased significantly. Significant difference was observed between disease activities and inflammation scores. [Conclusion] The results demonstrated that the decrease in numbers of not only lymphocytes in synovial lining cells and perivascular area but also lymphocytic infiltrations. It was suggested TCZ may have intensive anti-inflammatory effect for synovial tissue.

W43-2

The Usefulness of Measuring Bone and Cartilage Metabolism Markers in the Utilization of Tocilizumab (1)

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Conflict of interest: Yes

[Objectives] To examine the correlation of clinical assessment with bone and cartilage metabolism markers in RA patients who received TCZ. [Methods] Markers were examined in 20 RA patients who received TCZ at 3 facilities of Kinki University in 2010-12. Average age 57, stage I5/II5/III1/IV9, class I4/II14/III2/IV0, disease duration of 8.8years, Average use of MTX 6.5 mg/W, PSL 4mg/D. 13 RA had history of biological agent use, and they were evaluated comprehensively before administration and after 12, 24 and 52 weeks. [Results] DAS28 at 52 weeks was significantly decreased from 5.1pre-administration to 1.9, and all 7 patients using it as first choice met 100% of remission criteria. MMP-3 significantly decreased from 192 pre-administration to 102 ng/mL, together with PSL use to 2.5mg. At 24 weeks OC and DKK-1 fluctuated significantly, and variable DKK-1 and OC/NTX ratio showed a negative Spearman rank-correlation coefficient (ρ) of -0.8593 ($p<0.0001$). At 52 weeks DKK-1 had significantly decreased due to TCZ administration from 3194pre-administration to 2451pg/mL, and the OC/NTX ratio increased to 1.5 times that pre-administration. CTX-2, NTX and OPG showed no significant differences up to week 52. [Conclusion] TCZ suppresses RA disease activity and promotes bone formation.

W43-3

Periodontal condition in rheumatoid arthritis patients during tocilizumab therapy

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Conflict of interest: None

[Objectives] Interleukin-6 (IL-6) plays a role in the pathogenesis of rheumatoid arthritis (RA) and periodontitis. The authors thus evaluated periodontal condition of RA patients during tocilizumab (TCZ) therapy. [Methods] The study participants consisted of 30 and 29 patients in the treatment with and without TCZ (TCZ and control group), respectively. Baseline was set following TCZ therapy starts (mean 20.3 months). Periodontal and rheumatologic parameters and serum levels of IL-6, matrix metalloproteinase-3 (MMP-3), C-reactive protein, anti-CCP and anti-periodontopathogen titer were examined at baseline and 8 weeks later. [Results] No differences were observed between the groups at baseline in any parameters, except for serum IL-6 levels. The TCZ group showed significant improvement of periodontal condition and reduction in serum levels of IL-6 and anti-CCP than the control group. Other parameters including oral hygiene levels proved comparable between the groups. Furthermore, a significantly positive correlation was found between serum MMP-3 levels and periodontal inflammation, and between serum anti-CCP levels and periodontal destruction. [Conclusion] Serum levels of MMP-3and anti-CCP may influence the periodontal condition of RA patients during TCZ therapy.

W43-4

Does Early Stage Platelet Count Decrease in Rheumatoid Arthritis Patients who Received Tocilizumab Correlate with Treatment Response?

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Conflict of interest: None

Objectives: Correlation of changes in platelet count (plt) after TCZ treatment to treatment response was examined in RA patients. Methods: Subjects were 72 RA patients receiving TCZ treatment at our hospital for whom at least 24 weeks of administration was possible. The observation was 24 weeks and plt, WBC, DAS28 and CDAI were compared before start of treatment and after 4, 8 and 12 weeks. Baseline paired test, Wilcoxon rank sum test and Fisher's exact test were used for statistical analysis. Results: DAS28 and CDAI improved with statistically significant difference after 4, 8, 12 and 24 weeks. There was CDAI remission in 26 patients, and the change rate of plt change after 4 weeks showed statistically significant difference at -16.7±16.4% in the CDAI non-remission group and -26.1±9.9% in the remission group (p=0.006). When -25% was taken as cutoff for the change rate of plt 4 weeks after starting TCZ, CDAI remission rate after 24 weeks showed statistically significant difference at 76.9% (vs. 23.1%) (p=0.024). Conclusions: When the rate of change of plt 4 weeks after TCZ administration exceeded 25%, remission was more easily attained after 24 weeks, which could provide significant information in considering whether or not to continue treatment.

W43-5

The effect of Tocilizmab for anemia in rheumatoid arthritis patients

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Conflict of interest: Yes

[Background] Rheumatoid arthritis (RA) patients are often accompanied by anemia of chronic disorder (ACD). Recently, it is reported that ACD is regulated by hepcidin that is produced by the liver in response to pro-inflammatory cytokines such as IL-6. Therefore, it is possible that anti-IL-6 receptor antibody, Tocilizmab (TCZ), may improve anemia in RA patients by suppressing hepcidin. [Objectives] The aim of this study is to compare the effect of Tocilizmab with other biologics in improving anemia of RA patients. [Methods] RA patients who are registered in KURAMA (Kyoto University Rheumatoid Arthritis Management Alliance) cohort and started to be treated by biologics after May 1st in 2011 and continuously treated at least 6 months were enrolled. Relative values of hemoglobin before and 6 months after the treatment were compared between TCZ-treated and non-TCZ-treated groups. [Results] Among 77 enrolled patients, 19 were treated with TCZ, 58 with biologics other than TCZ. Relative value of hemoglobin 6 months after the treatment was higher in TCZ-treated group compared with non-TCZ-treated group. (TCZ-treated group; 110.7±14.1 % vs non-TCZ-treated group; 100.2±7.8 % (p=0.005)). [Conclusion] TCZ was shown to be superior in improving anemia of RA patients than other biologics.

W43-6

Change in white blood count after administration of tocilizumab and clinical response: Change in WBC count in initial phase and prediction of effectiveness at 6 months

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Conflict of interest: None

It is convenient if prediction of the effectiveness of biologic DMARDS is available. It has been known that complete blood cell count (CBC) change after the administration of tocilizumab (TCZ). We studied the relationship between the change in CBC and the clinical response after administration of TCZ. Subjects and Methods: Subjects were 50 patients with RA with a mean age of 50 years. The mean DAS28ESR at the introduction of TCZ were 4.7 (+/- 1.1). CBC and evaluation of clinical response ware done at every visit, and their relation was studied. Results: WBC count, and the number and the percentage (%) of neutrophils decreased significantly at 1 month and later. The number of eosinophiils did not change, but % of eosinophils increased significantly. There was a significant correlation between the decrease of neutrophil number at 1 and 2 months and the clinical response at 6 months. There was similar relationship between % increase of eosinophils and clinical response. If cut off points were set at more than 1000 decrease of neutrophils or increase in % eosinophils at 1 or 2 monoths, positive predictive value for clinical remission at 6 months was between 80 – 85 %. Conclusions: Changes in CBC in initial phase seem to be a

predictor of clinical response at 6 months.

W44-1

Safety and Efficacy of Open-label, 24-week Treatment with Subcutaneous Abatacept Following Double-blind, 24-week Treatment with Subcutaneous or Intravenous Abatacept in Japanese Rheumatoid Arthritis Patients with Inadequate Response to Methotrexate

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Conflict of interest: None

[Objectives] To assess the safety and efficacy Abatacept (ABA) by subcutaneous (SC) administration. [Methods] Patients with active RA and MTX-IR were initially randomized into two groups (1:1) during the double blind (DB) period, and subjected to SC (125mg) or IV (10mg/kg) for 24 weeks. All patients who underwent open-label extension (OLE) were treated by SC. [Results] During the DB, 118 patients were randomized and treated (59 in each group), of whom 112 (56 from each group) who entered the OLE completed the first 24 weeks. Baseline characteristics of the 112 patients at entry of theDB were similar between those who were treated consistently with SC treatment (SC group) and those who were switched from IV to SC administration (Switch group). The frequencies of adverse events were comparable between the SC and Switch groups (82.1% and 83.9%, respectively). Infections and infestations were reported in 45.5%. SC injection site reactions occurred in 0.9%. At week 24, ACR20, 50, and 70 were respectively 87.5%, 66.1%, and 51.8% in the SC group, and 94.5%, 74.5%, and 49.1% in the Switch group. DAS28-CRP remission in both groups were also maintained throughout the OLE. [Conclusions] In this study, safety during the OLE was comparable between the two groups and efficacy was maintained.

W44-2

Clinical outcomes of patients after switching to Abatacept in the observation period of 52 weeks. -TNF inhibitor vs Anti IL-6R Antibody-

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Conflict of interest: None

【Objective】To examine the efficacy and drug retention rates of abatacept (ABT) in the rheumatoid arthritis (RA) patients with previous biologics histories.【Methods】156 RA patients treated with ABT for longer than 52 weeks were included, from the 282 patients with ABT therapy in the Tsurumai Biologic Communication (TBC), which is the multicenter registry for RA patients taking biologics. They were divided into three groups : Bio-naïve, Switching from TNF inhibitor and Switching from anti-IL-6R antibody. The changes of CDAI, SDAI, TJC, SJC, VAS, ESR, CRP, MMP3 and RF were compared between each group at 0, 4, 12, 24and 52weeks. Furthermore, we compared the retention rates and safeties.【Results】ABT survival rates at 52 weeks of Bio-naïve, Switching from TNF inhibitor and Switching from anti-IL-6R antibody were 77.5, 70.1, and 68.7%, respectively. Both switching groups showed significant improvement in DAS28CRP, CDAI and SDAI at 52 weeks.【Conclusion】ABT showed appropriate efficacy and survival rate in the patients with switching from anti-TNF and anti-IL-6R antibody at 52 weeks.

W44-3

Abatacept Biologic-free Remission Study in Established Rheumatoid Arthritis Patients - the ORION study

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Conflict of interest: Yes

[Objectives] To evaluate the efficacy and safety of Abatacept (ABA) treatment restart post biologic-free remission. [Methods] ORION is a multi-center, non-randomized, 52 weeks (wks), prospective observational study of 51 rheumatoid arthritis (RA) patients with DAS28-CRP<2.3 at the end of a Japanese phase III study. ABA was continued or discontinued at patients' discretion and restarted during follow-up in case of disease flare (DAS28-CRP>2.7 at 2 consecutive visits) or upon doctor's order. The discontinuation group was tested with an anti-ABA antibody. [Results] Continuation and discontinuation groups included 17 and 34 patients, respectively. Of the latter, 9 restarted ABA. Mean age, disease duration, and DAS28-CRP at entry were 61.5±9.20, 7.56± 7.74, and 1.71±0.31 years, respectively. The mean period between discontinuation and restart was 149.6±34.5 days. DAS28-CRP at restart, 12, and 24 wks after restart were 5.02±1.13, 3.68±1.63, and 3.69±1.70, respectively. Two patients had DAS28-CRP<2.3 24 wks after restart, and 1 showed acute upper respiratory inflammation. Of 26 patients, 4 were anti-ABA antibody-positive at discontinuation, 2 at restart, and none 24 wks after. [Conclusion] The ORION study shows the efficacy and safety of ABA treatment restart after biologic-free remission.

W44-4

Long-term Clinical Efficacy and Safety of Abatacept in Japanese Rheumatoid Arthritis Patients

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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] 156 RA patients treated with ABT for longer than 52 weeks were included, from the 280 patients with ABT therapy in the Tsurumai Biologic Communication Registry (TBCR). We retrospectively reviewed the clinical data. [Results] Mean age was 63.4 years and mean disease duration was 11.6 years. 93 patients (60%) were taking concomitant methotrexate. 71 patients were biologics naïve and 85 patients had previous biologics history. Mean DAS28ESR before abatacept therapy was 5.2, mean CDAI was 23.3, and SDAI was 25.7. Drug retention rate was 76.3% 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 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.

W44-5

Clinical Efficacy of Abatacept in Rheumatoid Arthritis Patients with High Disease Activity

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Conflict of interest: None

[Objectives] Abatacept (ABT), a selective T-cell co-stimulation modulator, is a new biologic drug for rheumatoid arthritis (RA) patients. Although Japanese post marketing surveillance and some registry studies have been demonstrating the clinical efficacy of ABT, some people still believe that ABT has only insufficient therapeutic power in the active RA patients. [Methods] RA patients with high disease activity (DAS28CRP > 4.1) at baseline treated with ABT (n=90) or adalimumab (ADA, n=118) for longer than 52 weeks were included in this retrospective study, from the patients in the Tsurumai Biologic Communication Registry (TBCR). LOCF method was used for statistical analysis. [Results] Mean age was 63.9/ 57.4 (ABT/ ADA, p<0.01), proportion of patients with concomitant MTX was 59/ 77% (p<0.01), and proportion of bio-naïve patients was 42/ 67% (p<0.01). Mean DAS28CRP at baseline was 5.3/ 5.4. Both groups showed significantly decreased DAS28 value at 4 weeks (4.5/ 4.0), 24 weeks (4.0/ 3.6), and 52 weeks (3.8/3.5). [Conclusion] ABT demonstrated almost equivalent clinical efficacy compared to ADA in the patients with quite high disease activity. ABT would be a good first-choice biological treatment option even in the active RA patients.

W44-6

Analyzing of efficacy of low dose administration of abatacept

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Conflict of interest: None

Objective: We analyzed whether low dose of abatacept (ABT) therapy respond to RA patients. We defined low dose ABT therapy that administrated 250mg/body ABT therapy. Method: 9 (1 male/8 female) of RA patients treated with low dose ABT and 10 patients (all female) with normal dose of ABT at our clinics. RA activities were evaluated by CDAI. Result: 5 patients 50%) achieved remission with normal dose of ABT, however only one patient (11%) achieved remission with low dose of ABT. 3 of the 10 patients treated with low dose ABT. It took for 5.4 months to achieve remission in normal patient group and 7 months in low dose ABT group. After increased to normal dose in non-remission 8 patients with low dose ABT initial therapy group, all 8 patients had improved in CDAI. Adverse effects occurred in one patient (worsened of interstitial lung disease). Conclusion: It is suggest that low dose ABT is useful in few patients and increasing ABT to normal dose is effective to achieve remission in non-remission RA patients with low dose ABT.

W45-1

Analysis of rheumatoid arthritis patients who were treated with abatacept with rapid effectiveness from multicenter registry system (TBC)

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Conflict of interest: None

[Objectives] To analyze the patients' characteristics of RA patients who are treated with abatacept (ABT) with rapid effectiveness. [Methods] A multicenter registry database (TBC) was used in this study. This study utilized RA patients who continued ABT for 24 weeks and in whom DAS28-CRP was over 3.2 at initiation of ABT and below 3.2 at 24 weeks. Patients in whom improvement rate of DAS28-CRP (delta DAS28-CRP from 0w to 4w/delta DAS28-CRP from 0w to 24w) is over 50 % are called rapid effectiveness group (RG, n=35) and patients below 50% are called slow effectiveness group (SG, n=38). Patients' characteristics were compared between the two groups. [Results] Mean DAS28-CRP were 4.69(0w)3.03(4w)2.79(12w)2.43(24w) in RG and 4.58(0w)4.

10(4w)3.24(12w)2.45(24w) in SG. There was a significant difference between the two groups at 4w and 12w. The rate of bio naive was 77.1% in RG and 55.3% in SG (p=0.049). The rate of concomitant MTX was 62.9% in RG and 39.5% in SG (p=0.046). Serum IgG value at initiation of ABT was 1737mg/dL in RG and 1420mg/dL in SG (p=0.008). [Conclusion] Previous biologics may affects immunological condition in patients with RA and that may result in the differences in effectiveness pattern of ABT. Serum IgG may be a good predictive marker of rapid effectiveness.

W45-2

Clinical, functional and structural effectiveness of Abatacept (ABT), comparing the group of patients with different backgrounds

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Conflict of interest: None

[Objectives] Clinical, functional and structural effectiveness of Abatacept (ABT), comparing the group of patients with different backgrounds. [Methods] Thirty RA patients who received ABT from October 2010 to September 2011 were evaluated with regard to DAS28, CDAI and mHAQ for 52 weeks.We compared the groups of which the patients were divided into MTX combination: 13, or non-combination: 17, the stages,the DAS28 scores at the beginning, and the previous biological agents. We have also assessed X ray at 52 weeks. [Results] DAS28 and SDAI were significantly reduced in all groups, whilst the combination with MTX demonstrated slightly better efficacy than non-MTX combination. Stage I and II were better than III and IV. High disease activity group was better than low disease activity. Bio naïve patients had almost same improvement as the switching patients. mHAQ was not significantly decreased in most patients. However Stage I II group and MTX combination group showed slightly improving mHAQ trend. [Conclusion] There were higher efficacy observed in the patients with high disease activity, MTX combination and Stage I II than the other patients.ABT can be expected for not only clinical effectiveness but also structural improvement.

W45-3

Clinical and radiographic outcomes of abatacept therapy for patients with rheumatoid arthritis –Analysis using RA database of multi-center study group-

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Conflict of interest: None

[Objectives] To evaluate the clinical and radiographic efficacies of abatacept for RA patients. [Methods] Ninety one RA patients treated by abatacept were extracted from FIT (Fukui, Ishikawa, Toyama)-RA database of multi-center study group in Hokuriku area. We evaluated the retention rate of abatacept treatment, disease activity using DAS28-CRP and EULAR response at 6 months. In addition, we assessed ⊿mTSS of 34 patients who were observed at 1 year after abatacept treatment. [Results] Twelve patients withdrew from abatacept treatment before 6 months. Ten patients were judged as primary failure and 2 patients suffered from adverse events. The retention rate at 6 month was 86.8%. Using EULAR criteria, 31.8% of patients showed DAS remission after 6 months. Average ⊿mTSS at 1 year after treatment was 0.94 and 61.8% of the patients showed 0.5 or below in ⊿mTSS. [Conclusion] Abatacept treatment has suppressive effect on disease activity and radiographic progression in patients with RA.

W45-4

Comparisons of clinical efficacy of abatacept between Bio-naïve and Bio-switch patients in the TBC registry

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Conflict of interest: None

[Objectives] Clinical trials reported the outcome of abatacept (ABT) therapy after 24 weeks from initiation, but still uncertain in daily practice. We studied the clinical efficacy and retention rate of ABT for 52 weeks. [Methods] 156 RA patients treated with ABT for longer than 52 weeks were included, from the 282 is the multicenter registry for RA patients taking biologics. Disease activities were evaluated by using DAS28ESR, DAS28CRP, SDAI, and CDAI in Bio-naïve and Bio-switch group. Furthermore, EULAR response criteria and drug retention rate at 52 weeks were evaluated. [Results] Disease activities were significantly decreased at 4 weeks in both groups, and further decreasing were observed continuously. The clinical efficacy was superior in naïve group. At 52 weeks, naïve group showed 71.2% of EULAR response rate (good 32.7%, moderate 38.5%), while 47.2% in switch group (good 9.7%, moderate 37.5%). Drug retention rate at 52 weeks was 84.3% in naïve group and 73.2% in switch group. [Conclusion] Clinical trials demonstrated that the clinical efficacy of ABT is maintained between 6 months and 1 year, and ABT shows significant efficacy in both Bio-naïve and -switch patients. Our data suggest that ABT therapy shows sustained efficacy in daily practice even after 24 weeks from initiation.

W45-5

Evaluation of the efficacy of the abatacept in 37 patients with rheumatoid arthritis in clinical practice

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Conflict of interest: Yes

[Objectives] We aimed to clarify the efficacy of abatacept (ABT) in patients with rheumatoid arthritis (RA) in the clinical practice. [Methods] Thirty-seven patients who had ABT treatment were included. Of those 19 (51.4%) were received methotrexate

(MTX) and 13 (35.1%) were bio-naïve. RA disease activity was evaluated by DAS28-CRP, SDAI and CDAI at the baseline and at week 24. [Results] 1) DAS28, SDAI and CDAI were significantly decreased at week 24 (DAS28 4.14±1.06 to 2.86±0.89, SDAI 20.20±10.08 to 9.87±7.07, CDAI 18.59±9.88 to 9.02+6.83, $p<0.01$). 2) Remission and low disease activity were achieved in 2 and 7 patients evaluated by DAS28, 4 and 16 by SDAI and 4 and 16 by CDAI, respectively. 3) There was no significant difference of disease activity at week 24 between MTX combination group and non-MTX combination group (DAS28 2.76±0.82 vs. 2.97±0.99, SDAI 9.31±6.91 vs. 10.50±7.41, CDAI 8.57±6.76 vs. 9.52±7.08). 4) There was no significant difference of disease activity at week 24 between biologics bio-naïve group and bio-switch group (DAS28 2.79±0.90 vs. 2.79±0.76, SDAI 9.20±6.30 vs. 10.25±7.58, CDAI 8.44±5.85 vs. 9.35±7.43). [Conclusion] ABT was effective in RA patients in the clinical practice. The ABT efficacy might not be affected by combination with MTX or former biologic treatments.

W45-6

Assessment of abatacept in rheumatoid arthritis: outcome of multicenter study during 1-year follow-up

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Conflict of interest: None

[Objectives] To assess the usefulness of abatacept at 5 participating institutes. [Methods] Improvements in DAS28, SDAI, and HAQ and treatment adherence during 1-year follow-up period were evaluated in 57 patients. [Results] Average age was 60.1 years and average disease duration was 10.6 years. There were 23 patients in the bio-naïve group, 34 in the switch group, 38 in the MTX-combination group, and 19 in the non-combination group. DAS28ESR improved from 5.09 before administration to 4.04 after 12 months. SDAI remission was achieved in 17.5% after 12 months. SDAI remission was achieved in 30.4% after 12 months in the bio-naïve group and 11.8% in the switch group, indicating significant improvement of disease activity in the bio-naïve group. There was no difference in improvement between the MTX-combination and non-combination groups. HAQ was 1.08 on average before administration but improved to 0.93 after 12 months. Treatment was discontinued in 7 patients including 5 with inadequate effect and 2 with drug-induced hepatopathy. [Conclusion] Improvement of SDAI in bio-naïve patients was rapid. Administration was shown to be relatively safe and 1-year adherence was good. The suppressive effect on joint destruction will also be assessed in the future.

W46-1

Association analysis of *UBE2L3* and *TNIP1* polymorphisms in ANCA-associated vasculitis

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Conflict of interest: None

[Objectives] *UBE2L3* and *TNIP1*, both involved in the NF-κB pathway, were reported to be associated with systemic lupus erythematosus (SLE). In this study, we examined whether *UBE2L3* and *TNIP1* are associated with ANCA-associated vasculitis (AAV). [Methods] A case-control association study was performed in 216 Japanese patients and 510 healthy controls. [Results] *UBE2L3* rs131654T allele was significantly associated with MPO-ANCA-associated vasculitis (MPO-ANCA) (P=0.031, odds ratio [OR] 1.50) and microscopic polyangiitis (MPA) (P=0.012, OR 1.66) under the recessive model, and also under the allele model (P=0.019, OR 1.34; P=0.025, OR 1.36, respectively), when compared with healthy controls. *TNIP1* rs7708392 did not show significant association. However, when both genotypes were examined in combination, the association of *UBE2L3* rs131654T/T became more striking when *TNIP1* rs7708392C/C genotype was also present both in MPO-ANCA (P=0.0087, OR 2.06) and MPA (P=0.0041, OR 2.33, while significant association was not observed in individuals having rs7708392 C/G or G/G genotypes. [Conclusion] These results suggested that *UBE2L3* is a shared susceptibility gene to SLE and MPA/MPO-ANCA positive vasculitis, and *TNIP1* might have additive contribution to that of *UBE2L3*.

W46-2

Association analysis of *STAT4* and *IRF5* polymorphisms in ANCA-associated vasculitis

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Conflict of interest: None

【Objective】 Susceptibility genes are substantially shared by multiple autoimmune diseases. Here we investigated whether *STAT4* and *IRF5* polymorphisms associated with multiple autoimmune diseases including systemic lupus erythematosus (SLE), rheumatoid arthritis (RA) and systemic sclerosis (SSc) are also associated with ANCA-associated vasculitis (AAV). 【Methods】 A case-control association study was performed with 201 AAV and 510 healthy controls. *STAT4* rs7574865 and *IRF5* rs10954213, rs2280714 were genotyped using TaqMan allele discrimination as-

say and direct sequencing. 【Results】 *STAT4* rs7574865T/T was significantly increased in MPO-ANCA positive patients *(P*=0.0088, odds ratio [OR]:1.88). Unexpectedly, *IRF5* rs10954213A, the risk allele for SSc and SLE, was significantly decreased in MPA (*P*=0.042, OR 0.76) and in MPO-ANCA positive patients (*P*=0.041, OR 0.78). The carrier frequency of the A allele was also significantly decreased in MPA (*P*=0.049, OR 0.67) and in MPO-ANCA positive patients (*P*=0.031, OR 0.67). 【Conclusion】 *STAT4* risk genotype was found to be shared between MPO-ANCA positive vasculitis and other autoimmune diseases. On the other hand, the genetic effect of *IRF5* rs10954213A appeared to be opposite between MPA, MPO-ANCA positive vasculitis and other autoimmune diseases.

W46-3

Efficacy and safety of induction of remission with pulsed cyclophosphamide according to "CYCLOPS" in Japanese patients with Antineutrophil Cytoplasmic Antibody–Associated Vasculitis

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Conflict of interest: None

[Objective] To investigate efficacy and safety of European protocol of pulse cyclophosphamide (pCY) [Method] We retrospectively investigated 7 Japanese patients with ANCA associated vasculitis (AAV) with ANCA positivity, 4 with granulomatosis with polyangiitis and 3 with microscopic vasculitis, treated with pCY from July 2009. Administration of pCY and prednisolone were determined, to a maximum extent, according to the protocol of CYCLOPS (Ann Intern Med;150:670-). Remission, time to remission, adverse events were assessed. Disease activity was assessed every 6 wks until Week 72 by using Birmingham Vasculitis Activity Score (BVAS), in which new or worse signs of disease activity were scored, and remission was defined as BVAS≦1. [Results] The average ± SD of pCY and follow up were 8.3±3.2 and 64±39 (wks), respectively. Remission was achieved in 7/7 within a median of 12 wks (6 - 36). Leukopenia, oral candidaris, upper airway infection, nontuberculous mycobacterial infection and lung cancer were observed in 0, 5, 1, 1, 1, respectively. Two stopped pCY due to adverse events of lung cancer at W20 and nontuberculous mycobacterial infection at W14. [Conclusion] All of 7 Japanese patients with AAV achieved remission with pCY according to CYCLOPS, while two experienced serious adverse events.

W46-4

A comprehensive and sequential analysis of serum cytokine levels in a patient with granulomatosis with polyangiitis (Wegener's) treated with rituximab

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Conflict of interest: Yes

[Objectives] Rituximab (RTX) has been reported to be effective for granulomatosis with polyangiitis (GPA). To achieve a long-time remission after treatment with RTX, it is desirable that the therapy protocol is based on serum biomarkers reflecting the disease activity or drug efficacy. In this study, we have performed a comprehensive and sequential analysis of serum cytokine levels in a patient with GPA treated with RTX. [Methods] RTX (0.5g once weekly for 4 weeks) was administered to a 34-year-old woman with GPA, and her disease led to remission. Serum samples were divided into two groups: inactive stage (from pretreatment to 12 weeks after treatment, n=7) and active stage (from 16 to 42 weeks after treatment, n=7). Serum levels of 26 types of cytokines were measured by a bead-based multiplex assay. [Results] Serum levels of IL-4, IL-6, IL-15, eotaxin, G-CSF, IP-10 or TNFα were found to be higher (>4 times) in active stage in the patient compared with those of healthy controls. Among these cytokines, levels of IL-4, IL-6, IL-15 or G-CSF significantly ($p<0.05$) decreased in the stage of low disease activity. [Conclusion] This pilot study may contribute to the understanding of the pathophysiology and immunological reaction in vivo after administration of RTX in patients with GPA.

W46-5

Efficacy and Safety of Induction Therapy with Pulse Cyclophosphamide for ANCA-Associated Vasculitis

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Conflict of interest: None

[Objectives] To investigate the efficacy and safety of induction therapy with pulse cyclophosphamide for ANCA-associated vasculitis. **[Methods]** We included all patients newly diagnosed with Glanulomatosis with polyangitis (GPA) or Microscopic polyangitis (MPA) in our department from July 2009 to July 2012 who were treated with CYCLOPS (Ann Intern Med 2009;150:670). We investigated retrospectively initial remission rate, time to remission, remission rate at 6 months, and adverse events. Disease activity was assessed by using BVAS (Ann Rheum Dis 2009;68:1827), and remission was defined as BVAS=0. **[Results]** A total of 6 patients (GPA5, MPA1) were included. All of them had renal involvement (positive renal biopsy, 2+hematuria and 2+proteinuria, or proteinuria>1g/day). Mean age (±SD) was 66±11 years, and baseline BVAS was 20.8±4.8. Total follow-up duration was 15.9±17.5 months. Intial remission rate was 100% (6/6), and time to remission was 1.4±0.1months. Remisson rate at 6 monts was 100% (4/4). PSL dose at 6 months was ≤ 10mg in all patients. One episode of mild leucopenia, and two episodes of infection (acute appendicitis, acute upper respiratory infection) were recorded as adverse events. **[Conclusion]** CYCLOPS induced remission at 6 months in all patients, and demonstrated favorable safety.

W46-6

Analysis of clinical characteristics between elderly patients and younger patients with Large vessel vasculitis (LVV)

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Conflict of interest: None

[Objectives] To clarify the clinical differences in age of onset in patients with large vessel vasculitis (LVV). [Methods] Twenty one patients with new-onset LVV, who were admitted to our hospital from Feb 1999 to Oct 2012, were enrolled. We selected patients with findings of diagnostic imaging in Takayasu arteritis guidelines, and with the elevation of acute-phase reactants. We divided them in two groups with respect to the age of 40, and analyzed sex,

symptoms, hematological findings, image findings, therapies, and complications, retrospectively. [Results]1) Mean age of onset was 40.6 ± 19.9, and sex was 4 males and 17 females. 2) Elderly group (EG)/Younger group (YG): 10 cases/11 cases, Mean age of EG and YG was 59.4±12.8 and 24.1±5.6, respectively. 3) EG had fewer symptoms and physical findings associated with vascular stenosis compared to YG (50.0% vs 100.0%, P=0.01). 4) In the image findings, aortic calcification was more common in EG (90.0% vs 9.1%, P<0.01). 5) Immunosuppressants were used less frequently in EG (10.0% vs 54.5%, P=0.04), but EG less often relapsed (0.0% vs 45.5%, P=0.02). [Conclusion] Although it was often difficult to diagnose in EG who had only a few typical clinical finding, the response to treatment was better without concomitant use of immunosuppressants.

W47-1

Urinary T cells and macrophages reflect the disease activity and renal function in ANCA-associated vasculitis

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Conflict of interest: None

[Objectives] To examine the utility of urinary immune cell analysis in ANCA-associated vasculitis (AAV). [Methods] Thirty patients with AAV, who had been referred to Niigata University Hospital between 2004 and 2012, were recruited. The patients were divided into 2 groups according to their renal functions (renal involvement group (RI group, n=24) and non-renal ivolvement group (non-RI group, n=6)). The numbers of urinary CD3-positive cells (T cells) and CD14-positive cells (macrophages), laboratory markers, and BVAS, were examined in each subject. The data were also analyzed by Spearman's rank correlation coefficient to determine the relationship with urinary T cells and macrophages. [Results] The total number of urinary T cells and macrophages were significantly elevated (>120/ml of urine, Sakatsume et al. J Am Soc Nephrol, 2001) in all patients in RI group and 5 patients in non-RI group. The number of urinary T cells was positively correlated with serum ANCA (r=0.41, p=0.02) and BVAS (r=0.38, p=0.038), while the number of urinary macrophages was positively correlated with serum Cr (r=0.38, p=0.038) and negatively correlated with eGFR (r=-0.38, p=0.03). [Conclusion] These results indicated the usefulness of urinary immune cell analysis in the assessment of AAV.

W47-2

Clinical characteristics of interstitial pneumonia complicated by multiple pulmonary cysts in patients with microscopic polyangitis (MPA)

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Conflict of interest: None

[Objectives] MPA is known to cause various lung diseases, as well, some patients develop pulmonary parenchymal destruction. Here, we investigate the clinical characteristics of IP complicated by pulmonary cysts in patients with MPA. [Methods] We investigate in- and out- patients with MPA who visited our hospital. The patients associated with multiple pulmonary cysts were retrospectively assessed. [Results] The patients were 7 men and one woman. Mean age of onset was 65 years. 6 patients were smoker. (mean Brinkman Index was 430) Mean titer of MPO-ANCA at onset was 301 U/ml. The patients treated by the immunosuppressive therapy showed negative for MPO-ANCA, nevertheless, pulmonary involvement with cystic lesions was progressive. 4 patients received immunosuppressants in addition to steroid, however, two resulted in respiratory failure and the home oxygen therapy was induced. Moreover, one died from pulmonary dysfunction. Despite the severe IP, these patients indicated a low titer of KL-6 and LDH. Three needed a hospitalization for pneumonia that was difficult to diagnose bacterial infection or exacerbation of MPA.. [Conclusion] We suggest that some cases are associated with pulmonary cysts formation in IP with MPA, furthermore, it coluld be progressive in MPO-ANCA negative patients.

W47-3

Clinical characteristics of kidney limited MPO-ANCA-associated vasculitis

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Conflict of interest: None

[Objectives] We investigated clinical characteristics of kidney limited MPO-ANCA-associated vasculitis. [Methods] 11patients with kidney limited vasculitis (Group K) and 15patients with systemic vasculitis (Group S), were included in this study. We analysed the clinical features and laboratory findings of the two groups retrospectively. [Results] There were no significant differences of ANCA titer, serum creatinine (sCr) and proteinuria between two groups, however, CRP was significantly lower in Group K(p<0.05: 1.75±2.92 *vs* 9.94±7.85mg/dL). Hemodialysis was less necessary in Group K, for sever renal injury(9% *vs*. 40%). During first 6 months, there were no significant differences of ANCA titer, sCr and CRP, between two groups. While, over the duration of follow-up (the median time was 30.7 months), death and/or ESRD rates were lower in Group K than Group S (death; 9% *vs* 20%, ESRD; 9% *vs* 33%, death and ESRD; 18% *vs* 40%). [Conclusion] Our study suggests that kidney limited MPO-ANCA-associated vasculitis might differ from systemic vasculitis in pathogenesis at onset, resulting in better prognosis for long-time.

W47-4

The histopathological analysis of kidney in the early phase of microscopic polyangiitis

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Conflict of interest: None

[Objectives] To determine the pathology in the kidney in the early phase of microscopic polyangiitis (MPA), we performed the renal biopsy in patients with MPO-ANCA. [Methods] 3 patients fulfilled the Japanese criteria 1998 in our hospital were investigated retrospectively with their charts and analyzed the clinical features and pathological changes in the kidney. [Results] In all three cases, the finding of crescentic glomerulonephritis was detected under the light and/or the electronic microscope, although the findings of their urine examination and deterioration of renal function were trivial. There were no significant deposition of immunoglobu-

lin and compliment in glomeruli in the immunofluorescence analysis. [Conclusion] In the early phase of MPA, the renal involvement could be progressed, renal biopsy should be important for definite diagnosis and appropriate assessment.

W47-5

Factors associated with physical function in elderly patients with ANCA-associated vasculitis

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Conflict of interest: None

[Objectives] To assess physical function in older patients newly diagnosed with ANCA associated vasculitis (AAV). [Methods] Basic activities of daily living (BADL) were retrospectively studied in 35 patients older than 60 years clinically diagnosed with AAV and who received remission induction therapy. [Results] Mean age was 77. Mean BVAS was 15±7.5. 71.4% were MPO-ANCA positive. 13 patients were categorized as early systemic, 19 as generalized, 1 as severe, and 2 as refractory. We defined early systemic disease as mild form, and others as severe form. In each form, initial doses of PSL were 0.61mg/kg and 0.89mg/kg, the rates of using immunosuppressants were 0% and 63.6%, and BADL on admission were 16.4±5.81 and 16.0±4.19 (p=0.45), respectively. BADL on admission did not correlate with either BVAS or age. BADL after remission induction were 8.8±7.9 in patients with infection, and 17.6±4.0 in those without infection (p<0.01). Also, it had a significant correlation with BVAS (p<0.01), but no associations were seen with cumulative dose of PSL or immunosuppressive therapy. [Conclusion] Physical function was not associated with disease severity or age at the onset of AAV, but physical disability after remission induction correlated with BVAS at baseline and the complicated infections.

W47-6

Cohort Study of Remission Induction Therapy in Japanese Patients with ANCA-associated Vasculitis

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Conflict of interest: None

[Objectives] To investigate the effectiveness of remission induction therapy currently performed for ANCA-associated vasculitides (AAV) in Japan. [Methods] Remission and survival rate were evaluated in 156 AAV patients enrolled in the RemIT-JAV study undertaken by the MHLW intractable vasculitis research group. [Results] Finally, 14 patients were classified as having Churg-Srauss syndrome (CSS), 33 patients were granulomatosis with polyangiitis (GPA), 78 patients were microscopic polyangiitis (MPA), 16 patients were pulmonary limited vasculitis and 15 patients were unclassified. Almost patients reached remission and no difference was found between severity and treatment. No CSS patients, 2 GPA patients and 17 MPA patients were died in this period. In MPA patients, survival rate is different among disease severity statistically (P<.005, log-rank test). Concomitant use of cyclophosphamide (CY) tended to be more beneficial for survival in MPA patients but not significant. Multivariate COX-hazards analysis identified smoking history (hazard ratio (HR)=5.92), pulmonary co-morbidity (HR=8.90), cutaneous symptoms(HR=2.11), and chest symptoms (HR=1.71) as risk factors for survival. [Conclusion] In MPA patients, total evaluation of pulmonary damage may be important for their survival.

W48-1

Clinical characteristics of interstitial lung disease in patients with ANCA associated vasculitis

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Conflict of interest: None

To clarify the clinical characteristics of interstitial lung disease (ILD) in patients with ANCA associated vasculitis (AAV), we investigated clinical symptoms and laboratory data of 68 patients in our hospital. The diagnosis of AAV by Watts's algorithm revealed MPA in47 patients, EGPA in 13 and GPA in 8, respectively. The patient's median ages were 64.6 years old and median disease durations were 2.1 months. Laboratory data revealed positive test for anti MPO-ANCA and PR3-ANCA in 56 and 7 patients, respectively. All patients received oral corticosteroids. Twenty-three patients were treated with pulsed methylprednisolone, 33 patients with immunosuppressive drugs. Forty-three patients showed ILD. Although there is no significant difference of MPO-ANCA between ILD patients and non-ILD patients, BVAS score and RF positivity are significantly higher in ILD patients. Imaging findings by HRCT revealed UIP pattern in 25 patients and non-UIP pattern in 18 patients. During the follow up period for 4.3 years, 6 patients of UIP and 2 patients of Not UIP were died, respectively. Our data showed 58% of patients showed UIP pattern on HRCT. Because the prognosis of UIP patients was usually poor, it is important for a detailed examination of ILD with HRCT in patients with AAV.

W48-2

Clinical features of relapsing patients with microscopic polyangiitis(MPA)

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Conflict of interest: None

[Objectives] To assess the clinical features of relapsing patients with MPA after the initial therapy. [Methods] We investigated 39 patients (16 males and 23 females) with MPA, who were admitted to our hospital from Jan.2005 to Oct.2012. All patients were initially treated with steroid and immunosuppressive drugs. We compare the clinical features between remitted and relapsing patients. [Results] There were 33 patients with remission (group A) and 6 patients with recurrence (group B). BVAS and the incidences of rapidly progressive glomerulonephritis (RPGN) and interstitial pneumonia (IP) in Group B were higher than that in Group A (p=0.0027,p=0.0470,p=0.0077,respectively). [Conclusion] It is needed to pay attention to the recurrence in patients with highly active disease, RPGN and IP.

W48-3

Retrospective investigation of 101 patients with cutaneous polyarteritis nodosa at Department of Dermatology, St. Marianna University School of Medicine

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Conflict of interest: None

[Objectives] Cutaneous polyarteritis nodosa (CPN) is a necrotizing vasculitis of medium-sized arteries within the skin, without the involvement of internal organs. We investigated clinical and serological findings in patients with CPN. [Methods] We retrospectively investigated 101 patients with CPN seen at our department between 2003 and 2012. A diagnosis of CPN requires the presence of histological necrotizing vasculitis in the lower dermis and the subcutaneous fat, based on close biopsies, including consecutively deeper sections. [Results] Patients were 30 men and 71 women. Subcutaneous nodules on the lower extremities were observed in all of our CPN patients. This is optimal skin manifestation for skin biopsy. We found 84 with livedo racemosa, 67 with purpura, 49 with skin ulcers, 33 with inflammatory plaques, and 32 with sereve leg edema. Four patients had undergone surgery for hydrarthrosis by orthopedists before our diagnosis. We found 67 with arthralgia and 45 with myalgia. Mononeuritis multiplex was prevalent in 57 of the 101 patients. We treated 89 with anticoagulants including warfarin and 72 with prednisolone. [Conclusion] We propose cutaneous patterns in patients with CPN could be useful for clinicians faced with similar patients.

W48-4

Fieldwork research of Allergic Granuromatosis and angiitis in Japan

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Conflict of interest: None

[Objectives] Allergic granulomatous angitis (AGA) is a rare disease showing necrotizing granuloma vasculitis with specific clinical features. Characteristics of AGA in Japan is still elusive. We analyzed the patients' data and examined whether ANCA is related to specific clinical features or could be predictive factor of the condition and course of disease. [Methods] The AGA clinical investigation form (paper for the public support enrollment) of patients who had been newly diagnosed as AGA in Tokyo in 2010 were anonymized and used as a data base, and statistical analysis was undergone. We examined clinical data of 13 ANCA positive patients and 16 ANCA negative patients and determined whether the presence of ANCA had affected the clinical findings, choices and outcomes of treatment, and labo test. [Results] Patients with ANCA showed significantly higher rate of arthralgia but less eosinophils. They tended to show fever and kidney disorder. Patients without ANCA showed more skin lesion. [Conclusion] It is supposed that AGA patients with ANCA show different clinical features from ANCA negative patients. Eosinophilia and ANCA are the factors each of which can cause the disease alone.It is suggested that the cause of AGA is the result of complex interaction of those two factors.

W48-5

Gene expression profiles by RNA-seq analysis in an allergic granulomatous-angitis (AGA) patient before and after high-dose immunoglobulin treatment

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Conflict of interest: None

[Objectives] High-dose immunoglobulin treatment for allergic granulomatous angiitis (AGA) is effective, but the mechanism of its efficacy is still unknown. To clarify the mechanism of its efficacy, we examined the gene expression profile before and after treatment using RNA-seq analysis. [Methods] A case is 34-year-old AGA patient, who showed the paresthesia of lower limb and the weakness of left hand. A laboratory findings showed hypereosinophilia and positive P-ANCA (328.0 U/ml). The infiltration of eosinophil and vasculitis findings were confirmed. High-dose immunoglobulin treatment was remarkably effective. RNA sample were obtained from PBMC. We performed RNA-seq experiment using the ABI SOLiD 5500 system.Samples of other collagen diseases (RA2, SLE1, IgG4-related diseases 1) were used as control. [Results] We were able to evaluate the quantity of 24,366 gene expression. We focused the 1500 gene, which were statistically tested by Fisher's exact test. Finally, we found that PAX5, P2RX5, KCTD11, PAFAH1B3, and DBN1 significantly changed, which belong to GO: 0007399: nervous system development. [Conclusion] Our results suggests that RNA-seq is a powerful method and high-dose immunoglobulin treatment are directly involved in the nervous system.

W49-1

Weak TCR signaling due to repeated immunization with antigen induces TCR revision and *ai*CD4 T cell: implication to Self-organized criticality theory

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Conflict of interest: None

[Objectives] Autoimmune disease theory explains that autoreactive T cells derive either from thymus-bypassed T cell or *via* break of tolerance. However, their T cell receptor (TCR) repertoirs are evidently restricted, such cannot explain wide varieties of autoantibody seen in SLE. In Self-organized criticality theory, however, autoreactive *ai*CD4 T cell (autoantibody-inducing CD4 T cell) is generated from thymus-passed non-autoreactive T cells *via de novo* TCR revion, varieties of autoantibody can be guaranteed. [Methods] Signaling molecules were western blotted and its phosphorylation was examined. [Results] After repeated immunization with staphylococcus enterotoxin B (SEB), the amount and phosphorylation of CD3ζ, ZAP70, LAT, SLP-76, PLCγ1 and NFAT1/2, but not ERK, were decreased in splenic Vβ8+CD4 T cells. CD3ζ and ZAP70 were raised after 8x immunization. Re-appearance of RAG was cancelled when stimulated with PMA and ionomycin which bypass TCR signaling. [Conclusion] Since CD4 T cell promoter region is histone-acetylated/ H3K4 methylated and open, the TCR revision after repeated immunization depends primarily on the re-expression of RAG and thus, weak TCR signaling after repeated immunization induces RAG, finally leading to TCR revi-

sion and generation of *ai*CD4 T cell.

W49-2

Serum BAFF level in patients with SLE

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Conflict of interest: None

[Objectives] B cell-activating factor of the tumor necrosis factor family (BAFF) plays a crucial role in B cell development and autoantibody production. Here we analyzed the serum level of BAFF and its clinical association in patients with SLE. [Methods] BAFF was measured by ELISA. [Results] Serum BAFF level in patients with SLE was significantly higher than in healty individuals. [Conclusion] BAFF might be useful marker for predicting diseae activity in patients with SLE.

W49-3

Analysis of interleukin-21 producing cells in peripheral blood of systemic lupus erythematosus

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Conflict of interest: None

[Objectives] Interleukin (IL)-21 is known to be extensively involved in the formation of systemic lupus erythematosus (SLE)-like manifestations in mice. Here we have shown that increased expression of IL-21 mRNA in peripheral blood mononuclear cells (PBMC) of patients with SLE, and investigated the phenotype of IL-21 producing cells. [Methods] PBMCs were obtained from patients with SLE and healthy subjects (HS) and IL-21 mRNA expression was quantified by RT-PCR (TaqMan assay). $CD4^+$ T cells were isolated from PBMCs of patients with SLE and HS, and analyzed for IL-21, IFN-γ, IL-4, and IL-17 production by flow cytometry followed by TCR stimulation. [Results] IL-21mRNA expression was higher in PBMC of SLE patients. Both in PBMCs of SLE and HS there were IL-21 producing $CD4^+$ T cells which simultaneously produce IFN-γ, IL-4, or IL-17. Further investigation is now undergoing to investigate the correlations between these cells and clinical manifestations. [Conclusion] In the peripheral blood of SLE, IL-21 expression was increased. There were distinct subtypes of IL-21 producing CD4+ T cells in terms of cytokine producing profiles.

W49-4

The role of Btk and IL-21 for the full activation of human B cells

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Conflict of interest: None

Objectives:B cells play a pivotal role in pathological processes of autoimmune diseases. Btk is well known for its importance in BCR signaling and is considered as a suitable target for treating autoimmune diseases. However, its underlying mechanisms remain elusive. **Methods:** *AICDA* (cording gene of AID crucial for somatic hypermutation and class switching) expression and IgG production were assessed using peripheral human B cells and a B cell line, BJAB. **Results:** *AICDA* expression and IgG production in human B cells were slightly induced by IL-21 alone or by BCR and/or CD40/BAFF stimulation. However, combinatorial stimulation with BCR, CD40/BAFF and IL-21 caused robust *AICDA* expression and IgG production. Addition of Btk inhibitor (ONO-A) significantly abrogated these effects. The knock-down of Btk in BJAB revealed that phospho-Stat1, but not -Stat3, in the nucleus was decreased after IL-21 stimulation. **Conclusion:** We postulate that Btk-mediated BCR and CD40/BAFF signalling, which affect phospho-Stat1 in the nucleus, is prerequisite for efficient propagation of IL-21signaling for full activation of B cells. These results also underscore the potential role of Btk in B cell-mediated pathological processes in autoimmune disease.

W49-5

Mitochondrial dysfunction, oxidative damage and imbalanced expression of antioxidant enzymes in patients with systemic lupus erythematosus

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Conflict of interest: None

[Objective] A decrease in mitochondrial (mt) DNA copy number (CN) is correlated to the decrease in mtDNA encoded ND1 peptide in SLE patients. Electron leakage from the dysfunctional mitochondria may result in formation of reactive oxygen species (ROS) and trigger a ROS-induced ROS vicious cycle. [Methods] The association of mt dysfunction, oxidative DNA damage and antioxidant capacity was analyzed in plasma & leukocytes in SLE patients and controls. [Results] SLE leukocytes expressed lower mRNA levels of mt transcription factor A (TFAM), pyruvate dehydrogenase E1 component alpha (PDHa), and mtDNA- encoded ND1. SLE plasma had a higher concentration of 8-hydroxy 2'-deoxyguanosine (8-OHdG), positively related to leukocyte mtDNA CN decrease, but a lower leukocyte mRNA of human 8-oxoguanine glycosylase 1 (hOGG1), suggesting an accumulation of oxidative DNA damage without effective repair. Except for glutathione peroxidase-1 (GPx-1), SLE-leukocyte mRNAs were found to have a lower manganese superoxide dismutase (MnSOD), glutathione peroxidase-4 (GPx-4), glutathione reductase (GSR) and catalase, suggesting a lower antioxidant capacity. [Conclusions] mt dysfunction, accumulated oxidative DNA damage and insufficient antioxidant capacity contribute to a vicious inflammatory cycle in SLE.

W49-6

Clarification of the role of FcgRIIB for autoimmune disease using the cell-specific FcgRIIB conditionalknockout mice

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Conflict of interest: None

[Objectives] Fcγ receptor IIb (FcγRIIb) is expressed not only on B cells, but also on dendritic cells (DCs) and macrophages. In the present study, we investigate the role of FcγRIIb for the development of lupus nephritis. [Methods] We established cell-type specific FcγRIIb-deficient knockout mice, and introdued *Yaa* mutation into these mice. This study is done in collaboration with Dr. Sjef Verbeek (Leiden University Medical Center). [Results] *Yaa*-carring FcγRIIb-deficient mice lacking FcγRIIb expression on whole cell types developed severe lupus nephritis. In contrast, *Yaa*-carring mice lacking FcγRIIb expression on B cells showed immune complex deposition on glomeruli, but not develop severe lupus nephritis. *Yaa*-carring mice lacking FcγRIIb expression on DCs showed no autoimmune phenotype. [Conclusion] FcγRIIb-deficiency on B cells is not enough to induce lupus nephritis in *Yaa*-carring B6 background.

W50-1

Induction of granzyme B-producing regulatory B cells in normal subjects and SLE patients

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Conflict of interest: None

[Objectives] B-cell depletion therapy underscores a role of B cells in the pathogenesis of autoimmune diseases. Recent studies identified a regulatory B cell (Breg) that exerts regulatory functions mainly via production of IL-10, however whether Bregs could function in an IL-10-independent manner remains largely elusive. In this study, we show that granzyme B (GzmB)-producing B cells function as Breg in humans, and compare the induction of this novel population in normal subjects and SLE patients. [Methods] GzmB expression in B cells was assessed using quantitative PCR and intracellular staining. Bregs were co-cultured with T cells, and proliferation and IFNg production of T cells were assessed. [Results] IL-21 strongly induced GzmB expression in normal B cells, and this induction was augmented by costimulation with BCR. Naïve B cells expressed the highest levels of GzmB. GzmB-producing Bregs inhibited proliferation and survival of T cells. Intriguingly, GzmB expression in naïve B cells was impaired in SLE patients. We are now testing the mechanisms of defective induction of GzmB-producing Bregs in SLE. [Conclusion] These findings suggest that GzmB-producing B cells represent a novel Breg subset, and that defective induction of this subset contributes to the pathogenesis of SLE.

W50-2

Elevated serum levels of progranulin in patients with SLE and dermatomyositis

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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 PGRN is associated with SLE global activity and may have a role in the pathogenesis via increased cytokine production. We investigated whether its function was specific for TLR9 and its role in autoimmune diseases. [Methods] We measured the IL-6 concentration secreted by PBMCs incubated with 1) TLR ligands in the presence or absence of rhPGRN 2) lupus sera with or without DNase treatment in the presence or absence of a neutralizing anti-PGRN antibody. Serum PGRN levels were measured by ELISA in patients with other autoimmune diseases (n=116) including dermatomyositis (DM) (n=37) and healthy controls (HCs) (n=60). [Results] rhPGRN enhances IL-6 production from human PBMCs only with CpG. Lupus sera stimulated PBMCs to produce IL-6, whereas neutralization of PGRN dramatically attenuated such IL-6 production almost as same as the degradation of DNA in patients' sera. In DM patients, serum PGRN levels were significantly higher than HCs, and were associated with interstitial pneumonia and significantly correlated with serum ferritin levels. [Conclusion] PGRN may be involved in the pathogenesis of SLE and DM partly by enhancing TLR9 signaling.

W50-3

Expression and function of IRAK-M in B cells of normal subjects and SLE patients

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Conflict of interest: None

<Objectives> Aberrant TLR signaling leads to breach of B cell tolerance, a process closely related to the development of autoimmune diseases including SLE. IRAK-M negatively regulates TLR signaling in non-B cells. In this study, we compared the expression and function of IRAK-M in B cells of normal subjects and SLE patients. <Methods> IRAK-M expression was assessed using real-time PCR and western blotting. Overexpression and knockdown vector of IRAK-M were constructed and introduced into B cells, cell survival was then evaluated using annexin staining. <Results> In the absence of stimuli, IRAK-M was exclusively expressed in naïve B cells. BCR stimulation significantly down-regulated IRAK-M expression by a calcium-dependent mechanism, while TLR stimulation up-regulated its expression in B cells. Overexpression and knockdown of IRAK-M inhibited and augmented TLR-induced survival and cytokine production in B cells, respectively. Regulation of IRAK-M expression by BCR signals was altered in SLE B cells. We are currently elucidating the molecular explanation for this phenomenon. <Conclusions> These results suggest that dysregulation of IRAK-M expression and function causes aberrant TLR signaling, leading to breach of B cell tolerance in SLE.

W50-4

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

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Conflict of interest: None

Backgrounds: In lupus T cells, lower expression of CD3ζ-chain is a prominent feature. Recently, SF2 was reported to control splicing of CD3ζ-chain. RasGRP1 is an intracellular signaling protein highly expressed in T cells that activate Ras, the upstream of MAPK pathway. We previously reported that aberrantly-spliced RasGRP1 transcripts are abundant and RasGRP1 protein levels are lower in lupus T cells. In lupus T cells, low levels of DNMT1 have been known in relation with hypomethylation of autoimmune-related genes. Aim: To investigate the expression of splicing factors in lupus T cell, and to assess the effect of downstream signal transductions. Methods: In healthy subjects, SLE and RA patients, we measured the expression of SF2, RasGRP1 and DNMT1 mRNA in T cells by Real-time PCR method. Results: The expression levels of SF2 were significantly lower in T cells from SLE patients as compared with healthy subjects (SLE vs. Healthy: p=0.016). The expression levels of SF2 were strongly correlated with properly-spliced RasGRP1 and DNMT1 (SLE: r=0.789, p<0.001 [RasGRP1]; r=0.754, p<0.001 [DNMT1], Healthy: r=0.841, p=0.018 [RasGRP1]; r=0.689, p=0.087 [DNMT1]). Conclusion: Lower levels of SF2 may play an important role also in abnormal splicing in RasGRP1 and pathogenesis of SLE.

W50-5

Cyclophosphamide Predominantly and Immediately Suppresses Plasmablasts in Patients with Systemic Lupus Erythematosus

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Conflict of interest: None

[Objectives] To clarify the effect of cyclophosphamide (CY) on systemic lupus erythematosus (SLE) *in vivo* and *in vitro*. **[Methods]** We analyzed 13 patients with recent onset or recurrent SLE. SLE patients received monthly intravenous CY (0.5 g/m^2 of BSA bolus) and oral prednisolone. Subpopulation of B cells was determined by FACS. For *in vitro* assays, CD19$^+$ B cells from normal healthy donors were cultured with CpG ODN plus IL-10/IL-2 in the presence or absence of 4-hydroperoxycyclophosphamide (4-HC), activated congener to CY. B cell proliferation, differentiation, and antibody secretion were determined. **[Results]** The frequencies of plasmablasts in active SLE patients significantly decreased when re-analyzed 2 weeks after the initiation of IVCY than those before treatment (p = 0.0002). The proliferation of the stimulated B cells were significantly inhibited by 4-HC in a dose dependent manner. The frequencies of plasmablasts were lower in the unstimulated cells and the 4-HC-treated cells than in the stimulated cells. The production of IgM and IgG in the culture supernatants were also significantly inhibited by 4-HC (p < 0.05 in all comparisons). **[Conclusion]** Administration of CY predominantly and immediately suppresses activation and viability of plasmablasts *in vivo* and *in vitro*.

W50-6

Serum phosphatidylserine-specific phospholipase A1 (PS-PLA1) identified as a novel biomarker for systemic lupus erythematosus (SLE)

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Conflict of interest: None

[Objectives] Lysophosphatidylserine (LPS) is lyso- glycerophospholipid, similar to LPA and sphingosine 1-phospahte. The purpose of the present study is to determine the serum levels of PS-PLA1 and ATX in sera from patients with SLE, and to investigate their relationship with disease activity. [Methods] Serum levels of PS-PLA1 and ATX of 34 patients with active SLE were quantified by ELISA. As for 26 patients with SLE, serum PS-PLA1 levels after treatment were also measured, and their correlation with disease activity, as evaluated by SLEDAI and BILAG index, were examined. [Results] Serum PS-PLA1 levels were higher in patients with SLE than those in disease controls, while serum levels of ATX were similar. In SLE patients, serum levels of PS-PLA1 were positively correlated with global SLE activity indices and serum IgG, but negatively correlated with C3, WBC and lymphocyte counts. Furthermore, serum PS-PLA1 decreased after treatment in SLE. [Conclusion] PS-PLA1 may be useful for evaluation of SLE. The data suggest that LPS generated from PS-PLA1 may be involved in the pathogenesis of SLE. Collaborators:Dep Clinical Laboratory, Tokyo Univ, TOSOH Corp, Molecular Cellular Biochemistry Grad Sch Pharm Sci, Tohoku Univ.

W51-1

Initial introduction of treat-to-target strategy to patients with resent onset rheumatoid arthritis is more effective than delayed introduction of strategy with more clinical and functional remission achieved for 3-years: results of the T-4 study

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Conflict of interest: None

[Objectives] To compare the clinical, radiological and functional efficacy of initial versus delayed introduction of strategy which is treat-to-target to early RA patients. [Methods] A total of 243 RA patients were randomly allocated to one of four strategy groups: routine care (R group, n=62); DAS28-driven therapy (n=60); MMP-3-driven therapy (n=60); or both DAS28- and MMP-3-driven therapy group (Twin; T group, n=61). Targets were DAS28 <2.6 and MMP-3 normalisation for T group. From 56 weeks all patients were allocated to T group, treatment was adjusted every three months if the value in question did not fall below the previously measured level. 61patinets in initial treat-to-target introduced group (T group) were compared with 62 patients in delayed treat-to-target introduced group (R group) for 3 years. [Results] Clinical (SDAI≤3.3), functional (HAQ=0) and comprehensive remission at 3 years was achieved by more patients in initial treat-to-target introduced group (48%, 79% and 34%) than in delayed group (22%; p=0.0364, 62%; p=0.0396 and 15%; p=0.0123). [Conclusion] The results suggest that initial introduction of treat-to-target strategy to patients with resent onset RA is more effective than delayed introduction of strategy.

W51-2

Reactivation of Hepatitis B Virus in Autoimmune Disease Patients Receiving Immunosuppressive Agents

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Conflict of interest: None

[Objectives] Reactivation of resolved hepatitis B in patients undergoing immunosuppressive therapy sometimes results in severe fulminant hepatitis. We evaluated the prevalence of previous infection of hepatitis B virus (HBV) in patients with autoimmune disease and the incidence of its reactivation. [Methods] We enrolled 408 patients (72 males, 336 females) with autoimmune disease, who were receiving immunosuppressants at our hospital. Patients underwent serological examination including HBsAg, anti-HBs, and anti-HBc. When HBsAg, anti-HBs and/or anti-HBc were positive, HBV-DNA was measured using a real-time polymerase chain reaction assay. The immunosuppressants included methotrexate, tacrolimus, mizoribine, prednisolone at over 30 mg/day, azathioprine, cyclosporine, cyclophosphamide and biological DMARDs. [Results] One hundred and four patients were determined as past-HBV infected and six experienced its reactivation. Prevalence of resolved HBV patients were 26.2% at our hospital, and 5.8 % of them experienced its reactivation. In most cases, entecavir was effective, but we experienced one case that addition of adefovir was required. [Conclusion] Patients with resolved hepatitis B need careful monitoring when receiving immunosuppressive agents.

W51-3

Efficacy of plasma exchange therapy for thrombotic thrombocytopenic purpura associated with collagen disease: clinical outcome for 10 years in our hospital

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Conflict of interest: None

[Objectives] Thrombotic thrombocytopenic purpura (TTP) is disease characterized by thrombotic microangiopathy and thrombocytopenia. It is fetal without any treatment, but Plasma Exchange (PE) improved the prognosis of patients suffered with TTP. Recently, pathologic mechanisms of TTP get clear from knowledge about ADAMTS13. The aim of this study is to evaluate the efficacy of PE for TTP associated with collagen disease. [Methods] We retrospectively assessed the TTP patients associated with collagen disease, who treated with PE therapy about the primary diagnosis, patient's background, laboratory data, combination therapy, number of PE and final outcome etc. for the past 10 years in our hospital. [Results] Totally 23 patients developed TTP in the last 10 years. 7 patients passed away: the mortal rate was 30.4%. The number of SLE patients was 13 and the mortality was significantly better than non-SLE patients. The mean times of PE were 15, but some cases needed more than 20 times before they got a remission of TTP. [Conclusion] Plasma exchange therapy could introduce a remission of TTP in 17 cases but remain seven death cases. The death rate was approximately 30%. Furthermore examination is needed to assess the treatment resistance cases.

W51-4

Risk factors of glucocorticoid-induced diabetes in patients with rheumatic diseases

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Conflict of interest: None

[Objectives and Methods] Hyperglycemia is one of the critical adverse effects of glucocorticoids. To reveal risk factors for glucocorticoid-induced diabetes, we analyzed patients with autoimmune diseases who newly received the treatment with glucocorticoids. We excluded patients with diabetes, a fasting glucose level of 126mg/dl or above, or HbA1c (NGSP) levels above 6.5%. [Resluts] 17 of 35 patients (48.6%) developed diabetes mellitus (DM) within 4 weeks. Mean age and the ratio of HbA1c levels above 5.9% were significantly higher in DM group than that in non-DM group (65.9 vs. 46.8 years, 64.7% vs. 21.0%, respectively). No difference was detected in body mass index and serum lipid profile. Although there was no significant difference, the proportion of male in DM group was higher than in non-DM group. The patients with vasculitis more frequently developed DM than those with SLE, but the stratification with age eliminated the difference, suggesting that the difference occurred as a result of the variation in age of onset. No difference was found between two groups with glucocorticoid cumulative dose, indicating that the regimen of glucocorticoid therapy is minimally contributed to the development of DM among patients treated with high-dose, short-time glucocorticoid therapy.

W51-5

Relevance of inflammation to endothelial dysfunction in patients with RA, by assessing the reactive hyperaemia index (RHI) using Endo-PAT 2000

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Conflict of interest: None

In patients with RA cardiovascular events account for 24% of cause of death, therefore, atherosclerosis is crucial as a risk factor affecting life prognosis. We assessed the reactive hyperaemia index (RHI) using Endo-PAT 2000 and evaluated endothelial dysfunction in patients with biologics-naïve RA. 20 patients with active RA were enrolled (female 16, age 59, disease duration 208 months, DAS28 5.53, SDAI 28.6, CDAI 26.1). 11 patients were untreated and 9 were treated with MTX. Mean RHI (1.81) was lower than normal and 75% of them had an endothelial dysfunction, including that 12 were categorized in borderline and 3 were in dysfunction. RHI was negatively correlated with DAS28 and SDAI and CDAI showed similar tendency. However, RHI was not correlated with CRP, ESR and also glucose and lipid metabolism. Based on logistic regression analysis, DAS28 was the most crucial factor affecting RHI. Taken together, we clarified that an endothelial function was disturbed in RA patients and that it was most affected by DAS28, but not CRP/ESR. We here document the involvement of chronic inflammation in the endothelial dysfunction in active RA patients, lead to progression of atherosclerosis and vascular events

occurred in RA.

W51-6

The efficacy of Rituximab therapy for thrombotic thrombocytopenic purpura complicated with connective tissue diseases

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Conflict of interest: None

[Objectives] Recently, it has been described in many reports that B cell has important roles in Connective tissue disease (CTD). Rituximab (RTX) is anti-CD20 monoclonal antibody that is widely known as effective for patients with several CTD. Otherwise, thrombotic thrombocytopenic purpura (TTP) is developed in CTD, which is often resistant for total plasma exchange conducted for primary TTP as a first line treatment. We have reported in cases report that RTX treatment was effective for refractory TTP complicated with CTD. We examined the efficacy of RTX treatment for TTP complicated with CTD in our group at Kagawa prefecture. [Methods] Six patients complicated with CTD (SLE: 2, SS: 3, Dermatomyositis: 1) were investigated retrospectively. RTX was given at the doses of 375mg/m^2. [Results] All patients were conducted twice infusion of RTX in a month. Cytopenia related to TTP was improved immediately after initial administration of RTX. Neuropsychiatric manifestations were disappeared in all patients within 2 month. They all have sustained in remission for at least 24 weeks. [Conclusion] RTX treatment can be a useful agent for first line treatment of TTP complicated with CTD.

W52-1

Clinical characteristics of 13 cases of rheumatoid arthritis (RA) complicated with iatrogenic immunodeficiency-associated lymphoproliferative disorders (LPD)

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Conflict of interest: None

Recent strengthen medication against RA might increase the number of patients with iatrogenic immunodeficiency-associated LPD(IIDA-LPD; by WHO classification). We peformed a clinical analysis retrospectively of 13 cases of RA complicated with LPD. Their mean age was 69.3 y/o; male/female ratio was 2:11; and their mean disease duration of RA was 17.5 years. Average dose of methotrexate (MTX) was 8.3 mg/w and 5 patients received TNF inhibitors. Pathological findings revealed many types of LDP with diffuse large B cell lymphoma, Hodgkin's lymphoma, T cell lymphoma, B cell lymphoma in 8, 2, 2, and 1 cases, respectively. Epstein-Barr virus (EBV) dyeing of tumor cells revealed positive in 10 cases. Four cases died, 5 cases recovered by stop administering MTX and TNF inhibitors, and 4 cases achieved remission with chemotherapy against LPD. IIDA-LPD revealed various clinical features in terms of MTX dosage, administration of TNF inhibitors, pathology, and association of EBV, clinical course. IIDA-LPD should be recognized in the clinical course of RA treated with immunosuppressive agents.

W52-2

Risk of pneumocystis jiroveci pneumonia in immunocompromised elderly patients who do not receive PCP prophylaxis

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Conflict of interest: None

[Objectives] To clarify the risk of pneumocystis jiroveci pneumonia (PCP) in immunocompromised elderly patients who did not receive PCP prophylaxis. [Methods] We studied data from 122 elderly patients (≥ 60 years old) treated with moderate or high dose (≥0.5mg/kg) of prednisolone (PSL), retrospectively. [Results] Baseline characteristics were as follows; mean age, 76.2 y/o ; female, 63.1%; mean observation period, 20.7 months; mean dosage of PSL, 37.9 mg/day. 55 (45.1%) had vasculitis, 22 (18.0%) rheumatoid arthritis, 17 (13.9%) dermatomyositis/polymyositis and 28 (23.0%) other connective tissue diseases. 31 patients did not receive PCP prophylaxis because of side effects (14 patients) and decisions of physicians (17 patients). PCP was observed in 10 of the 122 patients. Kaplan-Meier analysis showed the more patients who did not receive prophylaxis developed PCP compared to the patients who received prophylaxis ($p<0.01$), and30.4% of the patients who did not receive prophylaxis developed PCP within 4 weeks after the treatment. Age, preexisting lung disease, diabetes, high dose of PSL and immunosuppressive agents were not related to the development of PCP. [Conclusion] PCP prophylaxis should be initiated in all of elderly patients receiving immunosuppressive therapy.

W52-3

Nocturnal blood pressure in the patient of rheumatoid arthritis

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Conflict of interest: None

[Background] Nocturnal hypertension is one of the most important factors of cardiovascular event. Since RA patients showed higher risk of cardiovascular event, we studied about nocturnal blood pressure in RA patients. [Objectives] To investigate about nocturnal blood pressure in the patients of RA. [Methods] We examined about the 24-hour blood pressure in 71 patients of RA who were hospitalized to control active inflammation. [Results] The nocturnal decline in systolic blood pressure is as low as 4.5% in the patient with rheumatoid arthritis, and 30 of them are non-dippers and 20 of them are risers. 70% of all had nocturnal hypertension. The nocturnal decline showed close negative correlation with DAS28ESR ($p=0.004$). In the longitudinal study, the nocturnal decline increased significantly up to 8.9% ($p=0.002$), moreover 7 of 14 patients showed improvement in the grade of blood pressure. [Conclusion] Higher risk of cardiovascular event in the patient with rheumatoid arthritis may be due to the nocturnal hypertension which is caused by active inflammation.

W52-4

Nocturnal hypertension in RA patients with DM

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Conflict of interest: None

【background】It is reported that both RA and DM patients have nocturnal hypertension in high rate. On the other hand, it is suggested that RA patients are easy to be complicated with type 2 DM.【object and method】The influence that having with DM or not in RA patients gives in nocturnal hypertension was investigated in 23 RA patients with DM and 40 RA patients without DM with 24 hour ambulatory blood pressure monitoring.【result】About 70% of RA patients with or without DM had a diagnosis of nocturnal hypertension. Moreover, the degree of nocturnal blood pressure decline in DM-RA patients and non DM-RA patients were 3.8% and 4.2%, respectively, there was no significant difference among both groups. However, both night and daytime systolic blood pressure in DM-RA patients was significantly higher than in non DM-RA patients. The incidence rate of cardiovascular disease in DM-RA patients and non DM-RA patients were 48% and 7.5%, respectively, cardiovascular disease risk was significantly higher in DM-RA patients than in non DM-RA patients.【conclusion】The 24-hour blood pressure levels was higher in DM-RA patients than in non DM-RA patients. It was suggested that continuous high blood pressure might be one of cardiovascular risk factors in DM-RA patient.

W52-5

A patient with rheumatic manifestation including enthesopathy due to chronic exposure to common environmental antigen, house-dust and cat hairs

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Conflict of interest: None

Background: As to the influence of environment on disease, there are well known cases such as reactive arthritis or the rheumatoid arthritis due to food allergy. However, whether or not chronic exposure to environmental antigens will induce rheumatic manifestations are not well characterized. **Profile of Case:** The patient was a 40 year-old business man, who started to experience nocturnal urticarial skin rash from 2010. From May 2012, he suffered from pain in the four extremities and felt difficulty in climbing up stairs because of pain in the heel. Because he also experienced dyspneic sensation, he visited our hospital on July 2012, while being treated with anti-depressant due to the diagnosis of fibromyalgia and nervousness. The patient had a past history of bilateral renal stones. His elder sister was with the diagnosis of fibromyalgia. On physical examination, he was 161cm high, 57Kg weigh, and afebrile. Erythema of 5mm diameter were spottedly distributed on his buttock and axitial body skin areas. Enthesitis was noted on bilateral Achilles tendons. Arthralgia were detected in left elbow and bilaterally in fingers II~IV PIP and II DIP, wrists and knees. Lab tests showed WBC 5,700/mm3, Hb 12.6g/dL, eosinophils 8%, monocytes 13.4%, CRP 0.04mg/dL, and total IgE 404 IU/mL. While the test of stool for worms were negative, IgE antibodies reactive against house-dust, cat hair, ciders were detected. HLA typing was A24, A2, B7, and B46. The patient's signs and symptoms all resolved within 2 months by avoid of allergens and subscription of daily 15mg of prednisolone.

W52-6

Study about cases who were treated with dialysis because of end stage renal failure caused by immune diseases

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Conflict of interest: None

[Objectives] Although the number of cases who were treated with maintenance dialysis because of end stage renal failure caused by immune diseases were decreased, the management of them is often difficult. So, we studied the characteristic of them. [Methods] We chose patients who were treated with maintenance dialysis because of end stage renal failure that were caused by immune diseases including collaged diseases and congenital immune deficiency in our hospital between April 2005 and September 2012. Then, we investigated their complications, laboratory data, and medicines and compared them with dialysis patients caused by other disease. [Results] The number of dialysis patients caused by immune diseases was nine among all 243 maintenance dialysis patients. In the nine patients, only one patient of the microscopic polyangitis has died. All of them had been treated with corticosteroid among long term, but three cases could stop it. They were complicated with infections including pneumonia and skin disease more than other dialysis patients. With respect to laboratory data, their hemoglobin was decreased than other dialysis patients. [Conclusion] We have to manage them carefully especially with respect to use of immunosuppressant and prevention of infection.

W53-1

Autoimmune hepatitis induced by the overexpression of T-bet in PD-1 knockout mice

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Conflict of interest: None

[Background] Programmed cell Death-1 knockout mice (PD-1KO) develop strain-specific autoimmune disease. Lupus-like glomerulonephritis was observed in C57BL/6 background PD-1KO after 24-48 weeks of age. The exact role of individual T helper cell subset in the pathogenesis observed in PD-1KO was not fully elucidated. **[Objective]** To clarify the effect of T cell specific T-bet overexpression on autoimmune disease in PD-1KO mice. **[Methods]** 1) PD-1KO x T-bet Tg mice (P/T) were generated by crossing T-bet Tg with PD-1KO. 2) The pathological evaluation of kidneys and other organs was performed. 3) FACS analysis was performed to evaluate cytokine production and transcription factor expression on $CD4^+$ T cells. 4) Splenocytes were transferred into Rag-2 knockout mice. **[Results]** 1) Most of P/T died within 10 weeks. 2) Although glomerulonephritis was not observed in P/T, infiltration of $CD3^+CD4^+$ T cells in liver was observed only in P/T. 3) FACS analysis showed high production of IFN-γ on $CD4^+$ T cells and significant reduction of $Foxp3^+CD4^+$ cells in P/T. 4) Transfer of splenocytes of P/T caused weight loss in Rag-2 knockout mice. **[Conclusion]** Autoimmune hepatitis might to be induced by high production of IFN-γ from $CD4^+$ T cells and the reduction of $Foxp3^+$ regulatory T cells in P/T mice.

W53-2

Risk factors for chronic kidney disease in rheumatoid arthritis

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Conflict of interest: None

[Objectives] A variety of renal disorders occur in patients with

rheumatoid arthritis (RA), drug related renal disease, various type of glomerulonephritis and renal amyloidosis. RA have been reported to have higher prevalence of metabolic syndrome (MetS). Components of MetS are shown to be associated with the prevalence of chronic kidney disease (CKD). However, it has not been clear whether components of MetS are associated with CKD in patints with RA. [Methods] We examined 323 patients with RA for 78 months.CKD was difined as eGFR <60 ml/min/1.73m^2 and/or presence of proteinuria captured by urine dipstick for ≧3 months [Results] The mean (SD) was : age 57.0 (12.4) years and eGFR 91.0 (19.8) ml/min/1.73m^2. In multivariate analysis, hypertension was independent determinants of abnormal eGFR (HR 2.90, 95%CI 1.35-6.6). CRP was independent determinants of proteinuria (HR 4.97, 95%CI 1.29-32.9). [Conclusion] Hypertension and CRP were assoaiated with CKD in patients with RA.

W53-3

Characteristics of 10 patients with paraneoplastic rheumatologic musculoskeletal manifestations

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Conflict of interest: None

[Objectives] Malignant neoplasms are associated with a wide variety of paraneoplastic rheumatological syndromes. [Methods] We studied a series of 10 patients with paraneoplastic rheumatological syndromes.This is a series of patients collected from our Division of Rheumatic Disease between 2006 and 2012. [Results] Our series consists of six men and women,with a mean age of 65.5(57–78 years). Of the 10 patients recruited, 4 had a haematological malignancy and 6 a solid cancer. Compared to solid tumours, haemopathy was diagnosed at a later time point (16.2 months vs 7.3 months). Extra-articular symptoms were associated with arthritis in 100.0 % of patients. Polyarthritis was the main rheumatologic musculoskeletal manifestations (50.0 % of patients). Musculoskeletal manifestations completely regressed in 60.7 % of patients after cancer therapy. In our study, paraneoplastic arthritis was observed in 1.4% of the 721 patients hospitalized for detailed examination and treatment for arthralgia. [Conclusion] Rheumatic disorders with atypical clinical presentation should alert clinicians to the possible coexistence of an occult malignancy. Especially in the case of haemopathy, the primary disease is unlikely to have manifested yet, making the diagnosis difficult.

W53-4

Biological agents for rheumatoid arthritis (RA) after the short term remission of methotrexate-associated lymphoproliferative disorders (MTX-LPD)

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Conflict of interest: None

[Objectives] The anchor drug for RA is methotrexate (MTX) that has rare indispensable problem of MTX-LPD. Because MTX must be stopped in MTX-LPD patients, the disease activity of their RA might often worsen, but the effective treatments have not been established yet. Here we investigated the efficacy and safety of biologics administration for RA after MTX-LPD improvement was retrospectively examined. [Methods] From September, 2007 to September, 2012, RA patients who developed MTX-LPD were enrolled. They had been observed about the activity of RA, treatments after cessation of MTX and the recurrence of LPD. [Results] Eleven patients developed MTX-LPD during MTX treatment. Cessation of MTX was necessary in all patients. Three patients needed chemotherapy for MTX-LPD. In the other 8 patients, the MTX-LPD improved only through cessation of MTX, with the arthritis deteriorating into high disease activity in 7 of the 8 patients. Etanercept (ETR) was administered for 5 patients and Tocilizumab (TCZ) for the 3 patients. All 7 patients maintained complete or partial remission of LPD, and RA activities improved after biologics treatment except for 1 patient. [Conclusions] ETR or TCZ was safe and effective for RA, with the short-term remission of MTX-LPD, at least on short-term observation.

W53-5

Clinical study on MTX-associated lymphoproliferative disorders in patients with RA

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Conflict of interest: None

Purpose: To clarify the clinical characteristics of MTX-associated lymphoproliferative disorders (MTX-LPD) in RA patients. **Methods**: We retrospectively reviewed the medical records of 39 RA patients (male 14, female 25) who developed MTX-LPD. **Results**: Clinical features at the diagnosis of MTX-LPD; mean age 64.3, mean disease duration of RA 11.4 years, MTX dose 7.8 mg/w, mean period of MTX treatment 4.8 years, CRP 7.5 mg/dL and MMP-3 314.5 ng/dL. Pathological diagnosis of LPD; diffuse large B 17, Hodgkin 5, follicular 3, etc. EBV was detected in 10 of 31 cases. MTX was stopped soon after the diagnosis of MTX-LPD in all but one patient who was very active RA and showed no aggravation of LPD. After MTX cessation, 16 patients needed chemotherapy for LPD. LPD resolved spontaneously in the other 22 patients, but DMARDs including biologics were prescribed later for RA flare and 11 developed LPD again. There were no significant difference of the prescription with or without LPD relapse. Among 8 patients who died, most of them belonged to the group who needed chemotherapy. **Conclusions**: MTX-LPD in RA developed more frequently in male patients who had long MTX treatment period and high CRP and MMP-3. Some of them had grave prognosis even though MTX was withdrawn.

W53-6

A case of immunodeficiency-associated lymphoproliferative disorder with RA

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Conflict of interest: None

A 72-year-old woman was diagnosed with rheumatoid arthritis (RA) in September 20X-2. She was started on methotrexate (MTX) in March 20X-1 and on adalimumab (ADA) in January 20X. In July of that year, she was switched from ADA to etanercept. Findings of left-sided suppurative tonsillitis appeared in August, and malignant lymphoma was suspected. A biopsy showed CD20-positive diffuse large B-cell lymphoma (DLBCL). MTX-associated lymphoproliferative disorder (MTX-LPD) was suspected, and MTX and ETN were discontinued, whereupon the lymph nodes re-

duced. Epstein-Barr virus (EBV) DNA was detected by polymerase chain reaction (PCR), suggesting reactivation of EBV. DLBCL is the commonest finding of immunodeficiency-associated lymphoproliferative disorders (IDA-LPD), and tumors often disappear spontaneously when immunosuppressive therapy is discontinued in EBV-positive patients. These characteristics were also evident in the present case, which was regarded as a case of IDA-LPD. DLBCL has also been reported as a complication in dermatomyositis treated with single steroid therapy, and we have previously treated a patient with RA who developed DLBCL as a complication while using tacrolimus. Lymphoma should be borne in mind in patients undergoing immunosuppressive therapy.

W54-1

Surgical treatment in rheumatoid arthritis patients treated with biologics — What are the risk factors for surgery? —

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Conflict of interest: None

[Objectives] The aim of this study was to identify the risk factors for surgery in rheumatoid arthritis (RA) patients treated with biologics. [Methods] Of 2072 RA patients registered in Tsurumai Biologics Communication Registry, 206 surgeries in 145 patients were performed while treated with biologics. The patient characteristics at initiation of biologics were analyzed. [Results] 114 received etanercept, 56 received infliximab, 15 received tocilizumab, 14 received adalimumab and 7 received abatacept at the time of surgery. Surgeries included 128 total joint arthroplasty, and 78 other procedures, and the duration from initiation of biologics to surgery was 2.1 years. Multivariate logistic regression analysis revealed that MTX naïve (P=0.033, odds ratio (OR)=1.80; 95% confidence interval (CI)=1.05–3.11), age (≧50, P=0.004, OR=3.99; 95% CI=1.57–10.16), RA duration (≧3 years, P=0.022, OR=2.36; 95% CI=1.13–4.89) and high disease activity (P=0.023, OR=2.06; 95% CI=1.1-3.83) were the independent risk factors for surgery. [Conclusion] MTX is an anchor drug for RA to prevent future surgery. Age is a risk factor for progression of joint destruction while it is a risk factor for drug treatment failure. Thus treatment according to age is necessary for RA patients in addition to early treatment.

W54-2

Orthopaedic surgeries in rheumatoid arthritis in 2002 - 2012

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Conflict of interest: None

[Objectives] Biologic agents changed the RA therapy drastically from starting to use biologics at 2003 in Japan. The rate of orthopaedic surgery may reflect trends in disease severity, management and health outcomes. [Methods] We showed the number and rate of orthopaedic surgeries in the last decade. [Results] We had 18,692 cases of orthopaedic surgery, including 487 rheumatoid surgeries. They contained 336 cases of total joint arthroplasties (69%), 28 spine surgeries (17%), 27 forefoot surgeries (6%) and 13 synovectomy (3%). The rate of rheumatoid surgeries decreased year by year (r = 0.5), especially, spine surgeries and total joint arthroplasties of lower extremity. We had 152 rheumatoid patients treated by biologics agents, including 40 rheumatoid surgeries with the biologic therapy. Half of rheumatoid surgeries were total joint arthroplasties (28 cases; 52%). The rate of arthroplasty of upper joint and forefoot in rheumatoid patients with biologic therapy was more increased than in the rheumatoid patients without biologics. [Conclusion] The surgery that improve the quality of life may increase in the rheumatoid patients with biologic therapy, because their disease activity and attitudes changed year by year.

W54-3

The clinical results of perioperative complications in the orthopedic surgeries for the patients with rheumatoid arthritis receiving the treatment using biological agents

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Conflict of interest: None

[Objectives] Biological agents have drastically shifted the paradigm of the strategy of the treatment for the patients with rheumatoid arthritis (RA). Many rheumatoid patients have gained great benefit by using biologics. On the other hand, it has also been advocated that the treatment using biologics may cause inappropriate events in perioperative course of orthopedic surgery; delayed surgical wound healings and surgical site infections (SSIs). However it has still been controversial. In this study, we aimed to reveal the perioperative risk in such patients based on our clinical outcomes. [Methods] Ninety-four cases (10 males, 84 females) who had been performed orthopedic surgeries since January 2006 to August 2012 in our hospital were included in this study. The mean age at the index surgery was 57.3 years. Fourteen cases had been received infliximab, 52 etanercept, 10 adalimumab and 18 tocilizumab. [Results] Of 94 cases, 2 cases of SSIs and 7 cases of delayed wound healings were noted. Of these 9 cases with perioperative complications, 7 cases had been treated using tocilizumab. [Conclusion] For the rheumatoid patients treated using biologics, especially tocilizumab, it was considered that the careful and strict perioperative managements were needed.

W54-4

Does use of biologic agent increase the incidence of postoperative infection?

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Conflict of interest: None

[Objectives]. There is no consistent evidence for an effect of biologic agents on surgical site infection and late infection. We investigated whether use of biologic agent increased the rate of postoperative infection in patients with RA. [Methods] The subjects were 356 RA joints treated with biologics in our department (bio group) and 331 RA joints that were not treated with biologics (control group). The biologic used were etanercept (ETN) in 285 joints,

infliximab (INF) in 18 joints, tocilizumab (TCZ) in 31 joints, adalimumab (ADA) in 20 joints, and abatacept (ABT) in 2 joints. [Results] In the bio group, surperficial infection in 1 joint, deep infection in 3 joints and late infection in 3 joints were found. In the control group, surperficial infection was found in 2 joints and no deep or late infection was detected. Prosthesis removal was performed in patients with deep or late infection. Pathogenic bacteria were commonly MSSA and P. aeruginosa. Infection subsided in all patients and biologics were re-administered with no relapse of infection. [Conclusion] Biologics did not increase the incidence of postoperative infection. However, careful intra- and postoperative observation is required due to the increased number of cases treated with surgery and biologics.

W54-5

Improved quality of life by surgery in patients with long-standing rheumatoid arthritis following treat-to-target recommendation with medication

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Conflict of interest: None

[Objectives] Even in RA patients who had longstanding disease, the treat-to-target (T2T) recommendations resulted in functional improvement. However some patients need surgical treatment to improve their QOL, because improvement in the existing joints proved insufficient. [Methods] In last three years, 9 cases and 10 operation were performed in RA patients who had longstanding disease and whose disease activity were less than 3.2 in DAS28ESR4. All cases were female, mean age at operation was 59.3±14.2, and mean disease duration was 18.8±10.9 years. [Results] Five operations were performed during the treatment with biologics; 3cases for forefoot deformity, 1 case for hand deformity, 1 case for TKA. In spite of disease activity was low and maintained with biologics, existing joint destruction prevented improvement in her quality of life. Since her motivation for better function was increasing, arthroplasty was performed. Five operations were performed during the treatment without biologics; 2 cases for wrist synovectomy, 1 case for TKA, 1 case for THA, due to the joint pain. Neurolysis of ulnar nerve in elbow was in 1 case. All patients were satisfied with operative treatment for better function. [Conclusion] Some patients satisfied with T2T need surgical treatment to improve their QOL.

W55-1

Efficacy of adalimumab in patients with rheumatoid arthritis after revision of MTX dose from multicenter registry (TBCR)

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Conflict of interest: None

[Objectives] To investigate efficacy of adalimumab (ADA) in patients with rheumatoid arthritis after revision of MTX dose from multicenter study (TBCR). [Methods] 40 patients with RA treated with MTX and ADA as first biologics were included in this retrospective study. 25 patients treated with baseline MTX below 8mg/w were called below-G and 15 patients treated with baseline MTX over 8mg/w were called over-G. Time course of disease activity from 0w to 24w and MTX dose were investigated and compared between two groups. [Results] Baseline MTX in below-G and over-G were 7.1mg/w and 11.5mg/w, respectively. Time course of DAS28-CRP in 0w-4w-12w-24w were 3.60-2.45-2.23-2.26 in below-G and 3.61-2.47-2.38-2.26 in over-G (not significant between groups). Remission in Boolean criteria at 24w were 36.0% and 26.7% in below-G and over-G. MTX dose from 0w to 24w were 7.1mg/w to 7.7mg/w in below-G and 11.6mg/w to 12.2mg/w. MTX dose escalation during 24w was performed in approximately 20% of patients. [Conclusion] MTX dose were adjusted for good outcome by RA specialists in real world clinical setting. there was no significant difference between two grouo in baseline disease activity and this is probably due to MTX dose adjustment before ADA initiation.

W55-2

Clinical results of Adalimumab administration of 121 patients in our hospital at week 52: Survey on disease duration and Bio-naïve vs. bio-Switch

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Conflict of interest: None

[Objectives] Survey on clinical efficacy at 52 week of Adalimumab (ADA) administration in rheumatoid arthritis (RA) patients. [Methods] In this study, the data of 121 RA patients in our hospital who received ADA from May 2009, to Oct 2010. Mean DAS 28 (CRP) was 3.7 and 4.4, for each group, in order. 86 patients were bio-nave (N group), while 35 patients were bio-switched (S group) and mean DAS 28 (CRP) was 4.0 and 3.9, for each group, in order. Clinical results of ADA administration at 52 week were compared among the groups. [Results] The percentage of DAS28 (CRP) remission in all patients at weeks 8, 24 and 52 were 54%,63% and 70.8%, respectively. At week 8, more than 50% of patients and at week 52 more than 70% of patients could gain clinical remission. Also, at week 52, more than 80% of patients could gain LDA. At weeks 8, 24 and 52, the percentage of DAS28(CRP) remission in <2-yr group and≧2-yr group were 52.0% vs. 47.1%, 68.4% vs. 52.9% and 78.5% vs. 52.9%, respectively and at all points the remission rates were significantly higher in <2-yr group. Also, EULAR good response was 65.0% vs. 33.3%and showed a higher clinical response in N group. [Conclusion] ADA administration in early RA and Bio-nave patients, with optimal MTX dosage, can earn high remission percentage.

W55-3

Efficacy and safety, drug survival rate of golimumab(GLM) in patients with rheumatoid arthritis—study from TBCR—

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Conflict of interest: None

[Objectives] Golimumab (GLM) is a biological agents that has been approved in Japan in 2011. Using Tsurumai Biologics Communication Registry (TBCR), we examined the efficacy, the safety and the continuity rate of 24 weeks. [Methods] In 69 patients were treated with GLM, 39 patients were older than 24 weeks after the start of treatment. We investigate the disease activity DAS28, SDAI, CDAI, and evaluate the continuity rate by Kaplan-Meier in the patient. [Results] The 39 patients was the mean age of 63.0 years old and the mean disease duration of 161.1 months. They treated combination with MTX in 28 cases (71.4%), BIONAIVE was 19 cases (48.7%). On the introduction, the disease activity was DAS28 4.99, SDAI 22.5 and CDAI 21.3. The value of disease activity showed a significant decrease 4 weeks after the treatment. The patients of high disease activity was a 51.5% prior to the introduction, It decreased to 23.7% after 24 weeks, and the following percentage of low disease activity has reached 42.1%, including clinical remission. Continuation rate was 69.6% at 12 weeks and 78.6% at 24 weeks. The reason for discontinuation was 1 case the patient would like, 7 cases disabling effects, adverse events in 3 cases. [Conclusion] GLM showed good clinical outcomes and tolerability at week 24

W55-4

Long-Term Safety, Efficacy, and Patient-Reported Outcomes of Certolizumab Pegol in Japanese Rheumatoid Arthritis Patients with an Inadequate Response to Methotrexate: 52 Week Results from an Open Label Extension of the J-RAPID study

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Conflict of interest: Yes

Objective: To evaluate the long-term safety, efficacy, and patient-reported outcomes of certolizumab pegol (CZP) in Japanese Rheumatoid arthritis patients (pts) with inadequate response to MTX. **Methods:** During the open label extension (OLE) study, pts withdrawn at 16wk of double-blind (DB) due to lack of efficacy (Group I, n=81) and completers without an ACR20 response at DB 24wk (Group II, n=19) received CZP 200mg Q2W+MTX. DB completers with an ACR20 response were randomized to CZP 200mg Q2W+MTX (Group III, n=93) or CZP 400mg Q4W+MTX (Group IV, n=92). **Results:** DB completers (Group II+III+IV) maintained their ACR20 responses (89.7% and 95.6%) and their DAS28-ESR remission rates (28.4% and 42.6%) at OLE entry and at 52wk, respectively. Improvements in HAQ-DI, Pain VAS, and SF-36 scores were also sustained. Efficacies in Groups III and IV were comparable. Serious adverse events were observed in 10.9% of all patients; no TB or death was reported. **Conclusion:** Patients with inadequate response to MTX showed long-term response to CZP 200mg Q2W and 400mg Q4W with MTX at similar efficacy and safety. CZP+MTX was well tolerated with no new safety signals.

W55-5

Clinical Response to certolizumab pegol at 12 Weeks Predicts Remission and the Extent of Radiographic Progression at 1 year in Japanese Patients with Rheumatoid Arthritis

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Conflict of interest: Yes

Objective: To determine whether the magnitude of DAS28 (ESR) nonresponse to certolizumab pegol (CZP) at wk12 can predict likelihood of achieving remission and extent of radiographic progression (mTSS) at 1 year (yr) in Japanese patients (pts) with rheumatoid arthritis. **Methods:** This post-hoc analysis included 82 (J-RAPID) and 116 (HIKARI) pts. They were treated with CZP 400mg at wks 0, 2, 4, then CZP 200mg Q2W during double-blind study, followed by open-label study with CZP 200mg Q2W or 400mg Q4W. The remission rate and the change in mTSS at 1 yr were assessed according to the levels of DAS28 response at wk12. **Results:** 77% of J-RAPID pts and 74% of HIKARI pts had a DAS28 change ≥1.2 at wk12 (responders). Remission was achieved by 41.3% and 34.9% of the responders in J-RAPID and HIKARI pts at 1 yr. Non-responders at wk12 had a <7% chance of achieving remission and had greater change of mTSS at 1 yr than responders. Similar results were observed in both J-RAPID and HIKARI pts. **Conclusion:** The majority of pts responded to treatment with CZP at wk12 in the broad pts population. Likelihood of remission and extent of radiographic progression at 1 yr could be predicted at wk12 based on the change in DAS28.

W55-6

Efficacy and safety of Golimumab therapy among patients with rheumatoid arthritis in our hospital

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Conflict of interest: None

【Objective】To evaluate the efficacy and safety of golimumab (GLM) therapy with rheumatoid arthritis (RA) patients.【Methods and Patients】All of 34 patients were started to receive subcutaneous injections every 4 weeks of GLM since Oct. 2011.【Results】Among all patients, 91% were female, the mean age was 52.5 years, disease duration was 10.5 years and rate of Stainbrocker stageIII and IV was 58.3%, the first biological agent (bio naïve) was 39.4%. 88% of all was treated with concomitant methotrexate (MTX). Bio naïve was treated with MTX mean dose 10.0mg/W, on the other hand the biological switchers (bio switch) was treated with 6.0mg/W. 39% of patients achieved DAS28 remission (score<2.3) at week 24. The mean score of DAS28 at baseline, week 4 and 24 were 4.0±1.0, 2.7±0.9, 2.4±0.9. Our result suggests that GLM was effective at the early weeks. At week 4 DAS 28 re-

mission rates was greater in bio naïve (40%) than in bio switch (18%). At week 24, rate of continuous GLM therapy was 70%, and two discontinued cases due to infections, and three due to unsatisfactory therapeutic effect. All of the three discontinuous cases due to not effective were belonged bio switch.【Conclusions】For patients with long duration RA, GLM therapy was effective at the early weeks. Bio naïve had greater effect than bio switch.

W56-1

Analysis of factors related clinical remission and the inhibition of bone and joint destruction by golimumab for rheumatoid arthritis

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Conflict of interest: None

[Objectives] To investigate the related factors to the clinical effects and inhibition of joint destruction by golimumab in rheumatoid arthritis (RA). [Methods] 48 patients treated with golimumab of RA including 7 males, 41 females mean age of 64.3 years, mean disease duration of 16.5 years, 11 of naive and 37 of switch patients were analyzed DAS28(CRP), CDAI, SDAI, serum TNF-alpha and IL-6 at 24 weeks. [Results] The remission rate at 24 weeks were 26.7% of DAS28, 20% of CDAI, and 222% of DAI. DAS28 of MTX plus versus MTX(-) were 6.7 % and 36.7% in remission. TNF-alpha was decreased in naive and MTX plus cases significantly. Disease duration (p=0.0408) and MMP-3 (p=0.0103) were significantly correlated with DAS28 at 24 weeks in multiple regression analysis. Continuation rate of golimumab showed 88% at 52 weeks by Kaplan-Meier method. Disease duration (0.0073), TNF-alpha(p=0.021), CRP(p=0.0356) were correlated with ⊿ sharp score at 24 weeks. [Conclusion] Predict factors of remission by golimumab in RA were disease duration and MMP-3 and those of inhibition of joint destruction were disease duration, TNF-α and CRP at 24 weeks. Therefore early stage and high disease activity are possible to use golimumab to induce clinical and radiographic remission.

W56-2

Factors affecting adherence to second biologics after discontinuation of anti-tumor necrosis factor alpha in rheumatoid arthritis patients

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Conflict of interest: None

[Objectives] It is important to find the longest possible use of second biologics for rheumatoid arthritis (RA) patients who withdrew anti-tumor necrosis factor-alpha (TNF-α) therapy because of inefficacy or adverse events as first biologics. [Methods] We analyzed an observational cohort database of 169 RA patients withdrew anti-TNF-α therapy as first biologics and received another anti-TNF-α agents or tocilizumab (TCZ) as second biologics more than 52 weeks at the Tsurumai Biologics Communication registry. The data were analyzed using the Cox proportional hazards model. [Results] The patient cohort consisted with an average age of 55.4 ± 13.4 and an average duration of RA was 9.7 ± 8.7 years. The survival rate was 79.3% at week 24 and 69.2% at week 52. Administration of etanercept (ETN) as first biologics (HR 2.86, 95% CI 1.46-5.76, p = 0.0021) led to significantly lower survival rate of second biologics. Administration of ETN (HR 0.26, 95%CI 0.07-0.76, p = 0.0138) or TCZ (HR 0.27, 95%CI 0.11-0.57, p = 0.0003) as second biologics indicated significantly higher survival rate at week 52. [Conclusion] Administrating ETN as first biologics showed low adherence rate and ETN or TCZ as second biologics indicates high adherence rates for patients who withdrew anti-TNF-α therapy.

W56-3

Analysis of infliximab(IFX) level and anti-infliximab antibody(AIA) in RA patient under IFX medication

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Conflict of interest: None

[Objectives] Fifty five RA patients under IFX medication at our hospital since August, 2008. [Methods] Thirty two patients were treated with dose escalation IFX protocol from 3 mg/ml to 4.5 mg/kg or 6 mg/kg according to disease activity. We measured trough level of IFX and the AIA both before and 2 months after dose escalation. Moreover, values of 23 RA patients that maintained low disease activity or remission at 3mg/kg were measured similarly. [Results] The trough levels of IFX in dose escalation group significantly increased from 0.59 μg/ml to 1.77 μg/ml (p = 0.0004). The trough level of IFX in 3mg/kg maintenance group was 1.64 μg / ml. The trough level of IFX in 5 RA patients whose AIA values increased (AIA increase group) was 0.0 despite dose escalation. Meanwhile, the trough level of IFX in 27 RA patients whose AIA values reduced (AIA reduction group) significantly increased from 0.64 μg/ml to 2.08 μg/ml (p = 0.0006). The continuation rates of AIA reduction group were significantly higher compared to those of AIA increase group, 77.78% vs 20% (six months, p = 0.0418) and 66.67% vs 0% (one year, p = 0.0232) respectively. [Conclusion] The variability of the AIA closely affected the trough levels of IFX, and was suggested for a better predictor of the tolerability.

W56-4

The safety of etanercept and adalimumab in RA patients with renal dysfunction

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Conflict of interest: Yes

[Objective] Not metabolized in kidney, biologics are often prescribed to RA patients with low estimated glomerular filtration rate (LeGFR). However, it may increase adverse event (AE), since patients with either biologics or renal dysfunction are prone to infection. We examined the safety of etanercept (ETN) and adalimumab (ADA) use to RA patients with LeGFR. [Patients] Seventy-five RA patients to whom ETN or ADA were introduced at our Department from Jul. 2005 to Nov. 2009 were observed for 3-years. [Methods]

LeGFR is defined as eGFR less than 60mL/min/1.73m^2, and normal eGFR (NeGFR) is above this. Outcomes of patients were retrospectively compared. [Result] Sixty-one patients were ETN users and 9 of them were with LeGFR. Among patients with LeGFR, 5 patients could not have clinical remission (CR) and 4 patients withdrew ETN due to AE (1 declined renal function, 1 infection, 2 interstitial pneumonia: IP). Significantly more patients with LeGFR withdrew ETN due to AE than those with NeGFR (p=0.047, Chi-Square test). Fourteen patients were ADA users and 2 of them were with LeGFR. Among patients with LeGFR, 1 patient could not have CR and 1 patient withdrew ADA due to AE (IP). [Conclusion] AE may be increased when RA patients with low eGFR are treated with anti-rheumatic biologics.

W56-5

Background comparison of functional assessment (mHAQ) and X-ray assessment (TSS) of rheumatoid arthritis patients on Adalimumab (ADA) ~from the standpoint of blood concentration of ADA and anti adalimumab antibodies of Adalimumab (AAA)

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Conflict of interest: None

[Objectives] We have reported the clinical validity (⊿DAS･DAS response･) of Adalimumab (ADA) based on blood concentration of ADA and anti adalimumab antibodies of Adalimumab (AAA).This time, we examined the background comparison of the functional assessment (mHAQ) and X-ray assessment (TSS) based on blood concentration of ADA and AAA. [Methods] 56 rheumatoid arthritis patients under the treatment of ADA. [Method] Tested DAS28･･mHAQ prior to the study and every 4 weeks. X-ray assessments (TSS) were performed after 52 and 104 weeks.Blood concentration of ADA and AAA were measured after 4 weeks after administration. [Results] Weak correlation was seen between ⊿mHAQ and⊿DAS; however, there was no correlation between ⊿TSS and DAS or ⊿mHAQ. ADA did not differ in the groups for ⊿TSS comparison; however, positive rate of AAA were high in the group greater than 5 for ⊿TSS. ⊿mHAQ had a tendency to improve in the group of ADA blood concentration greater than 5μg/ml In the comparison of ⊿TSS in concomitant medication groups, MTX or TAC group showed a favorable trend. [Conclusion] ADAconcentration and AAA are also signigicant factors of functional and structural efficacy of ADA

W56-6

Assessment the efficacy and safety of treatment with Golimumab 50mg and 100mg usage for the patients of rheumatoid arthritis

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Conflict of interest: None

[Objectives] To evaluate of the validity of treatment with Golimumab (GLM) 50mg and 100mg usage for [Methods] Seventy-seven RA patients treated with GLM, patient background, validity, persistence rate, and adverse events were examined. The validity of 100 mg medication was also examined. [Results] Baseline characteristics of patients who started GLM were 52years-old, duration 9.5years, %methotrexate (MTX) 88.2, dose of MTX 10mg/week, %prednisolone 47.4, dose of prednisolone 5mg/day. The history of biologics use: 50.6% cases were none, 32.5% cases were1 agent, and 16.9% cases more than 2 agents. Retention rate at 6 months was 88.9%. DAS28 (median) improved from 4.5 to 3.1 As for the GLM dosage, 68 cases(88.2%) were started GLM 50mg. The dose increased to 100mg was performed to 15 examples during process of 50mg use. Nine cases (11.8%) started GLM by 100mg. Seven cases started GLM without MTX treatment. Retention rate at 6 months was 100% and DAS28 improved to 2.7 in 100mg without MTX groups. Improved DAS28 at the 3 months 4.3 to 3.2 after dose increased. The adverse events which resulted in the discontinuation GLM was six cases. They were all the examples of 50mg medication groups. [Conclusion] GLM 100mg without MTX and the dose increased from 50mg to 100mg were both useful.

W57-1

Abatacept among biologics in patients with rheumatoid arthritis: prognostic factors for clinical, functional and structural remission

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Conflict of interest: None

[Objectives] The efficacy of abatacept (ABT) has been established in patients with RA. In the current study, prognostic factors affecting clinical outcomes by the treatment with ABT were estimated in active RA patients. [Results] 87 patients treated with ABT were enrolled;.Means of age 63.2, disease duration10.1y, MTX users 71.3%, SDAI 29.8, mTSS 58.4, HAQ 1.5, CRP 1.8, RF 159.2. The retention rate was 83.6% at week 52. ABT improved SDAI, HAQ, ⊿TSS, CRP, RF at week 24 and 52. The rate of clinical (SDAI<3.3), functional (HAQ≦0.5) and structural (⊿TSS<0.5) remission were 14%, 28% and 75% at week 24, 22%, 30% and 66% at week 52, respectively. The prognostic factors predicting clinical, functional and structural remission were RF, HAQ and CRP at baseline and cutoff value were RF≧67.9, HAQ≦0.9 and CRP≦1.5. [Conclusion] ABT improved clinical, functional and structural measures especially in RA patients with RF≧67.9, HAQ≦0.9 and CRP≦1.5, indicating that ABT appears to have a benefit in RA patients with strong immunologic abnormalities by inhibiting T cell activation.

W57-2

Efficacy of abatacept for rheumatoid arthritis based on comparisons with other biological agents and focused on disease duration

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Conflict of interest: None

[Objectives] We studied the efficacy of ABT and other biological drugs for established RA. [Methods] Biologics-naïve patients taking ABT, Adalimumab (ADA), or Tocilizumab (TCZ) for longer than 24 weeks were included, from the Tsurumai Biologics Communication Registry (TBCR). We retrospectively reviewed the clinical data in the early RA group (<2years of disease duration) and the established RA group (>10 years of disease duration). [Results] Numbers of patients were 27/46 (early/established) in ABT, 13/24 in ADA, and 57/42 in TCZ. Mean DAS28 were 5.0/5.3 for ABT, 5.7/5.6 for ADA, 5.7/5.2 for TCZ group at baseline, and at 24 weeks, 3.7/3.8 for ABT, 3.1/3.5 for ADA, 2.3/3.2 for TCZ group. Drug retention rate were 88.9/93.5% for ABT, 61.5/54.2% for ADA, 98.2/90.5% for TCZ group at 24 weeks. [Conclusion] In ADA and TCZ groups, mean DAS28 at 24 weeks and drug retention rate in early RA were better than in established RA. On the other hand, in ABT group, there was no difference between the two groups in DAS28 at 24 weeks and drug retention rate in established RA was better than in early RA. These data provide additional support for the possible use of ABT in biologic-naïve patients with established RA in routine care.

W57-3

Body mass index(BMI) does not influence the efficacy of abatacept in Bio-Naïve RA patients with an inadequate response to MTX

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Conflict of interest: Yes

[Objectives] Recently, There are some reports that RA patients with a high BMI response less well to TNF inhibitors. The purpose of this study was to determine whether BMI affects response to abatacept (ABT) in Bio-Naïve RA patients investigated prospectively from ABROAD study. [Methods] In 129 analyzable patients with active RA with from ABROAD study, the BMI was calculated before initiation of ABT treatment (BMI: categorized as the group(1) of BMI <20, the group(2) of BMI20-25 and the group(3) of BMI >25). After 24 weeks of ABT treatment, changes in disease activity were assessed with SDAI andDAS-28-CRP. [Results] At baseline, No significant differences were seen in either SDAI or DAS-28-CRP among the 3 different BMI groups ((1),(2),(3)). After 24 weeks of ABT treatment, a SDAI≦3.3/DAS28-CRP≦2.3 was noted in 11.8%/38.2% of the patients (group(1)) with a BMI<20, 21.1%/43.1% of the patients (group(2)) with a BMI 20-25 and 28.6%/53.3% of the patients (group(3)) with a BMI>25 (no significant among the 3 different BMI groups). [Conclusion] Unlike TNF inhibitors, these data show that BMI does not influence the efficacy of abatacept in Bio-Naïve RA patients with an inadequate response to MTX.

W57-4

Analysis of the associated factor with clinical remission achieved by abatacept in biologics-naïve patients with rheumatoid arthritis (ABROAD study)

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Conflict of interest: Yes

【Objective】 In the present study using ABROAD (ABatacept Research Outcome as a first-line biological Agent in the Real worlD) patient cohort in the west side of Japan, we intended to clarify an associated factor with clinical remission achieved by abatacept (ABT) in biologics-naïve rheumatoid arthritis (RA). 【Methods】 Clinical remission rate and the associated factor with remission induction in 155 patients (female = 83.2%, 61.3±13.6 years old at the ABT initiation, and disease duration= 8.1±9.6 years) were examined at 4, 12, and 24 weeks retrospectively. 【Results】 In our patients, 37.4% (DAS28-CRP) and 16.0% (SDAI) showed remission at 24 weeks. While 71.6% of our patients were methotrexate (MTX) users, clinical remission rates defined by both criteria were not affected by the concomitant use of MTX at any periods. DAS28-CRP remission at 24 weeks, however, was more frequently observed in patients with (48.7%) than without (21.1%) anti-cyclic citrullinated peptide antibodies (anti-CCP Abs) (p <0.05). 【Conclusion】 We conclude that ABT is one of the agents rapidly inducing biologics-naïve RA to clinical remission and the effectiveness may be significant in anti-CCP Ab-positive patients.

W57-5

Multicenter prospective study of clinical usefulness of abatacept in patients with rheumatoid arthritis (2nd report)

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Conflict of interest: None

[Objectives] A multicenter prospective study was performed to analyze clinical usefulness of abatacept in patients with rheumatoid arthritis (RA). [Methods] 78 cases that completed the study for 12 months were subjected. The mean age: 61.3 year-old, male:female=15:63, mean disease duration: 9.9 years (3m~45y). 61 were on methotrexate (MTX), 17 were not. Mean MTX dosage: 8.9 mg/week. 31: Bio-Naïve, 47: Bio-Switched. [Results] Remission rate at 12 months were 16.9% in all cases, 30.0% in Bio-Naïve, and 8.5% in Bio-Switched, 22.0% in MTX+, 0% in MTX-, evaluated with SDAI. ΔmTSS was -0.18 at 12 months compared to 3.94 at 0 month (p<0.01). The percentage of subjects that attained ΔmTSS less than 0.5 was 88.9%. Serum IL-6 level was significantly decreased at 12 months compared to 0 months (21.8 and 1.4 pg/ml). There was no significant difference in serum TNFa level. Abatacept was discontinued in five cases, including bacterial pneumonia, pneumocystis jirovecii pneumonia, non-tuberculous mycobacterial infection, liver dysfunction, and vertigo. [Conclusion] These findings suggest that abatacept is useful and more effective in Bio-Naïve compared to Bio-Switched. MTX may strengthen the effect of abatacept in some patients. Abatacept may have greater effect on IL-6 compared to TNFa.

W57-6

The efficacy and safety of abatacept in patients with rheumatoid arthritis for 52 weeks

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Conflict of interest: None

[Objectives] The efficacy and safety of abatacept (ABT) in rheumatoid arthritis (RA) patients were evaluated. [Methods] 50 patients received ABT for at least 52 weeks; 27 patients had just started ABT, mean age was 65.2 years and the mean disease duration was 9.7 years. 26 patients had a history of lung disease. [Results] The mean values of each factor at baseline/Week 52 were as follows: CRP 1.99/0.80, ESR 44.3/27.5, MMP-3 195.6/91.1, DAS28-CRP 4.13/2.68, DAS28-ESR 4.78/3.31, SDAI 23.5/9.6, and ΔTSS 7.56/0.75. The remission rates of DAS28-CRP, DAS-28ESR, and SDAI were 34.0%, 32.0%, and 22.0%. 9 patients discontinued treatment. One patient discontinued due to adverse reactions. Clinical remission was a significant decrease in MMP-3. Total CRP and total MMP-3 until Week 52 were significantly lower in patients with structural remission compared to patients without structural remission. Factors related to the progression of joint destruction were RF negative, no use of MTX, and switching treatments. [Conclusion] In RA treatment by ABT, MMP-3 is a useful index of efficacy. For the evaluation of structural remission, it is useful to monitor total CRP and total MMP-3. Patients with risk factors for joint destruction should be closely monitored including more frequent TSS assessments.

W58-1

Helper T cell pathogenicity and its contribution to responsiveness to ABT treatment in patients with RA

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Conflict of interest: Yes

[Purpose] Abatacept (ABT) works through a different mechanism of action from TNF inhibitors in RA treatment. However, little is known about cell populations targeted by ABT. We investigated the phenotype of helper T cells associated with responsiveness to ABT treatment. **[Results]** The proportion of $CD4^+CD28^-$ cells increased in RA patients compared to healthy donors (HD). Baseline levels of CD28 on $CD4^+$ cells have positively correlated with ⊿DAS28 and ⊿SDAI. By contrast, baseline proportion of $CD4^+CD28^-$ cells was higher in patients who failed to achieve a remission at 24 week after treatment. $CD4^+CXCR5^+$Tfh and $CD4^+CXCR3^+$Th1 cells increased in RA, compared to HD. $CD4^+CD28^+$ cells consisted of activated Tfh and Th1 in naïve and central memory phase: the proportion of Tfh cells increased in APCA-positive patients, whereas that of Th1 cells was correlated with disease activity. $CD4^+CD28^-$ cells consisted of Th1 in effector memory phase, showing no correlation to disease activity. **[Conclusion]** These results imply that $CD4^+CD28^+$ cells, which consist of Tfh associated with production of autoantibody and Th1 associated with disease activity, are target of ABT, whereas $CD4^+CD28^-$ cells, which consist of terminally differentiated Th1, might be associated with refractoriness to ABT treatment.

W58-2

Abatacept treatment suppresses T cell activation in anti-cyclic citrullinated peptide antibodies (ACPA) positive patients but not in ACPA negative patients

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Conflict of interest: Yes

[Objective] We have reported that elevated activation of CD4+ T cells was observed in anti-cyclic citrullinated peptide antibodies (ACPA)(+) compared with (-) patients (JCR2013, Murakami et al). Thus we compared treatment effect, T cell activation markers, T cell subsets and cytokine profiles between ACPA (+) and (-) patients during abatacept (ABA) treatment. **[Methods]** PBMCs were isolated from 45 patients enrolled in ABROAD study before and at 24 weeks of treatment. Proportions of CD25 in CD4+ T cells, Treg, Th1, Th2 and Th17 were analyzed with FACS. The ACPA and cytokines were measured with EliA CCP and CBA Assay kit, respectively. **[Results]** There was no difference in DAS28-CRP at baseline between ACPA(+) (n=38) and (-) (n=7) patients. ΔDAS28-CRP was greater in ACPA(+) than in (-) patients. Remission was more frequently achieved in ACPA(+) than in (-) patients (43% vs 14%). Activated CD25+ T cells were decreased in ACPA(+) but not ACPA(-) patients. Treg, Th2 and Th17 significantly decreased in ACPA(+) patients. Plasma IL-6 decreased in both ACPA(+) and (-) patients. **[Conclusion]** Activated CD4+CD25+ T cells decreased by ABA treatment in ACPA(+) but not in ACPA(-) patients. It is suggested that abatacept has therapeutic effect in ACPA(-) patients by different mechanism of action.

W58-3

Effects of abatacept on antibody production of human B cells

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Conflict of interest: None

[Objectives] Biological agents provide significant beneficial clinical effects in RA patients. However, the precise immunomodulatory effects of biologics remain unclear. The current study was therefore undertaken to explore the effects of abatacept on antibody production of human B cells. [Methods] PBMC were obtained from healthy adult volunteers by centrifugation of heparinized venous blood over sodium diatrizoate-Ficoll gradients. B cells were purified from monocyte-depleted cells by E rosette formation. PBMC (1.25×10^6/ml) were cultured with staphylococcal enterotoxin B(SEB, 100 pg/ml) in the presence of abatacept or control IgG Fc(10-100 μg/ml) for 10 days. B cells(5×10^5/ml) were cultured with IL-2(0.5 U/ml) and Staphylococcus aureus Cowan I (SAC) in the presence of abatacept or control IgG Fc(10-100 μg/ml) for 10 days. The concentrations of IgM in the culture superna-

tants were measured using ELISA. [Results] Abatacept appeared to suppress the IgM production of both SEB-stimulated PBMC and SAC-stimulated human B cells, although it did not reach the statistical significance. [Conclusion] The data indicate that the inhibition of immunoglobulin production by abatacept involves the suppression of T cell responses, as well as the direct effects on B cells.

W58-4

Study of the antibody titer by influenza vaccination in patients with rheumatoid arthritis

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Conflict of interest: None

[Objectives] Study how the antibody titer by influenza vaccination for patients who have been treat abatacept (ABT) in rheumatoid arthritis patients change. [Methods] It is targeted for people 33 patients who began treatment in the post-marketing ABT. The vaccine was examined seroconversion rate, rate of change antibody, the antibody positive rate was measured before and after the treatment of the antibody titer to dose 1 H1N1, H3N2, influenza mixing B. [Results] When it is determined in EMEA evaluation criteria are based on global evaluation of the efficacy of influenza vaccines in the case of 33 patients, efficacy was not apparent as a whole. I've evaluated separately in 22 cases and 60 cases of elderly people over the age of 11 young people under the age of 60.In the group of young people showed the effectiveness of, H3N2 H1N1. However, do not meet the criteria in all serotypes seroconversion rate, rate of change of antibody, antibody prevalence in the elderly group efficacy was not observed. [Conclusion] In patients treated by ABT, the result of this, the effect of the vaccine for the elderly did particularly low. Was future, the difference in the effectiveness of the vaccine effect of other types of biologic agents, by age, such as the need to consider multiple doses of the vaccine.

W58-5

Experimentation about serum cytokines in rheumatoid arthritis patients treated with abatacept by using multi-cytokine ELISA system

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Conflict of interest: Yes

BACKGROUND: Abatacept (ABT) is an only biologic whose target is not directly to cytokines. The kinetics of serum cytokines in rheumatoid arthritis (RA) patients treated with ABT remain unclear. **OBJECTIVE:** To examine the mechanism of ABT for RA patients on the basis of serum cytokine levels. **METHODS:** Clinical data of 43 RA patients who had not been treated with any biologics was collected. The levels of cytokines, IL-6, TNFα, IL-1β, IL-2, IL-8, IL-10, IL-12p70, IFNγ, GM-CSF were quantified using multi-cytokine ELISA at a baseline(Week 0), Week 2, 12 and 24 of treatment with ABT. The relations between the levels of cytokines and clinical data were analyzed. **RESULTS:** The mean age was 64.9 years, with the mean disease duration of 8.3 years. Mean DAS28-ESR was 5.34/3.69/3.51 at Week0/12/24 respectively. EULAR good/moderate/no response rate at Week 24 was 42/39/19% respectively. The levels of all 9 cytokines at Week 24 were not significantly different from those at Week 0. Changes of the levels of the cytokines were not also correlated with those of DAS28-ESR. The levels of serum IL-6 decreased in EULAR good response patients and increased in EULAR no response patients, but which was not statistically significant. **CONCLUSION:** ABT is effective for RA with mechanism other than cytokines.

W58-6

The effect of abatacept on bone homeostasis in rheumatoid arthritis

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Conflict of interest: None

[Objectives] Abatacept (ABT) improved the pathogenesis of rheumatoid arthritis (RA). However, the effects of ABT on bone homeostasis in RA are poorly understood. In this study, we investigated the effects of ABT on biochemical markers of bone, serum RANKL, osteoprotegerin (OPG), and plasma osteopontin (OPN) in patients with RA. [Methods] 24 patients with RA were started on treatment with ABT for 24 weeks. Circulating levels of NTx, osteocalcin, RANKL, OPG, and OPN were examined by ELISA at baseline and after 12 and 24 weeks. [Results] After 24 weeks of ABT treatment, DAS28-CRP and SDAI decreased significantly from the baseline (4.6 vs 2.5; $p<0.01$, 26.7 vs 8.6; $p<0.01$, respectively), so that 14 patients achieved DAS28-CRP remission. After 12 weeks, average of NTx level decreased significantly from the baseline (16.27 vs 14.23nmol BCE/l; $p<0.01$). After 24 weeks, average of osteocalcin level increased significantly (5.80 vs 6.45ng/ml; $p<0.05$) and average of OPN level decreased significantly (101.57 vs 71.76pg/ml; $p<0.01$), whereas average of RANKL and OPG levels did not change significantly from the baseline. [Conclusion] These results suggest that ABT may improve abnormal bone homeostasis in RA via the regulation of OPN expression in activated T lymphocytes.

W59-1

DNA microarray analysis of labial salivary glands in IgG4-related disease: Comparison with Sjögren's syndrome

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Conflict of interest: None

[Objectives] We previously showed high expressions of IL-10, TGFβ, and AID in labial salivary glands (LSG) of IgG4-related disease (IgG4-RD). The purpose of this study was to clarify the molecules which played pathogenic roles in IgG4-RD exhaustively. [Methods] 1) Gene expression was analyzed by DNA microarray in LSG of IgG4-RD (N=3) and Sjögren's syndrome (SS) (N=3). Differentially expressed genes (DEGs) in IgG4-RD and SS were identified, and gene-annotation enrichment analysis of these DEGs was performed using Gene Ontology (GO) annotation. 2) Validation of the result was performed by quantitative PCR using LSG

from IgG4-RD (N=8), SS (N=11), and controls (N=3). [Results] 1) Gene expression patterns in IgG4-RD and SS were quite different in hierarchical clustering. In IgG4-RD, 580 up-regulated and 280 down-regulated genes were identified as DEGs. GO analysis indicated the up-regulated set of DEGs in IgG4-RD encoded proteins that function in T cell activation, chemotaxis, and immune responses. 2) PCR validated significantly higher expression of CCL18 which related to chemotaxis and fibrosis, in IgG4-RD than in SS and controls ($P<0.05$). [Conclusion] The results indicated the gene expression pattern of IgG4-RD was different from SS, and CCL18 might relate to pathogenesis of IgG4-RD.

W59-2

RP105-negative B cells in IgG4-related disease

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Conflict of interest: None

[Objectives] We studied a recently recognized novel systemic inflammatory disorder, IgG4-related disease, focusing on B cell dysregulation. B cell dysregulation was speculated in the disease. However, there has been little information about circulating B cells. [Methods] We examined RP105-negative B cells in peripheral blood from 4 patients with IgG4-RD using a flow cytometry. [Results] The percentage of RP105-negative B cells in the IgG4-RD patients (mean +/- SD) was 20.7 +/- 9.2 %, range 8.3-29.7%. The populations of RP105-negative B cells were larger in all of four patients with IgG4-RD compared with the healthy subjects (n= 31, mean +/- SD; 2.6 +/- 1.6 %, range 0.8-7.8%) ($p=0.01$). [Conclusions] IgG4-RD is the fourth disease of increased RP105-negative B cells. Our findings may contribute to investigate pathophysiology of IgG4-RD and establish a new target for the therapy in B cell activated diseases.

W59-3

Investigation of cut off value of IgG4-positive plasma cell number and IgG4-positive/ CD138-positive cell ratio in typical lesions of patients with IgG4-related disease

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Conflict of interest: None

[Objectives] To investigate the validity of the different cut off values of IgG4+ plasma cell (PC) number and IgG4+/CD138+ cell ratio proposed by Japan comprehensive diagnostic criteria (CDC) and international consensus statement on the pathology (CS) of IgG4-related disease (IgG4-RD) in typical lesions of patients with IgG4-RD. **[Methods]** We evaluated IgG4+ PC number and IgG4+/CD138+ cell ratio in 22 specimens from 11 IgG4-RD patients having two typical enlarged, hypertrophic or nodulous lesions. **[Results]** We evaluated 7 submandibular, 6 ophthalmic, 4 skin, 2 pancreatic lesions, and one each lesion of kidney, bronchus, and prostate. Concerning IgG4+ PC number, all 22 lesions fulfilled the cut off value of CDC. Most ophthalmic, pancreatic, kidney, and bronchial lesions also fulfilled the cut off value of CS, whereas submandibular and skin lesions seldom fulfilled it. Almost all lesions fulfilled the cut off value of IgG4+/CD138+ cell ratio. In 4 problematic cases, one lesion fulfilled the cut off value of CS and the other did not in the same patient. **[Conclusions]** Our results suggest the necessity to evaluate the sensitivity and specificity of the existing cut off values of IgG4+ PC number and IgG4+/CD138+ cell ratio in the affected lesions of IgG4-RD in larger studies.

W59-4

The clinical course of IgG4-related kidney disease

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Conflict of interest: None

[Objectives] To examine the clinical course of IgG4-related kidney disease (RKD) [Methods] We retrospectively examined the clinical course of 43 patients with IgG4-RKD, of whom most patients were treated with, and maintained on, corticosteroids. [Results] In 34 of the steroid-treated patients whose follow-up period was more than 12 months, the eGFR before treatment was >60 ml/min in 14 patients (group A), and <60 ml/min in 20 patients (group B). In group B, eGFR before treatment (34.1 ±15.8 ml/min) was significantly improved at 1 month after the start of treatment (45.0±13.8 ml/min), and renal function was maintained at a similar level at the last review. Although all of the renal radiologic abnormalities characteristic of IgG4-related kidney disease were improved at 1 month after the start of treatment, renal atrophy had developed in 12 of the 24 evaluated patients (2/8 in group A and 10/16 in group B) at the last review. [Conclusion] Corticosteroid therapy is effective for rapid, but not total, amelioration of renal lesions, and also for preservation of renal function in a low-dose maintenance setting in patients with IgG4-related kidney disease, although a prospective study will be necessary to elucidate the need for maintenance therapy.

W59-5

Comparison of clinical features of IgG4-related retroperitoneal fibrosis and IgG4-not-related retroperitoneal fibrosis

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Conflict of interest: None

[Objectives] To elucidate clinical differences of IgG4-related and not-related retroperitoneal fibrosis (RF). [Methods] We compared clinical charesteristics of 4 patients (male 2, female 2) of IgG4-related RF and 3 patients (male 1, female 2) of IgG4-not-related RF who are outpatient of our department as of November 2012. [Results] Mean age at diagnosis among the patients of IgG4-related RF was significantly lower than IgG4-not-related RF. 2 of patients among IgG4-related group had comorbid allergic disease, such as asthma, rhinitis, and urticaria, but none of the patients among IgG4-not-related groups (not significant). On laboratory findings, serum IgG4/IgG ratio was significantly higher in IgG4-related group, but serum IgG4, C-reactive protein, creatinine, estimated GFR were not significantly different in two groups. On computed tomography, IgG4-related RF existes in perirenal space

in all patients and extended to periaortic tissue in 1 patient, but IgG4-not related RF localized in periaortic tissue. 2 of the patients of IgG4-related RF and 2 of IgG4-not-related RF treatment with oral predonisolone was started, and mean initial dose was significantly higher in IgG4-not-related group (49.75 vs 32.5, $p<0.05$). [Conclusion] There is room for investigation for these 2 groups.

W60-1

Transcriptome analyses of IgG4-related disease

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Conflict of interest: None

[Objectives] IgG4-related disease(IgG4-RD) is a novel disease entity. We explored the cause of IgG4-RD by transcriptome analyses. [Methods] We conducted DNA microarray analyses by using RNA of peripheral blood mononuclear cells from two IgG4-RD patients and four healthy controls, and we validated by real-time PCR for 18 IgG4-RD patients and 13 healthy controls. [Results] DNA microarray; we chose genes that showed more than three-hold change between pre and post steroid therapy. Three-hold changing genes between the patients and healthy controls were also chosen. These contain a number of innate immunity-related genes, therefore we suspected relations between IgG4-RD and innate immunity. Real-time PCR; PCR was performed for innate immune-related genes of transcobalamin I (TCN1), bactericidal/permeability-increasing protein (BPI), secretory leukocyte peptidase inhibitor (SLPI), myeloperoxidase (MPO) and lactotransferrin (LTF). TCN1 was significantly reduced in the patients compared to the healthy group. TCN1, BPI and SLPI were significantly higher after steroid therapy than before. There were no significant differences in other factors. [Conclusion] There is a possibility that low expressions of the innate immune-related genes and low amount of some substances in neutrophils may cause IgG4-RD.

W60-2

Predominance of Th2 and regulatory cytokines in the serum of a patient with IgG4-related lymphadenopathy (IgG4-RL)

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Conflict of interest: None

[Objectives] IgG4-related disease sometimes involves lymph nodes. However, patients with hyper-IL-6 syndromes frequently show lymph node involvement and often fulfill the diagnostic criteria for IgG4-RL. Therefore, diagnosis should not rest on pathological findings alone but be supplemented with additional laboratory analyses. We have performed a comprehensive analysis of serum cytokine levels in a patient with IgG4-RL. [Methods] The patient was a 76-year-old man with multiple lymphadenopathy. Serum IgG4 increased at 1140 mg/dl. After left inguinal lymph node biopsy, he was diagnosed with IgG4-RL. He was treated with prednisolone (30 mg/day). Serum levels of 26 types of cytokines were measured by a bead-based multiplex assay. [Results] Levels of Th2 and regulatory cytokines such as IL-4, IL-5, IL-10, and IL-13 in the patient's serum before treatment were markedly higher than in the serum after treatment and higher than in healthy controls. Levels of IL-6, IL-8, TNFα, and IFNα2 were modestly increased in the patient's serum before treatment, while serum levels of IFNγ and IL-17 were increased after treatment. [Conclusion] Markedly raised levels of serum IL-4, IL-5, IL-10, and IL-13 may be useful to support the diagnosis of IgG4-RL, but this should be confirmed in larger cases.

W60-3

Proteomics analysis in IgG4-related disease

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Conflict of interest: None

[Objective] We conducted a comprehensive analysis of proteins that change in a disease specific manner, using the serum of patients with IgG4-related disease before and after treatment, and that of healthy individuals, in order to identify proteins that are associated with the pathogenesis of IgG4-related disease. **[Method]** After protein removal as a pretreatment, two-dimensional electrophoresis of the serum was conducted and silver staining method was used. We also cut out the spots which changed before and after treatment and detection was performed by ESI-MS/MS. In addition, we identified proteins whose expression significantly changed before and after treatment, as well as those between healthy individuals and patients and confirmed the results with ELISA. **[Results]** From two IgG4-related disease cases, we extracted 38 proteins which significantly changed expression before and after treatment. We found the increase in IgG1 and IgG4 as well as in inflammatory factors such as Alpha-1 antitrypsin, Complement 4 and C1q in serum. **[Conclusion]** It was suggested in this study that the balance between protease and protease inhibitor may be responsible for the induction of class-switching and related to the regulation of IgG4 synthesis in pathological condition of the IgG4-related disease.

W60-4

Clinical characteristics and their changes associated with corticosteroid therapy in IgG4-related periaortitis/periarteritis

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Conflict of interest: None

[Objectives] To clarify the clinical characteristics and changes after corticosteroid (CS) therapy in IgG4-related periaortitis/periarteritis (PA) **[Methods]** We evaluated clinical data, imaging findings, and changes after CS therapy in 10 patients with PA among 59 patients with IgG4-related disease (IgG4-RD). **[Results]** All 10 patients were men (average age 66 years). 9 patients had other organ involvement that fulfilled the diagnostic criteria of IgG4-RD. No patients had any subjective symptoms from PA. Patients with PA showed significantly higher male predominance, higher frequency of pancreatic lesion, and more other organ involvement than those without. The affected aorta/artery comprised 8 abdominal aortas, 1 thoracic aorta, 8 iliac arteries, and 1 superior mesenteric artery. 8 patients were treated with prednisolone (PSL), and reduction in the size of the perivascular lesions was observed in 7

patients, 2 of whom showed aneurysm formation of the affected lesions. Recurrence during PSL tapering was observed in one patient. **[Conclusions]** In our study, we found some characteristics such as scanty subjective symptoms and much other organ involvement. Since some patients showed aneurysm formation of the affected lesions after corticosteroid therapy, careful observation is needed.

W60-5

For analysis of cinicopathological features fo IgG4-related disease(IgG4-RD), 104 cases were registered in Multicenter diagnostic study for IgG4$^+$MOLPS, Castleman's disease, and other polyclonal hypergammopathies

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Conflict of interest: None

For analysis of cinicopathological features fo IgG4-related disease(IgG4-RD), 104 cases were registered in Multicenter diagnostic study for IgG4$^+$MOLPS, Castleman's disease, and other polyclonal hypergammopathies. 65 cases of definite diagnosed IgG4-RD, 29 suspected case o f IgG4-RD, 2 Sjogren's syndrome (SS), and 4 Castleman's disease were registered. Average age of definite IgG4-RD cases were 64.0 years old, 41 male and 20 female. 25 cases had only one involved organ, 22 had 2 organs, and 18 had 3 or more involved organs. The site of involved organs were 35 cases of salivary glands, 19 pancreas, 12 lacrimal gland, 12 lymph nodes, 10 retroperitoneum, 8 orbit, 8 thyroid, 6 bile duct, 4 prostate, 4kidney, and 3 lung. 8 cases had bronchial asthma and 14 had allergic rhinitis. Average levels of each laboratory data were IgG 2252.7mg/dL, IgG1 1092.6mg/dL, IgG2 809.2mg/dL, IgG3 77.8mg/dL, IgG4 715.4mg/dL, IgE 536.8 mg / dL. C3 87.3 mg/dL, C4 18.8mg/dL, and CH50 42.8mg/dL. IL-6 2.55pg/mL, CRP 1.46mg/dL,and RF 7.8U/mL,and 18 cases had positive antinuclear antibody. We continue analysis including pathological central review.

W61-1

Efficacy and safety of abatacept in patients with refractory systemic lupus erythematosus

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Conflict of interest: None

Abatacept (ABT) has been emerged as a novel treatment strategy for RA. To estimate efficacy and safety of ABT in patients with refractory SLE, ABT was administered in 7 patients with refractory SLE (3 have RA) and estimated at 0, 1, 6 months. Informed consents were obtained, Disease activity of SLE and RA at the baseline is as followings; SLEDAI 9.5, BILAG 7.2, DAS28 4.37, SDAI 14.7. During 6 months treatment with ABT, most frequent adverse events were infection (2/7) but they were tolerable. In terms of efficacy of ABT, disease activity at 1 month; SLEDAI 3.9, BILAG 3.3, DAS28 3.03, SDAI 7.0 and at 6 months SLEDAI 2.1, BILAG 2.3, DAS28 3.39, SDAI 2.3. Based on SLE Responder Index, SLEDAI score reduced by at least 4 points in 6/7 patients, no BILAG A or no more than 1 new B was 7/7 patients at 6 months.. Based on the EULAR response criteria, 1 and 2 achieved a good and moderate response, respectively, and 1 and 2 reached SDAI-LDA and SDAI-REM, respectively at 6 months. Taken, together, ABT is tolerable and effective in refractory SLE patients who do not respond to glucocorticoid plus immunosuppressants. Thus, this pilot study indicates a potential of ABT in refractory SLE and it would warrant further assessments in multi-center trials.

W61-2

Efficacy of Tacrolimus combination therapy during the maintenance phase of Systemic Lupus Erythematosus

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Conflict of interest: None

[Objectives] Efficacy of the Tacrolimus (TAC) combination therapy was examined during the maintenance phase of SLE. If the clinical symptom was worsening and/or decreasing titer of serum complement, added TAC to existing formula, because of the decreasing the dosage of prednisolone (PSL). [Methods] Since 2009 to 2012, 38 patients were examined during the 1 year study period. If the clinical symptom was worsening and/or decreasing titer of serum complement (C3c), TAC combination therapy (from 1mg to 5mg per day) was received. Score of the SLEDAI, dosage of PSL, serum level of C3c, titer of the anti-dsDNA and proteinuria were examined. [Results] Twenty-eight patients were effective. 1) Dosage of PSL was reduced from 11.7±5.6 to 8.2±4.2 (mg/day) ($P<0.001$). 2) Serum level of C3c increased from 74.7±21.9 to 86.4±17.8 (mg/dl) ($P=0.006$).3) Titer of anti-dsDNA was decreased from 39.6±68.0 to 24.8±49.1 (U/ml) ($P<0.001$) 4) Score of the SLEDAI improved from 6.2±3.7 to 2.6±2.3 ($P<0.001$). Although proteinuria decreased from 46.0±95.7 to 30.7±74.2 (mg/dl), there were no significant difference ($P=0.23$). On the other hand, 8 patients were not effective or worsening and 2 patients discontinued due to an adverse effect. [Conclusion] TAC combination therapy was clinically useful for the maintenance phase of SLE.

W61-3

Efficacy and safety of tacrolimus for thrombocytopenia in SLE patients

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Conflict of interest: None

[Objectives] To evaluate the efficacy and safety of tacrolimus (TAC) for thrombocytopenia in SLE patients. [Methods] Twenty-

six SLE patients (21 female, average age 46.6±17.7) who had received TAC for thrombocytopenia from April 2006 to March 2012 were enrolled for this retrospective analysis. Thrombocytopenia was defined as less than 148,000/μl (lower limit of the normal range). Primary end point was platelet count at 12 weeks after TAC was started. Secondary endpoints were platelet count at week 24, SLEDAI score at week 12, the dosage of concomitant corticosteroid (CS) at week 12 and adverse events during 24 weeks. [Results] At the start of TAC, platelet count was 9.5±4.4 $\times 10^4$ /μl, SLEDAI score was 4.4±3.6, and average dosage of concomitant CS was 19.4±16.8 mg/day. Platelet count was significantly elevated to 14.5±8.2$\times 10^4$/μl at week 12, and restored at week 24 (14.7± 7.9$\times 10^4$/μl; $p<0.05$, 0.01). SLEDAI score significantly decreased to 2.1±2.8 ($p<0.05$) and dosage of CS was tapered to 10.7±2.7mg/day ($P<0.05$) at week 12. Adverse events were seen in 4 cases (eruptions in 2, alopecia and worsening of diabetes), but all of them were not severe. [Conclusion] TAC seems to be safe and effective for not only lupus nephritis but also thrombocytopenia in SLE patients.

W61-4

Long-term efficacy and safety of tacrolimus for lupus nephritis

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Conflict of interest: None

[Objectives] To evaluate long-term efficacy and safety of tacrolimus for the treatment of lupus nephritis. [Methods] A total of 29 patients with lupus nephritis were enrolled in the study for at least five years. Patients were administered for tacrolimus at the dose of 2-3 mg/day once daily after the evening meal. [Results] The values of U-prot/ U-creat and serum albumin were significantly improved as early as 8 weeks and 4 weeks, respectively, after the initiation of tacrolimus. The effect of tacrolimus continued at least until 208 weeks. The values for serum complement and anti-dsDNA Ab were significantly improved after the treatment of tacrolimus. Tacrolimus treatment was continued for 64.5% of the patients at 208 weeks. Steroid-sparing effect of tacrolimus was evident, because initial daily steroid dose (11.25mg) was gradually and significantly reduced to 7.0mg at 208 weeks. [Conclusion] Long-term efficacy and safety of tacrolimus for lupus nephritis was demonstrated in the present study

W61-5

Treatment of refractory SLE with combination of tacrolimus and mizoribine

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Conflict of interest: None

[Objectives] We have focused on combination therapy with tacrolimus (TAC) and mizoribine (MZR) as induction or additional therapy for refractory SLE, such as lupus nephritis and cytopenia,. [Methods] We evaluated 19 consecutive patients (average age:44 years, 4 men) treated with this protocol since Apr. 2009. [Results] Nine cases, out of which four were affected with lupus nephritis, three were with cytopenia, one with eruption and the other with arthritis, were initially treated with this protocol and ten cases were additionally recieved. Ten cases treated additionally included three patients suffering with lupus nephritis, three with eruption and hypocomplementemia, three with fever, and one with cytopenia. It was possible to reduce the dose of predonisolone without flare in sixteen cases, which showed improvement of clinical findings, decrease of the autoantibodies, and elevation of complement. One case presented cardiac hypertrophy which is suspected to be due to TAC administration (and it resolved with discontinuation of this drug), another case died from cryptococcal meningitis 9 months after the initiation of the therapy, and the other case showed an elevation of serum creatinine. [Conclusion] It seems that the combination therapy with TAC and MZR is effective for refractory SLE.

W61-6

Successful treatment of refractory acquired pure red cell aplasia with anti-thymocyte globulin (ATG) in a patient with systemic lupus erythematosus (SLE)

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Conflict of interest: None

Pure red cell aplasia (PRCA) is characterized by an absence of red cell precursors in the bone marrow. PRCA is also known as a rare complication of SLE. We experienced a case of SLE with refractory PRCA, who was successfully treated by ATG. The patient was a 36-year-old woman. In 1988, she was diagnosed as SLE with hemolytic anemia and was treated with high dose of prednisolone (PSL). In 1994, she had lupus nephritis (WHO IV) and was treated with high dose of PSL in combination with intravenous cyclophosphamide (IVCY). In February 2008, she showed macrocytic anemia and the bone marrow aspiration showed remarkable decrease of erythroblast. She was diagnosed as PRCA complicated with SLE. After initial treatment with cyclosporine A (CsA), her hemoglobin rapidly increased and stayed in remission for 15 months. However in April 2010, PRCA relapsed and was resistant to further treatments including IVCY, tacrolimus, and steroid pulse therapy. We administrated ATG in combination with CsA in June 2011. 20 days after treatment, her hemoglobin normalaized and she became independent of transfusion. She has stayed in remission for 17 months without any remarkable adverse effect.

W62-1

The cause of death in patient with systemic lupus erythematosus

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Conflict of interest: None

[Objectives] We studied the causes of death in patient with systemic lupus erythematosus (SLE),particularly focusing on changing with the times. [Methods] We retrospectively studied patient with SLE who died between 1991 and 2011.Causes of death and

complications were identified on the basis of medical record and postmortem examination.Then we compared the causes of death before 2000 with after 2001. [Results] A total of 44 patients died;53.1years old was the average age of death and the mean years from a diagnosis were 22.7years.The number of the death of the patient by infectious disease,vascular disease,active disease manifestation of SLE,malignant neoplasm were 14,14,9,6,respectively.The portion of death during an exacerbation period of SLE decreased from 75% to 36% after 2001 from before 2000(p=0.01). The average age of death and mean period from diagnosis of SLE having malignant neoplasm or vascular disease were 64 years old,28.2years and 55.3years old,25.1years,respectively. [Conclusion] The prognosis of SLE has been improved recently. The early detection of malignancy and reduction the risk of vascular disease are important.

W62-2

Brain MRI findings in patients with diffuse psychological/neuropsychiatric syndromes in systemic lupus erythematosus

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Conflict of interest: None

[Objectives] To investigate the association of abnormal findings on brain MRI and various parameters in patients with diffuse psychological/neuropsychiatric syndromes in SLE (lupus psychosis, LP). **[Methods]** Twenty-five patients with LP admitted since 2000 were studied. The relation of MRI abnormalities with various parameters was examined. **[Results]** Of 25 patients (total 18 acute confusional state, 3 psychosis, 2 anxiety disorder, 2 mood disorder and 2 cognitive dysfunction), 15 patients [60%] had abnormal MRI findings, in which 13 had high intensities in the white matter (T2 in 8, FLAIR in 11 and DWI in 6) and 2 had meningeal lesions. MRI findings were ameliorated after treatment in 7 patients. The presence of MRI abnormalities was not correlated with the ages at the onset of LP, LP manifestations, serum autoantibodies or CSF IL-6. However, disease duration of SLE was significantly longer in patients with abnormal MRI findings (p=0.0284). **[Conclusion]** These results indicate that LP could be classified into 3 different groups of different pathogenesis depending on the MRI findings. Especially in LP patients with improvement of MRI abnormalities, vasculitis might be involved in the pathogenesis. The role of autoantibodies in these differential MRI findings remains to be clarified.

W62-3

Detection of cerebral microvessel lesions in patients with Neuropsychiatric systemic lupus erythematosus by 7Tesla MRI

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Conflict of interest: None

[Objectives] The cerebral microvascular (CV) lesions of patients with neuropsychiatric systemic lupus erythematosus (NPSLE) have not been fully elucidated. The 7Tesla(T) MR scanner has high image resolution and can be expected to detect CV lesions that have never before been visible.We examined the CV lesions of NPSLE using a 7T MR scanner. [Methods] We studied 5 NPSLE (mean age 30.2 years old) 10 non-NPSLE (mean age of 33.7 years old). Two radiologists performed the interpretation without clinical information. Diagnosis of NPSLE was determined by a neurologist, psychiatrist and rheumatologist. [Results] Examination by the 7T MRI revealed CV lesions in 4 of 5 NPSLE patients (acute phase, 3; past history, 1). These findings were not detected in any of the patients with non-NPSLE. The CV lesions were found around the central sulcus especially in T2WI. These MRI findings disappeared after central nervous symptom improvement in 2 of the 3 acute phase patients. However, we did not find a direct association between the MRI findings and the neuropsychology dysfunction. [Conclusion] CV lesions could be detected in patients with NPSLE by 7T MRI, suggesting that 7T MRI is a useful tool for diagnosing the cerebral lesions of NPSLE.

W62-4

Validity and Reliability of the Systemic Lupus Activity Questionnaire (SLAQ): A Prospective Study

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Conflict of interest: None

[Objectives] Traditional assessments of SLE disease activity, such as the SLE Disease Activity Index 2000 (SLEDAI-2K) are based on physician's assessment and laboratory evaluation. A self-administered questionnaire, the Systemic Lupus Activity Questionnaire (SLAQ) has been previously developed. The purpose of the present study was to translate and adapt the SLAQ to Japanese and further investigate its validity and reliability. **[Methods]** The English version of the SLAQ was translated, back-translated and culturally adapted to Japanese. Japanese SLE patients were asked to complete the SLAQ and other related demographic questionnaires and physicians were asked to complete the SLEDAI-2K. Patients were prospectively followed for a repeat assessment next year. **[Results]** A total of 273 patients and 30 physicians participated. The SLAQ had a weak correlation with the SLEDAI-2K-nolab (Spearman's $\rho = 0.18$) but not with SLEDAI-2K. The SLAQ demonstrated acceptable internal consistency, with a Cronbach's α of 0.85. The intraclass correlation coefficient was 0.85, which means good test–retest reliability. The SLAQ did not demonstrate a good responsiveness by the longitudinal analyses. **[Conclusion]** We have successfully translated, adapted and validated the Japanese version of the SLAQ.

W62-5

The Relationship between Health Related Quality of Life (SF-36) and Disease Activity and Damage in Japanese Patients with Systemic Lupus Erythematosus: A Two Year Consecutive Study

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Conflict of interest: None

[Objectives] It has been recommended that a measure of health-related quality of life (HRQoL) such as SF-36 be included in systemic lupus erythematosus (SLE) outcome studies. However, little has been studied about HRQoL in Japanese SLE patients. We sought to investigate associations between SF-36 and SLE disease activity and damage measures in Japanese. **[Methods]** Japanese SLE patients were asked to complete the SF-36 and other related demographic questionnaires and physicians were asked to complete the SLE Disease Activity Index 2000 (SLEDAI-2K) and the

SLICC/ACR Damage Index (SDI). Patients were prospectively followed for a repeat assessment next year. **[Results]** A total of 233 patients were analyzed. Most of the domain scores of the SF-36 were lower than norm-based scores. The SDI showed negative correlation with PCS. The SF-36 did not demonstrate a good responsiveness when patients were classified according to the changes in SLEDAI-2K or SDI. The SF-36 demonstrated acceptable internal consistency and good test–retest reliability. **[Conclusion]** The SF-36 is internally consistent and proves construct, discriminatory, and criterion validity among Japanese patients with SLE. HRQoL is reduced and rather independent from disease activity or disease damage in Japanese patients with SLE.

W62-6

Validity and Reliability of the Lupus Damage Index Questionnaire (LDIQ): A Prospective Study

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Conflict of interest: None

[Objectives] The SLICC/ACR Damage Index (SDI) is a validated instrument for assessing organ damage in SLE. A self-administered questionnaire, modeled after the SDI, the Lupus Damage Index Questionnaire (LDIQ) has been previously developed. The purpose of the present study was to translate and adapt the LDIQ to Japanese and further investigate its validity and reliability. **[Methods]** The English version of the LDIQ was translated, back-translated and culturally adapted to Japanese. Japanese SLE patients were asked to complete the LDIQ and other related demographic questionnaires such as Medical Outcomes Study Short Form-36 (SF-36) and physicians were asked to complete the SDI and the SLE Disease Activity Index 2000 (SLEDAI-2K). Patients were prospectively followed for a repeat assessment next year. **[Results]** A total of 273 patients and 30 physicians participated. The LDIQ had a substantial correlation with the SDI (Spearman's $\rho = 0.75$). The damage domains of the LDIQ were not associated with each other, which was reflected in low Cronbach's α (0.54). The intraclass correlation coefficient was 0.85, which means good test–retest reliability. The LDIQ demonstrated a good responsiveness. **[Conclusion]** We have successfully translated, adapted and validated the Japanese version of the LDIQ.

W63-1

Clinical characteristics of muscular symptoms in patients with systemic lupus erythematosus

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Conflict of interest: None

[Objectives] SLE cases that presented with muscular symptoms at this facility were examined clinically. [Methods] The disease activity, MRI image findings of the muscles, muscle breakdown enzymes and histological findings of 7 SLE patients were examined. These patients presented with muscular symptoms between January 2010 and October 2012. [Results] At the time of muscle symptom onset, the mean patient age was 32.7 years, with a male-female ratio of 1:6. All cases showed low complement levels, and showed elevated levels of ds-DNA antibodies. The mean SLE Disease Activity Index (SLEDAI) was 16. CK was elevated in 1 out of the 7 cases. Meanwhile, all cases showed increased Ald and the STIR sequence MRI of the muscles revealed a high intensity signal showing myofascial dominance over muscle. Moreover, *en bloc* biopsy was conducted in 4 cases and like the MRI findings, myofascial-dominant mononuclear cell infiltrates were observed. In all cases, a moderate to high dose of prednisolone was administered and muscle symptoms improved. This was accompanied by an improvement in muscle symptoms, decreases in Ald, ds-DNA antibodies and SLEDAI, and an increase in complement levels. [Conclusion] SLE induced myalgia may be a symptom caused by fasciitis, and Ald may become an index of activity.

W63-2

The analysis of risk factors for thrombosis in systemic lupus erythematosus

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Conflict of interest: None

[Objectives] To clarify the risk factors for thrombosis in SLE patients. [Methods] 97 patients with SLE (female 87) in the absence of past thrombotic events were recruited from 2001 to 2012. The endpoint was defined as development of thrombosis. The risk factors to develop thrombosis were retrospectively analyzed. [Results] Median age and follow-up periods in our patients were 32 years and 46 months, respectively. 14 patients developed thrombosis with the median follow-up period of 3.5 months. Cerebral infarction developed in 8 patients, pulmonary embolism in 5, deep vein thrombosis in 3. Multivariate analysis with Cox's proportional hazards model showed that older age at SLE onset (OR 2.01 for every ten age, 95%C.I. 1.26-3.20), aCL-IgG positivity (OR 8.37, 95%C.I. 2.15-32.6) and aCL-IgM positivity (OR 6.14, 95%C.I. 1.68-22.5) were statistically significant risk factors for thrombosis and statin use was significantly protective (OR 0.17, 95%C.I. 0.036-0.764). Disease activity, anti-thrombotic drugs and elements of accelerating artheriosclerosis were not related to thrombosis. [Conclusion] This study suggests that older age at SLE onset, aCL-IgG positivity, aCL-IgM positivity are risk factors and statin use is protective for thrombosis in SLE patients.

W63-3

Clinical features of hemophagocytic syndrome in patients with systemic lupus erythematosus and with adult-onset Still's disease

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Conflict of interest: None

[Objectives] We analyzed the clinical features of hemophagocytic syndrome (HPS) that developed in patients with systemic lupus erythematosus (SLE) or with adult-onset Still's disease (AOSD). **[Methods]** Splemomegaly, concentration of hemoglobin, white blood cell count, platelet count, levels of ferritin, and treatments were retrospectively analyzed in patients with HPS. **[Results]** A total of 16 HPS patients were enrolled in whom 8 patients had SLE and 8 patients had AOSD. At the diagnosis of HPS was made, splenomegaly was observed in 5 SLE and 5 AOSD patients. Concentration of hemoglobin was significantly lower in SLE patients (median 10.8 g/dl) than that in AOSD patients (median 12.0 g/dl), (p=0.0394). White blood cell count was significantly lower

in SLE patients (median 3,000/μl) than that in AOSD patients (median 9,950/μl), (p=0.0148). Steroid pulse therapy was undergone in 8 SLE and 7 AOSD patients, and additional immunosuppressants were administered to 5 SLE and 4 AOSD patients. **[Conclusions]** This study showes there are some differences of clinical features of HPS between patients with SLE and that with AOSD. Basic characteristics of SLE and AOSD may influence to those differences.

W63-4

Correlation between anti-Ro/La antibody and clinical findings and renal pathological findings of patients with systemic lupus erythematosus

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Conflict of interest: None

[Objectives] To investigate the relationship between anti-Ro/La antibodies and clinical findings and renal pathogenesis of patients with SLE. [Methods] We extracted patients who meets a SLE classification classification criteria (ACR 1997) and had anti-Ro/La antibody positive from Tomishiro central hospital's electronic medical records between 2002 and 2012 and analyzed these clinical and renal pathological finding data. [Results] 6 patients had anti-Ro/La antibody positive, met SLE classification criteria and underwent renal biopsy. All case had dry mouth or dry eye and arthritis. One case had mononeuropathy martiplex, 2 cases interstitial lung disease, one case serositis. In Urinary findings, 3 cases had proteinuria, 3cases had proteinuria and hematuria. In renal biopsy findings all cases are consistent to lupus nephritis. 3 cases were type V and two cases type IV and V, one case type III. Furthermore, we investigated also clinical manifestations of the cases which have not underwent the kidney biopsy [Conclusion] The many SLE patients with anti Ro/La antibody positive have sicca symptom and arthritis in clinical sympton and type V renal pathological findings.

W63-5

Examination of CT findings of the lupus peritonitis

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Conflict of interest: None

[Objectives] Serositis is commonly seen in systemic lupus erythematosus (SLE). However, peritoneal involvement (lupus peritonitis; LP) is extremely rare, and clinically seen in a small group of patients. We investigated the characteristics of clinical and CT findings in LP. [Methods] 10 SLE patients complicated LP between 2001 and 2012 were included in this study. We evaluated the disease activity, immunological and abdominal CT findings at the onset of LP. CT finding was analyzed by two radiologists independently. [Results] Following abnormal findings were revealed by CT; the wall abnormality (all surrounding wall thickenings, target sign), mesenteric abnormality (hyperplasia of mesenteric vessels, rise in mesenteric fatty density), ascites. Additionally, these findings were demonstrated in the upper gastrointestinal tract more frequently compared with the lower. We could not reveal the association between CT findings and SLE activity or immunological abnormalities. [Conclusion] The specific abnormal CT findings in LP was all surrounding wall thickenings related to target sign complicated with ascitis. The SLE activity at the onset of LP was high generally, but was unrelated to the quantity of each view of the CT and degree of the activity.

W63-6

The study of retention rate of Trimethoprim-sulfamethoxazole in our department

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Conflict of interest: None

[Objective] Trimethoprim-sulfamethoxazole(TMP-SMX) is widely used to auto immune disease patients with immunosuppressive therapy, in prophylaxis of Pneumocystis pneumonia (PCP). On the other hand, we often experience adverse events such as fever and rash which are thought to be due to TMP-SMX.SLE patients often have allegies to some drugs such as sulfa drugs, but there are few reports of TMP-SMX that has a similar structure to sulfa drugs. [Methods] We investigated the 204 cases, started TMP-SMX in our department, during February 2006 to October 2012. We classifies two groups; SLE group(n = 76), non-SLE(n = 128), and we investigated the continuation rate. In addition, PCP cases diagnosed and treated in our department for the same period (n = 15), we have examined the contents of the underlying disease and treatment. [Result] The discontinuance rate due to adverse events of TMP-SMX, is 26.6% in the non-SLE group, and 38.2% in the SLE. In addition, among the 15 cases of patients with PCP, 14 cases of patients were in use DMARDS and/or biologics for rheumatoid arthritis (RA). [Conclusion] SLE patients have many adverse events of TMP-SMX, so we should be sufficient upon administration. In addition, we should consider for the prevention of PCP medication with the high-risk RA patients.

W64-1

Combination of radiolunate arthrodesis and midcarpal arthroplasty for the rheumatoid wrist

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Conflict of interest: None

[Objectives] Radiolunate arthrodesis is an effective procedure to produce stability in the rheumatoid wrist while preserving mobility. However, in some wrists, contracture at the midcarpal joint progresses after the operation. The objective of this study is to investigate the influence of midcarpal arthroplasty on prevention of wrist contracture. **[Methods]** The procedure was performed in 40 wrists in 40 patients with RA. The mean age at the operation was 59 years, and the mean follow-up period after the operation was 3.5 (1~7) years. The operation was performed on the wrists in Larsen grade III or IV with persistent pain despite current medical treatment, and both with deterioration and joint space narrowing at the midcarpal joint. Combined with radiolunate arthrodesis, capitates head resection and interposition of a tendon ball were done at the midcarpal joint. **[Results]** Preoperative pain disappeared in all operated wrists, and the mean grip strength increased by 45mmHg. Radiologically, fusion occurred at the radiolunate joint in all wrists, and widening of the space was observed at the lunocapitate joint in 80% of the wrists. **[Conclusion]** This combination is an effective method to prevent progression of arthrosis at the midcarpal joint under tight control in the era of biologics.

W64-2

Postoperative complication of total elbow arthroplasty in rheumatoid arthritis

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Conflict of interest: None

[Objectives] Total elbow arthroplasty (TEA) for RA are improving progressively and have been reported as stable outcome. Surgical skill is necessary to succeed TEA, furthermore issues such as postoperative complications are left. We examined postoperative complications of TEA. [Methods] We intended for 31 cases 37joints performed TEA for RA. There were 32 joints of 27 women and 5 joints of 4 men. 34 joints performed as primary surgery, and 3 joints were revision surgery. 32 unlinked type and 5 linked type implants were used. We assessed the complications after surgery. [Results] We observed four ulnar neuropathy. Three joints were transient, but one joint underwent surgery for nerve damage after TEA. In a case, she had revision after loosening of implant and injured a fracture of ulna. We have performed removal of the implant with a deep infection after re-revision. [Conclusion] TEA has been popularized as a treatment for rheumatoid elbow, but we should watch out for preoperative planning and intraoperative complications. It is essential to improve surgical techniques and to determine accurately the state of the elbow. In addition, by using a new twist to utilizing image processing technology, we lead to the improvement of performance after surgery.

W64-3

Clinical results of surgical treatment of the Nalebuff type I (boutonniere) rheumatoid thumb deformity

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Conflict of interest: None

[Objectives] The thumb deformity and dysfunction deteriorates the whole hand function. We have reviewed the clinical results of surgical treatment for the Nalebuff type I (boutonniere) rheumatoid thumb deformity. [Methods] 18 reconstructions in 16 patients were included in this study. The mean age of patients at the surgery was 62.1±11.0 years and the average follow-up period was 21.5±15.4 months. 13 interphalangeal joint arthrodesis and 16 silastic implant arthroplasty of the metacarpophalangeal (MCP) joints were performed. The clinical evaluations included the range of extension, flexion and arc of MCP joint, pinch, pain-related VAS, DASH and radiographic assessment. Statistical analysis was performed using Wilcoxon signed-rank sum test. [Results] The mean preoperative extension, flexion, arc of MCP joint, pinch, DASH were -54.8±15.5°, 80.0±18.1°, 25.2±15.7°, 0.6±0.6kg, and 56.7±17.7, respectively. The mean postoperative extension, flexion, arc of MCP joint, pinch, DASH were -7.6±13.8°(p=0.01), 56.1± 14.8°(p=0.004), 48.4±16.9°(p=0.004), 1.4±0.9kg (p=0.03) and 42.6±16.7 (p=0.01), respectively. [Conclusion] The hand function was improved by our surgical treatment. The improvement might be resulted in the better strength of pinch and the movement for the arc of motion towards extension.

W64-4

The postoperative exercise of ruptured extensor tendons in rheumatoid hands

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Conflict of interest: None

[Objectives] Rupture of extensor tendons of fingers occurs frequently in patients with rheumatoid arthritis (RA), especially in little fingers and ring fingers. This study was undertaken to compare the postoperative outcome of tendon transfer cases in which postoperative exercise was performed using dynamic splints or tension-reduced early mobilization. [Methods] From 2001 to 2005, 16 ruptured extensor tendons were treated surgically by tendon transfer in 8 patients with RA (5 women and 3 men). Postoperative exercise of fingers was performed using dynamic splints from the 3rd postoperative day for 6 weeks. On the other hand, from January 2012 to September, 8 ruptured extensor tendons were treated surgically by tendon transfer in 4 patients with RA in whom tension-reduced early mobilization was performed from the second postoperative day for 6weeks successively. As for postoperative evaluation, ROM of MP joints of the fingers, wrist joints and DAS-28 were examined in those cases at the time when 3 months have passed after the operation.

W64-5

Appearance Outcome of the Soft Tissue Procedure for Ulnar Drift in Rheumatiod Arthritis

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Conflict of interest: None

[Objectives] We herein present appearance outcome of the soft tissue procedure for ulnar drift in rheumatoid arthritis. [Methods] Thirty fingers of seven patients (1 man, 6 women) were evaluated. The mean age of the patients at the operation was 71 years old. Chief complaint of all patients is the appearance of the deformed rheumatoid hand rather than functional impairment and they have no destroyed MCP joints. The soft tissue procedures consist of ulnar intrinsic release and fix the extensor tendon in the proximal phalanx by a non-absorbable suture without resection the tendon (Modified Zancolli procedure). The mean follow-up period was 15 months (range, 3-36 months). The follow-up evaluation included the range of motion of the DIP, PIP and MCP of the finger. Appearance outcome was evaluated with Visual Analog Scale (VAS). 【Results】 The average of the range of motion of the DIP, PIP and MCP was maintained at the preoperative level. However, the average of VAS significantly decreased from pre-operation 7.3 points to post-operation 2.6 points. 【Conclusion】 Modified Zancolli procedure was a useful method for ulnar drift in rheumatoid arthritis on improvement of the appearance.

W65-1

Total power Doppler score-8 is a useful diagnostic marker of musculoskeletal ultrasonography for screening and activity measurement of rheumatoid arthritis

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Conflict of interest: None

[Objectives] To clarify the optimal number and combination of joints to be assessed by power Doppler (PD) ultrasonography (US) in rheumatoid arthritis (RA). [Methods] PDUS were performed in 24 joints (all PIP, MCP, bilateral wrist and knee joints) in 225 RA patients. PD images were scored semiquantitatively from 0 to 3 in each joint, and total PD score-24 was calculated as the sum of scores of 24 joints. The patients were divided into PD-positive (total PD score-24 ≧ 1) and PD-negative (total PD score-24 = 0) groups. [Results] The PD-positive (PD score ≧ 1) rate was high in wrist, knee, MCP 2 and 3 joints, while low in other MCP and PIP joints. Higher correlation coefficients were found between total PD score-24 and PD score of MCP 2, 3 and wrist joints, whereas correlations between total PD score-24 and PD score of knee and PIP joints were weak. When we counted the PD score of reduced 8 joints (bilateral MCP 2, 3, wrist, and knee joints), the sensitivity and the negative predictive value of PD signal were 98% and 96%, respectively. Moreover, the sum of PD scores of the 8 joints (total PD score-8) showed very high correlation with the total PD score-24 (r_s = 0.93, P < 0.01). [Conclusion] Total PD score-8 is simple and useful enough for screening and activity measurement for RA.

W65-2

Site of inflammation in patients with elderly-onset rheumatoid arthritis assessed by power doppler sonography

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Conflict of interest: None

[Objectives] To identify sonographic feature in patients with elderly-onset rheumatoid arthritis (≧75 yrs) (EoRA). [Methods] Power doppler sonography (PDS) was used to identify the site and degree (PDS score) of arthritis in patients with newly-developed EoRA (average 82.5 yrs) and in younger (<75 yrs) RA (YoRA) patients (average 54.6 yrs). Dominant side of shoulder (longhead of the biceps tendon〔LBT〕, subacromial-subdeltoid burusa, glenohumeral joint), wrist, finger and knee joints were included for examination. As for EoRA, correlation of clinical indices and PDS score were analyzed for each joint. [Results] Compared with YoRA, a higher number of EoRA patients showed positive result for PDS for shoulder joints (50.0% and 81.8%, respectively, p <0.05) and among the shoulder components, LBT demonstrated the highest positive ratio (68.2%, p<0.05) in EoRA. There were no significant PDS differences between EoRA and YoRA for the remaining joints examined. Although no significant correlation with the clinical indices was identified, PDS score of the shoulder joint tended to be correlated with HAQ value (r=0.45, p=0.09). [Conclusion] Shoulder joint inflammation, especially LBT tendinitis is a primary manifestation and seems to be correlated with functional disability in EoRA patients.

W65-3

Clinical miscount of involved joints denotes the need for ultrasound complementation in usual practice for patients with rheumatoid arthritis

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Conflict of interest: None

[Objectives] Ultrasound (US) examination can visualize and clarify involved joints anatomically in patients with rheumatoid arthritis (RA), and it enables physicians to verify the accuracy of clinical assessments of the involved joints. Here, we studied the practical “miscount” and analyzed the possible contributing factors for increased miscount. [Methods] The study population consisted of 137 patients with RA. Physical joint examination was performed by 3 assessors with different levels of experience in rheumatology, and was followed by US joint examination. Miscount was calculated for all patients and multivariate analysis was conducted on possible contributing factors for miscount. [Results] A high variability in concordance rate among the joint sites was observed among the 3 assessors. The average miscount was 1.07 (SD, 5.19; range, 18 to –11). ESR and patient GA were determined as significant contributing factors for false-positive miscount, whereas PD score and age were significant factors for false-negative miscount. [Conclusion] IThe patients’ background can lead to increased miscount. Assessors should be blinded to patients’ background information, and US complementation should be included in usual clinical joint examinations.

W65-4

PDUS and synovial condition in knee joint echography

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Conflict of interest: None

[Objective] The signal strength of the power Doppler signal is affected by the number of blood vessels. The present report considers actual findings by looking at macro and micro findings pertaining to the knee joint. [Method] When performing an artificial knee displacement technique, joint echography is carried out. After development and checking of the articular capsule, in order to carry out a macro observation, obtain additional tissue and observe microvessels, a histological study is conducted. [Results] (1) It was possible to clarify the extent of the synovium. (2) In the joint echography, for the parts where the synovium had obviously grown, synovial growth was also macroscopically observed. (3) Even in parts where no power Doppler signal was observed, in reality, several blood vessels were observed. [Consideration] We frequently experience cases in which the PDUS signal disappears for as much as a month. In the present research, it is suggested that it is possible that there is not necessarily a correlation with the number of blood vessels. PDUS signals are invertible, and PUUS(-) is a condition in which the blood flow temporarily decreases, and we believe that it should be understood that this could become (+) at any time.

W65-5

Correlation of power doppler ultrasonography with histopathology of thesynovial tissue

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Conflict of interest: None

[Objectives] To assess the significance of power doppler ultrasonography (PDUS) in the evaluation of synovitis of the knee joint by comparing the PDUS findings with histopathological findings of synovial tissue. [Methods] We studied 23 patients who were undergoing arthroplasty of the knee joint because of rheumatoid arthritis (RA) or osteoarthritis (OA). The joint were examined with US before arthroplasty. The synovitis was classified semiquantitatively with grey scale (GS) and PDUS findings. A sample of synovial tissue was obtained during the arthroplasty, and histopathology of the synovial tissue was evaluated by haematoxylin and eosin staining and immunohistochemical staing with factor VIII. [Results] PDUS findings were well correlated with histopathological grades of synovitis. Sensitivity and specificity of PDUS findings for histopathological vascularity were 91% and 58%, respectively. [Conclusion] Our results showed that positive findings of PDUS closely were associated with histopathological findings of active synovitis. However, half of joints without PDUS findings indicated high score of histological vascularity. We confirmed the disconnection between PDUS and vascularity.

W65-6

Comparison of the image of ultrasonography and synovium pathology of the joints in the patients with rheumatoid arthritis (the second report)

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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 large joints (LJ) with those in the small joints (SJ). Materials and methods: Rheumatoid arthritis (RA) related orthopaedic surgery was performed at 138 joints including 2 shoulders, 18 knees, 18 elbows, 51 wrists, 30 fingers and 15 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. Shoulder, knee and elbow were classified into LJ, and wrist, ankle, finger and toe were into SJ. Results: There were 14 LJ and 43 SJ in grade 0,1 (group L) in PD signal and 25 LJ and 56 SJ in grade 2,3 (group H). DAS28, CRP and Rooney score in group H were significantly higher than those in group L. Difference between the DAS28, MMP-3, and CRP in the group L and those in the group H was more in the group L than in the SJ. On the contrary, difference between the Rooney score was less in the group L than in the SJ. Conclusion: PD signal in the image of US reflects synovium pathology and clinical indicators, but some differences were seen in the degree by the size of the joint.

W66-1

Ultrasonographic (US) evaluation of articular and tendon manifestations in systemic lupus erythmatosus (SLE) and rheumatoid arthritis(RA)

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Conflict of interest: None

[Objectives] Although arthropathy and tendinopathy are frequently found in SLE and RA, differences of the joint manifestations between these diseases are not yet confirmed. To clarify the articular and tendon manifestations in SLE and RA using US technique. [Methods] Twenty SLE patients with episode of clinical joint symptoms (18 women and 2 men) were recruited, and age- and sex-matched patients with RA were used for disease control. Bilateral wrist, MCP, PIP and IP joints and extensor and flexor tendons were assessed for grey scale and power Doppler activity. [Results] Whereas synovitis and tendonitis were detected in 14 cases and 10 cases of 20 SLE patients, synovitis and tendonitis were detected in 13 and5 cases of 20 RA patients. Tendonitis were found more frequently in SLE patients, compared with RA patients. [Conclusion] US-detected tendonitis was modestly frequent in SLE.

W66-2

The X-ray outcome of non-tender and non-swollen joints with pulse doppler signal detected by ultrasonography or high intensitiy on synovia detected by low-field magneteic resonance imaging in patients with rheumatoid arthritis

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Conflict of interest: None

[Objectives] To clarify the outcome of non-tender (non-TEN) and non-swollen (non-SW) joints with pulse dopller signal (PD) detected by ultrasonography (US) or high intensity on synovia detected by plain low-field magnetic resonance imaging (cMRI) in patients with rheumatoid arthritis (RA). [Methods] Hands of 35 patients with RA (700 joints) were examined by physicians, US and cMRI. X-rays were taken at around the three tests and after them. The frequencies of developed or deteriorated bone erosion (BE) and joint space narrowing (JSN) detected by X-rays were calculated. [Results] (1) The mean age of the patients was 53.7±14.2 years old. Ten male and 25 female were examined. The mean disease duration was 6.0±5.3 years. The mean period between X-rays was 40.0±20.3 weeks. (2) One new BE (2.9%) and one JSN (2.9%) were pointed in 34 non-TEN and non-SW joints with PD. (3) Two new BEs (3.4%) were pointed in 58 non-TEN and non-SW joints with synovia accompanying high intensity of cMRI and it was higher than that (0.0%) in 470 non-TEN and non-SW joints with normal synovial signal ($p<0.05$). Two new JSNs (3.4%) were pointed in those 58 joints. [Conclusion] Non-TEN and non-SW joints with PD or synovium accompanying high intensity detected by cMRI developed bone erosions and JSNs.

W66-3

Relation of the synovial blood-flow evaluation by PDUS to the joint destruction by simple X-ray films in the Tocilizumab administration cases

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Conflict of interest: None

[Objectives] The relation of the blood-flow evaluation in the joint synovialis by PDUS and advance of the osteoclasia by a simple X-ray examination was investigated. [Methods] Continuation of 48 or more week administration is possible in our hospital which started Tocilizumab administration. The evaluation by a PDUS evaluated a total of 22 places of a finger and a wrist joint by 3 from grade0 using power Doppler. The evaluation by simple X-ray evaluated by performing scoring of the formation of joint space narrowing, and a bone erosion according to the appraisal method

of Sharp/van der Heijde. [Results] In evaluation by the synovialis blood flow by PDUS, the improvement was accepted with 8 in 9 cases case. There was no case which the joint space narrowing score has improved among these eight cases, the number of no changes was five and aggravation was three examples. About the bone erosion sore, the improvement was accepted by two examples among 8 cases, and each of these two examples was less than two years from the onset to the administration start. [Conclusion] In the TCZ administration case, it was thought that the synovial blood-flow evaluation by PDUS was the useful method which can predict a bone and cartilage destruction.

W66-4

Time-integrated synovitis activity assessed by power Doppler ultrasound significantly correlates with radiographic progression in rheumatoid arthritis patients treated with methotrexate alone but not in those treated with TNF antagonists

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Conflict of interest: Yes

[Objectives] We aimed to demonstrate that the cumulative synovial power Doppler (PD) scores correlate with the radiographic progression more significantly than the conventional measures do. [Methods] Patients with rheumatoid arthritis (RA) who newly received either methotrexate (MTX) (n = 17), a TNF antagonist (n = 23), or tocilizumab (n = 8) were enrolled. Patients underwent clinical, laboratory, ultrasonographic and radiographic assessment at baseline, 12 weeks, and 24 weeks. [Results] Time-integrated total PD scores significantly correlated with DTSS ($P = 0.022$), whereas time-integrated DAS28-CRP and total GS scores did not ($P = 0.056$ and $P = 0.472$, respectively). In sub-group analyses, while the correlation between time-integrated total PD scores and DTSS was even more significant in MTX-treated group ($P = 0.015$), the correlation was not significant in TNF antagonist-treated group ($P = 0.809$) due to minimal radiographic progression in the presence of comparable synovial PD activity. [Conclusion] Synovial PD activity reflects active synovial inflammation which causes joint destruction more accurately than conventional measures do. TNF antagonists can inhibit radiographic progression independently of synovitis activity in RA.

W66-5

The evaluation of MRI and ultrasonography in rheumatoid arthritis patients in clinical remission by biologics

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Conflict of interest: None

[Objectives] We evaluated the evaluation of MRI and ultrasonography (US) which detected residual inflammation in rheumatoid arthritis patients in SDAI remission by biologics and assessed the association of HAQ and the Rheumatoid Arthritis Impact of Disease (RAID) score with those imaging analysis. [Methods] Of 125 RA patients, a total of 119 patients had data available. Thirty one of 119 patients have maintained SDAI remission for six months and underwent MRI and ultrasonography. The composite scores based on patient reported outcomes such as HAQ and RAID score were assessed. [Results] In 31 patients in SDAI remission, MRI showed that 71% had active inflammation such as synovitis, bone marrow edema, and tenosynovitis, and US showed that 35% had power Doppler signal. There were no significant differences between the residual inflammation on the imaging and HAQ or RAID score. [Conclusion] These findings suggest that MRI is more sensitive than US to detect residual inflammation. However, we have not yet known how much it contributes to the future structural progression. We must continue to assess whether RA patients in clinical remission with the residual inflammation detected by imaging can maintain structural and functional remission in the future.

W66-6

Ultrasonography may predict a recurrence of rheumatoid arthritis after discontinuing biological agents

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Conflict of interest: None

[Objectives] We investigated the usefulness of ultrasonography to detect early relapse after discontinuing biological agents. [Methods] We performed ultrasonography for RA patients in remission, and 10 patients without imaging activity(GS≦2,PD≦1,evaluated in echography) were enrolled. In these patients biological agents were discontinued after informed consent, followed every three months, and evaluated with ultrasonography. [Results] Ten patients were enrolled and followed for at least 6 months. Among these patients, 3 patients were treated with infliximab, 3 with etanercept, 3 with adalimumab, and 1 with tocilizumab. Methotorexate were administered in 9 patients and the average dose was 7.1mg/week. Two patients have relapsed clinically, and ultrasonography showed active synovitis(GS≧3,PD≧2) in these patients. Five patients have not relapsed clinically, however ultrasonography showed active synovitis. Only 3 patients remained in remission both in clinical evaluation and in image examination. [Conclusion] Ultrasonography could detect relapse after discontinuing biological agents earlier than clinical evaluation.In some patients with subclinical synovitis, adding or increasing the dose of DMARDs resulted in the improvement of the synovitis.

W67-1

A Multi-Biomarker Disease Activity (VECTRA™ DA) Score and its relevance to Radiographic Progression in Rheumatoid Arthritis Patients Treated with Tofacitinib

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Conflict of interest: None

Background The ability of a multi-biomarker disease activity (MBDA) score to track disease activity in rheumatoid arthritis (RA) patients has recently been reported. However, relationship with RA patients treated with a JAK-inhibitor tofacitinib has yet to be evaluated. Methods MBDA score, SDAI and mTSS were evaluated at baseline and at week 52 in 37 patients. The MBDA score

combines 12 biomarkers (VCAM-1, EGF, VEGF-A, IL-6, TNF-RI, MMP-1, MMP-3, YKL-40, Leptin, Resistin, CRP, SAA) ranging in between 1 and 100. Results (1) MBDA score, SDAI and estimated ⊿mTSS decreased; MBDA 60.8 to 28.5, SDAI 37.7 to 6.2, ⊿mTSS 14.7 to 0.9 Radiographic progression (RP) was prevented in 26 patients. (2)⊿MBDA score and ⊿SDAI from baseline to week 52 were significantly correlated ($p<0.01$). (3) Among the 12 components serum IL-6 decreased at week 52 and correlated with ⊿mTSS ($p<0.01$). When patients were stratified based on their median value of IL-6 at week 52, 83% of patients with low IL-6 (<9.0 ng/ml) had no RP against 58% in the high concentration group. Conclusion MBDA was well correlated with SDAI, indicating usability as a composite measure to determine RA disease activity and IL-6 at 52 weeks mostly correlated with ⊿mTSS, suggesting that tofacitinib could prevent RP partly through IL-6-inhibition.

W67-2

IL-6 increases the number of osteoclast precursors in bone marrow via up-regulating S1PR2

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Conflict of interest: None

Introduction Recent studies have shown that sphingosine-1-phosphate (S1P) controls the dynamic intermigration of osteoclast precursors (OCPs) between the blood and bone marrow, via the S1P receptor 2 (S1PR2) expressed on the surface of OCPs. The purpose of this study was to investigate whether IL-6 regulates the expression and function of S1PR2, and whether IL-6 has any influence on the localization of OCPs in the course of bone loss in collagen induced arthritis model. **Results** Trabecular bone volume in arthritic mice (day 35) was significantly decreased and the percentage of OCPs in bone marrow significantly increased compared with normal mice. Moreover, the expression of S1PR2 in arthritic mice was significantly increased compared with normal mice. Administration of anti-IL-6 receptor antibody to arthritic mice (day 0, day 35) inhibited systemic bone loss in arthritic mice and decreased the number of OCPs and the expression of S1PR2. In vitro, IL-6 induced S1PR2 in OCPs. In the presence of IL-6, S1P-directed chemotaxis of OCPs was inhibited compared with medium control. **Conclusions** The results demonstrated that IL-6 increases the number of OCPs in bone marrow via up-regulating S1PR2, and plays a crucial role in systemic bone loss.

W67-3

Regulation of synovitis and osteoclastgenesis in exprerimenta arthritis by connexin 43

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Conflict of interest: None

[Objectives] Connexin 43 (Cx43) is the main protein in gap junction connecting between cells in a tissue. Cx43 plays an important role in the regulation of various immune processes. The objective of this study was to determine whether the expression of Cx43 effected on inflammatory conditions in rat fibroblast-like synoviocytes (FLS) and on rat model of rheumatoid arthritis (RA). [Methods] The expression of Cx43 in rat FLS stimulated with lipopolysaccharide (LPS) was confirmed by real-time RT-PCR. The effects of siRNA targeting Cx43 (siCx43) on pro-inflammatory cytokines were assessed by real-time RT- PCR and ELISA. The therapeutic effects of siCx43 in a rat model of collagen-induced arthritis (CIA) were examined by in vivo electroporation method. [Results] LPS markedly enhanced Cx43 gene expression in rat FLS, with transfection of siCx43 suppressing the over-expression of pro-inflammatory cytokines. Treatment of CIA rats with siCx43 significantly ameliorated paw swelling, and significantly reduced histological arthritis scores and radiographic scores. In histological appearance of rat ankle joints, siCx43 treatment significantly decreased the number of osteoclast-like cells. Cx43 may be important in pathogenesis of RA, and be a target molecule in new therapies for RA.

W67-4

Novel IL-10 induction pathway mediated by Egr-2 in IL-27-stimulated T cells

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Conflict of interest: None

IL-10 producing T cells play a role in the regulation of autoimmune diseases. IL-27 is one of the IL-12 family cytokines suppressing immune responses through induction of IL-10 production. We have previously shown that forced expression of Egr-2, a transcription factor required for T cell anergy induction, induces IL-10 and LAG-3 expression and confers regulatory activity *in vivo* on naïve $CD4^+$ T cells. Among various IL-10 inducing factors, only IL-27 induced high levels of Egr-2 and LAG-3 expression. Other IL-12 family cytokines, such as IL-12 and IL-23 could not efficiently induce Egr-2 and LAG-3 expression. Intriguingly, IL-27 failed to induce IL-10 in Egr-2-deficient naïve $CD4^+$ T cells. Moreover, IL-27-mediated induction of Blimp-1, a transcriptional repressor important for IL-10 production in $CD4^+$ T cells, was also impaired in the absence of Egr-2. Luciferase assay and ChIP assay revealed Egr-2-mediated control of Blimp-1 expression. This Egr-2 induction by IL-27 was abrogated by STAT3-deficiency, not by STAT1-deficiency. IL-6 could also induce Egr-2^+LAG3^+ T cells, but IL-10 mRNA induction by IL-6 was lower than that by IL-27. These results suggest that STAT3-dependent IL-27 signal transduction through Egr-2 and Blimp-1 cascade plays an important role for IL-10 production.

W67-5

IL-33 promotes mast cell survivial via inhibition of apoptosis associated with enhanced expression of Bcl-X_L

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Conflict of interest: None

[Objectives] IL-33 exerts potent effects on mast cell (MC) phenotype and function. We tested the hypothesis that IL-33 might also regulate MC proliferation and survival, including the development of synovial mastocytosis in the context of inflammatory arthritis. [Methods] Murine bone marrow derived MCs (mBMMCs) were generated from wild (WT) mice and animals lacking the IL-33 receptor ST2. Cell viability, proliferation and apoptosis were examined after exposure to IL-33. Expression of Bcl-2 and Bcl-X_L

were determined. To examine the role of IL-33 in vivo, fluorescently-labeled mixed WT and ST2$^{-/-}$ mBMMCs were transferred into the peritoneum of ST2$^{-/-}$ mice. Synovial tissue MCs were enumerated in WT and ST2$^{-/-}$ animals. [Results] Exogenous IL-33 was able to support the survival of WT but not ST2$^{-/-}$ mBMMCs after IL-3 withdrawal. This effect arose via inhibited apoptosis associated with enhanced Bcl-X_L expression. Correspondingly, WT mBMMC persisted better than ST2$^{-/-}$ mBMMC in IL-33-treated recipients. The density of synovial MC was similar in both strains. [Conclusion] These findings identify a novel role for IL-33 as an promoter of murine MC. However, at least in the short term K/BxN arthritis model, other pathways appear sufficient to enable and maintain tissue MCs.

W68-1

A novel role of orphan nuclear receptor RORγt in spontaneous sialadenitis like Sjögren's syndrome

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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 under the promoter of hCD2 spontaneously developed sialadenitis like SS. [Methods] 1) Infiltrating cells of salivary glands were analyzed by fluorescent immunostaining and flow cytometer. 2) Subsets of T cells in salivary glands were examined by quantitative PCR. 3) Splenic CD4$^+$ or CD4$^-$ cells were transferred to Rag2$^{-/-}$ mice (CD4$^+$or CD4$^-$→Rag2$^{-/-}$) and histological analysis was examined. 4) Compartment of CD4$^+$CD25$^+$Foxp3$^+$ in spleen and lymphonode was investigated [Results] 1) Majority of infiltrating cells were CD4$^+$ T cells at early phase of sialadenitis, and B cells were gradually increased at late phase. 2) Expressions of Th17 (IL-17, IL-23r), Th1 (IFN-γ, T-bet), Th2 (IL-4, GATA3) and Tfh (IL-21, Bcl-6) related molecules were increased. 3) In CD4$^+$→Rag2$^{-/-}$, sialadenitis was observed, but not in CD4$^-$→Rag2$^{-/-}$. 4) Number of CD4$^+$CD25$^+$Foxp3$^+$ cells were significantly reduced in Tg mice, compared with WT mice. [Conclusion] These results suggested that the overexpression of RORγt in CD4$^+$ T cells induced up-regulation of Th17, Th1, Th2, Tfh cells in the salivary glands and down regulation of CD4$^+$CD25$^+$Foxp3$^+$ cells, resulting in spontaneous sialadenitis like SS.

W68-2

Enhanced expression of BAFF receptor leads to abnormal BAFF signaling in peripheral monocytes of patients with primary Sjögren's syndrome

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Conflict of interest: None

[Objectives] We revealed that BAFF induced robust increase in the production of IL-6 by primary Sjögren's syndrome (pSS) monocytes. We also found that the expression levels of BAFF receptor (BR3) and NF-IL-6 and NF-kB2 were enhanced in pSS monocytes compared to the controls. The purpose of this study is to elucidate the possible abnormalities of a BAFF signaling pathway in pSS monocytes. [Methods] The expression level of BR3 on peripheral monocytes was analyzed by FACS. Peripheral monocytes were stimulated in vitro with soluble BAFF (sBAFF), and the production of IL-6 by the cells was measured by ELISA. The expression levels of IKK-alpha and IKK-beta were analyzed by western blotting. [Results] FACS analysis showed that the expression level of BR3 was significantly elevated in pSS monocytes compared to the controls. Moreover, the expression level of BR3 on pSS monocytes was positively correlated with the amount of IL-6 produced by monocytes triggered by sBAFF. In addition, phosphorylation levels of IKK-alpha and IKK-beta in the pSS monocytes were enhanced upon stimulation with sBAFF. [Conclusion] These data strongly suggest that BAFF acts through BR3 to activate monocytes to produce IL-6 and that IKK-alpha and IKK-beta are involved in the BAFF signaling.

W68-3

Diagnostic usefulness of the criterion in patients with Sjogren's syndrome regarded as early stage of desease

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Conflict of interest: None

【Background】Recently immunosuppressive therapy such as mizoribine or rituximab was reported to be valid to Sjogren's Syndrome (SS), and it is expected that the effectiveness of therapy increases by the early diagnosis and the early treatment as the rheumatoid arthritis therapeutic.【Methods】Dagnostic usefulness and the issue of the three criterion (Ministry of Health, Labour and Welfare revision criterion, the American-European revised classification criteria, and the ACR criteria by SICCA) in the early stage of the desease are studied in this research. We studied 21 cases who were negative in Gum test and were positive in the labial salivary grand biopsies among patients diagnosed as SS in the Tokyo Medical Center.【Results】Three oral subjective symptom items of the AECG criteria were negatives in 11 examples, and ocular subjective symptom were negative in eight cases. Schirmer's test were negative in 11 cases. Two cases were both anti SS-A / SS-B antibody negative and were anti centromere antibody alone positive, and were negative RF. In the ACR criteria, one case was not diagnosed for the lack of the ophthalmic examination and as for anticentromere antibody alone positive.【Conclusion】In 21 cases who comparatively seemed that early stages of desease, diagnosis utility of the ACR criteria was thought to be a decrease in the case with positive only anti-centromere antibody.

W68-4

Validation of 2012 ACR classification criteria for Sjögren's syndrome (SS) from the viewpoint of salivary gland function

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Conflict of interest: None

[Objective]To validate ACR SS criteria, which exclude salivary function as a criterion, by using quantitative measures of salivary gland scintigraphy (J Rheumatol 2006;33:2470-4). **[Methods]**Patients who underwent scintigraphy were classified as 94 SS and 53 non-SS. Patients with at least one of anti-centromere, RNP, SS-A or SS-B were named Ab+, and those without antibodies were named Ab-. **[Results]**Compared with non-SS, SS patients were

young and had low amount of saliva and high focus scores. All quantitative measures but excretion fraction were lower in SS than non-SS. The quantitative measures did not differ between 1°and 2°SS. Patients were divided into 4 groups: 88 with Ab+SS (A), 6 with Ab-SS (B), 18 with Ab+non-SS (C) and 35 with Ab-non-SS(D). All quantitative measures but excretion fraction were lower in group A than D. Group C had higher uptake speed than group A and low excretion speed compared with group D. Among all subjects, patients with anti-centromere had lower excretion fraction than Ab-. There was a negative correlation between the anti-RNP titers and quantitative measures of peak count and excretion speed. **[Conclusions]**Patients with SS classified by ACR criteria showed impaired salivary gland function. Anti-centromere and anti-RNP affected salivary gland function.

W68-5

Dysgeusia in Sjögren syndrome patients

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Conflict of interest: None

[Objectives] To evaluate dysgeusia and decline in saliva secretion in Sjögren syndrome patients. [Methods] We took a survey on taste sensation and conducted gustometry in 30 Sjögren syndrome patients. We prepared solutions with 5 primary tastes: sweet, sour, salty, umami, and bitter; with six different levels of concentration and 0.5ml each was sprayed in candidate's mouth. Concentration level 1 was adjusted to the median taste sensitivity of healthy individuals, and the concentration was doubled every time the level increased. We also carried out salivary flow test. [Results] Proportions of the candidates who complained reduced taste sensation was greatest in sweet with 20%, followed by umami and salty with 13%, acrid with 10%. Hypergeusia was predominant in sour and acrid with 20%, followed by salty with 17%. Average threshold values of taste perception were 3.3 for sweet, 2.4 for sour, 2.4 for salty, 1.5 for umami, 1.8 for bitter, indicating remarkable impairment in sweet perception similar to the result obtained by the survey. Relationship between diminished taste sensitivity and decline in saliva secretion was suggested. [Conclusion] Depending on the type of taste, Sjögren syndrome patients display diminished taste sesitivity associated with decline in saliva secretion.

W68-6

Long-term follow-up of 77 cases with primary Sjögren's syndrome in Japanese children - The 3rd report from Working group for Sjögren's syndrome in children

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Conflict of interest: None

[Objective] In order to elucidate the pathophysiology of Sjogren's syndrome (SS), we studied the long-term clinical course of patients with SS who were diagnosed in childhood. [Methods] A retrospective review of medical records of 77 pediatric patients with primary SS was performed at eight institutions of Pediatric Rheumatology in Japan. [Results] Mean follow-up duration was 7.8 years. No patient died in observational period. Twenty-two patients needed immune-suppressive therapy. Sicca symptoms developed in 36 patients. Sialography was re-examined in 13 patients, and stage progressed in 6 patients. Ten patients underwent re-biopsy of labial glands; stage progressed in 4 patients. Twenty-two patients needed prednisolone, 6 patients underwent mPSL pulse therapy. Most used immunosuppressant was mizoribine. Many patients used artificial tears, as a treatment for dry eye. The most used oral medicine was cevimeline. [Conclusion] The prognosis is not poor in childhood SS. However, among about 30% of patients needed immune-suppressive therapy for extra-glandular manifestations, and gland disorder progresses slowly. We should follow-up childhood SS patients for long time, and develop therapy to prevent progression of extra-glandular manifestations and gland disorder.

W68-7

Single nucleotide polymorphisms of muscarinic acetylcholine receptor M3 gene are associated with adverse events of pilocarpine

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Conflict of interest: None

[Purpose] Pilocarpine is effective for sicca symptoms of Sjögren' s syndrome, but some patients are subject to stop taking due to adverse events such as nausea. The aim of this study is to find some single nucleotide polymorphisms (SNPs) which may be associated with adverse events of pilocarpine. [Methods] Ninety three patients in our department in Kyoto University Hospital who took pilocarpine and agreed to the genetic study were enrolled in this study. Three SNPs (rs1080278, rs685550, rs2165870) of Muscarinic acetylcholine receptor M3 gene (CHRM3) were typed by TaqMan and the association with nausea was analyzed. [Results] Thirty patients quit taking pills within two months due to insufficient effect (4 patients), adverse events (19 patients), other reason (1 patient), and unknown reasons (6 patients). Out of 19 patients with adverse events, 12 suffered from nausea, 7 suffered from sweating, and 3 suffered from other adverse events (the numbers partly overlapped). We found statistically significant associations between nausea and the risk allele possession of rs10802789 or rs685550 (p=0.007, OR 6.9, 95%CI 1.4-33.5, for both). [Conclusions] Muscarinic acetylcholine receptor M3 gene polymorphisms may be associated with gastrointestinal adverse events by pilocarpine.

W68-8

Efficacy of Tramadol hydrochloride Acetaminophen (Tramacet®) for fibromyalgia and chronic pain patients

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Conflict of interest: None

[Objectives] To evaluate efficacy of tramadol-Acetaminophen (Tramacet®) for fibromyalgia and chronic pain patients [Methods] VAS(Visual Analog Scale) was evaluated individuals medicated tramadol-Acetaminophen with nine fibromyalgia and 15 chronic pain i.e. secondary fibromyalgia patients (five systemic schrerosis, five systemic lupus erhytematosus, three rheumatoid arthritis, one polymyalgia rheumatica, one Takayasu's disease and one Bechet disease) who were insufficient effects of non-steroidal anti-inflammatory drugs (NSAIDs). Previous medications were 14 pregabalin, 10 prednisolone and six duloxetine included two or all medications. [Results] All patients were medicated metoclopramide and laxatives. Four out of 23 were discontinued medicaions due to nausea. Most frequent dosage was three tablets tid. The medicaion of tramadol-Acetaminophen reduced mean of VAS from 8.56 to 4.86. [Conclusion] The medicaion of tramadol-Acetaminophen is a promissing for fibromyralgia and chronic pain (secondary fibromyalgia) patients.

W68-9

Fibromyalgia patients with autoimmune disease predisposition are resistant to drug therapy

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Conflict of interest: None

[Objectives] To investigate the involvement of immune system in fibromyalgia (FM), drug response to FM drugs were examined in patients with medical history of autoimmune diseases. [Methods] Thirty-five patients who were diagnosed as FM were investigated, and precise hearing of medical history of them and their family were done. Patients were treated with drugs (anti-depressant, anti-convulsant or NSAID) and the responses were determined by patients' subjective evaluation. [Results] Among 35 patients, 9 patients had medical history of autoimmune diseases, and 13 patients had that of mental disorders. Only 3 patients (33.3%) with autoimmune disease claimed as effective to anti-depressant drugs, whereas 8 patients (61.5%) with mental disorder history claimed. Moreover, only 4 patients (44.4%) claimed as effective to anti-convulsant drugs whereas 9 patients (69.2%) claimed. Only 2 patients (22.2%) with autoimmune disease history and 3 patients (23.1%) with mental disorder claimed as effective to NSAIDs. [Conclusion] Patients with medical history of autoimmune disease had tendency to resistant to any drugs for FM. These data may clarify the involvement of immune system in developing FM.

W69-1

Study on clinical effect in 2 different starting doses (50 mg/week vs 25mg/week) of etanercept and dose reduction after attaining low disease activity or remission in rheumatoid arthritis

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Conflict of interest: None

[Objectives] To design the starting doses of etenercept (ETN) according to disease activity and advance dose reduction when responded well to ETN in RA. **[Methods]** We assessed 135 RA patients using DAS28. Dose reduction of ETN was advanced after attaining low disease activity or remission. **[Results]** In 35 patients ETN was started with 50 mg/w. ETN was reduced to 25mg/w in 21 patients. Out of them, ETN was, moreover, reduced to 25mg/2 week in 5patients. In 100 patents ETN was started with 25mg/w. ETN was increased to 50 mg/w in 19 patients because of insufficient effect and returned to 25 mg/w again in 6 patients. ETN was reduced to 25mg/2 week in 7 patients. One year continuation rate of ETN and DAS 28 remission rate (LOCF) were 71.9% and 37.5% in 39 patients started with 50mg/w (average DAS was 5.64 at start), and 78.3% and 42.4% in 92 patients started with 25 mg/w (average DAS was 4.72 at start). And those were 74.4% and 30.8% in 39 patients with high disease activity and 83.3% and 45.2% in the patients with moderate disease activity when ETN of 25mg/w was started. **[Conclusion]** Patients with high disease activity should be started with 50mg/w of ENT and with moderate disease activity could be started with 25mg/w. A few patients respoded to 25mg/2w of ETN.

W69-2

Clinical findings and outcome of rheumatoid arthritis patients treated in switching of the multiple biological agents

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Conflict of interest: None

[Objectives] Cases which require switching of **biological agents (BIO)** due to invalidity and adverse reaction are not a few in the rheumatoid arthritis treatment. The problem of switching of the multiple BIO was examined. **[Methods]**For 19 examples who had the administration from third to 5th BIO of 214 examples introduced BIO during past 8 years, the patient background and outcome were investigated. **[Results]**The titer of IgM-RF (392.7 U/ml) and anti-CCP antibody (544.5U/ml) were high-priced positive when the first BIO started. Finally-administered BIO were tocilizumab for 7 examples, abatacept and golimumab for 5 examples in each, adalimumab for 2 examples. The object was classified into the 3 groups. Group A had 6 examples in which over 2 BIO were in second invalidity, and group C had 6 examples who were stopped by first invalid or adverse reaction. Group B between group A and B had 7 examples. Though examples in group C had the poorer prognosis factor, and the low disease activity (LDA) achievement of DAS28-ESR(4)<3.2 was a half. In group A, introduction and maintenance to LDA was seen in all of patients. **[Conclusion]**New BIO are necessary in order to maintain all of patients in LDA or clinical remission.

W69-3

Clinical results of switching to Adalimumab (ADA) in rheumatoid arthritis(RA)patients in Japan: A survey on 35 switch patients out of 121 treated with ADA in our department

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Conflict of interest: None

[Objectives] In this study, the clinical efficacy of switching to ADA in RA patients who were non-responder to other biologics was investigated at our hospital. [Methods] In this study, 35 out of 121 RA patients who treated with ADA from May 2009 to Oct 2010, in our hospital were investigated. These patients switched to ADA due to non-responding to prior biologics. [Results] The percentage of DAS28 (CRP), SDAI,CDAI remissions at 24 weeks af-

ter switching to ADA were 51.5%, 39.4% and 33.3%, respectively. Also, 33.3% of patients showed EULAR good response and 61% of patients showed more than EULAR moderate response. According to MTX dosage, in 18 patients MTX dosage was equal or more than 10mg(≧10mg group) and in 13 patients MTX dosage was less than 10mg(<10mg group) whose data were able to be analyzed. At 8 weeks after switch to ADA, the early changes of DAS28(CRP), SDAI and CDAI at were compared which were -1.6,-16.1 and -15.7, in ≧10mg group whereas were significantly higher as -1.0,-10.8,-10.5 in <10mg group, respectively. [Conclusion] In non-responder to Bio treatment patients, introduction of combination of ADA and adequate dose of MTX (10 mg/week) together is an effective treatment option.

W69-4

Estimation on clinical, functional, and structual remission of intentional ADA switching as second Bio-therapy after successfully stabilized the disease activity by IFX,ETN, or TCZ treatment as first Bio-therapy in RA patietnts with more than moderate disease activity

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Conflict of interest: None

【Objectives】IFX, ETN, or TCZ treatment was intensively changed to ADA to maintain clinical remision in RA patients. We estimated this trial of new Bio-switching therapy.【Methods】Disease activity of 14 RA patients was reduced after prior treatment with IFX, ETN or TCZ, and then the patients were switched to ADA. Changes in DAS28-ESR and serum MMP3 values, and HAQ scores were examined for statistically significant differences. In addition, joint deterioration or changes in bone erosion were compared by radiography at the mean of 84 weeks.【Results】Mean DAS28-ESR at screening, after the switch, at 12 weeks, and 52 were 5.16, 2.29, 2.10, and 2.04, respectively. Further deep remission was achieved from the switch to ADA. The mean serum MMP3 values were significantly reduced from the switch. For 12 patients in whom HAQ was measured the final progress observation, patients of less than 0.5 were 11, and the mean value was 0.21. In the radiological evaluation of joints, the changes were recovery from bone erosion and joint degradation in 7 patients, and inhibition of bone erosion in 7 patients.【Conclusion】Followed by IFX, ETN or TCZ, the next bio-switch to ADA resulted in high remission rates of the clinical, functional and structural assessments on RA patients.

W69-5

The long-term efficacy of high-dose infliximab treatment using an on-demand dose-escalation protocol

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Conflict of interest: None

Objective: The validity and safety in high-dose infliximab (IFX) medication for patients with rheumatoid arthritis (RA) were shown by the RISING study. However, there are few reports using the dose-escalation IFX method according to disease activity. Methods: We established a dose-escalation IFX protocol in 2009, and have treated patients with RA according to this protocol for 2 years. Results: Nineteen patients were treated with the dose-escalation IFX protocol (dose-escalation group) and their outcomes were compared with those of 22 historical controls treated with fixed dose of IFX (control group). No significant differences were found in the backgrounds between these groups. Since there were no early discontinuations due to poor response to IFX among the dose-escalation group, the rate of IFX continuation was higher. The remission rates of the dose-escalation group, using the measures of DAS28<2.6, SDAI≦3.3, CDAI≦2.8 and Boolean Remission Criteria were significantly improved compared to those of control group ($p<0.05$, chi-square test). The incidence rates of adverse events between these groups were not significantly different. Conclusion: The dose-escalation IFX therapy was well tolerated for RA and contributed to better remission induction.

W69-6

Effects of dose escalation of golimumab from 50mg/4w to 100mg/4w in patients with rheumatoid arthritis ~Multicenter study TBCR~

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Conflict of interest: None

[Objectives] To evaluate dose escalation of golimumab (GLM) from 50mg/4w to 100mg/4w after GLM initiation. [Methods] Data from multicenter study TBCR was used. Dose escalation of GLM was performed in 7 cases among 39 cases registered to TBCR. Change of disease activity (DAS28-CRP, SDAI, CRP) from intiation of GLM to dose escalation was compared with that after 4 weeks, 8 weeks, 12 weeks from dose escalation. Usage of concomitant DMARDs was also investigated. [Results] 7 cases (21.9%) experiences dose escalation among 32 cases who started GLM at the dose of 50mg. One case were prescribed only one 100mg GLM because of inefficacy. 6 cases were all female. Age was 50-68yo. RA duration was 48-656m. One case was bio-naive and 5 cases were bio-switch. Change of disease activity from initiation to dose escalation, dose escalation to 4-week after, to 8-week after, to 12-week after were below. ΔDAS28-CRP(-0.19, 0.54, 0.64, 0.52), ΔSDAI(-3.5, 2.1, 4.9, 8.1), ΔCRP(-1.72, 0.38, 1.69, 1.02). Addition of MTX was performed in 2 cases and Addition of TAC was performed in one case. [Conclusion] Although disease activity from initiation of GLM to dose escalation got worse, it got better after dose escalation. Concomitant DMARDs therapy was combined to GLM dose escalation in real-world clinical setting.

W70-1

Comparison of continuation rate on the first biologics therapy in rheumatoid arthritis patients 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) might be related to the inefficacy of infliximab compared to other TNF inhibitors. [Objectives] To compare the continuation rate of the first biologics (Bio) in rheumatoid arthritis

(RA) patients with anti-Ro. [Methods] Sixty-seven patients with anti-Ro (infliximab: IFX; 29, etanercept: ETN; 27, adalimumab: ADA; 6, abatacept: ABA; 3, and tocilizmab: TCZ: 2) were studied the continuation rate after one year and over one year from beginning of the first Bio. We classified the patients into 2 groups; A: the group of patients treated with anti-TNF-α antibodies IFX or ADA, B: the group of patients treated with anti-TNF-α receptor ETN or ABA, or TCZ. [Results] The continuation rate of the group A was lower than the group B after one year and over one year from beginning of Bio (one year: 65.7% and 81.3%, respectively; p=0.175, over one year: 37.1% and 75.0%, respectively; p=0.003). Moreover, all the 12 patients in group A who discontinued for the lack of efficacy improved clinically and has been continued after switching to ETN or ABA, or TCZ as the second or third biologics. [Conclusion] It was suggested that the use of ETN, ABA, or TCZ might be related to higher continuation rate in RA patients with atni-Ro.

W70-2

Efficacy of surgical treatment to persistent rate of Biologic DMARDs

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Conflict of interest: None

[Objectives] Adding dose of oral methotrexate, biological DMARDs (BIO), shortening of the dosing period of BIO have been made in order to enable long-term continuous BIO. However there is no report of whether surgical treatment to continue long-term BIO. [Methods] We examined whether the effect of surgical treatment on the continuation rate of Infliximab (IFX) and etanercept (ETN) in patients with rheumatoid arthritis (RA) by Kaplan-Meier method. [Results] 67 RA patients were included in this study. 39 patients were treated with IFX and 31 with ETN. 12 had gone surgical treatment in IFX group and 16 in ETN group. We divided these patients into two groups whether treated with surgery, there is no significant difference in these groups (P=0.43). We compared adding dose of drugs group (ADG) and surgical treatment group (SG) in point of the continuation rate of BIO after the additional treatment. The continuation rate of IFX was 20% in ADG and 76.9% in SG15 months after the additional treatment (P<0.05). The continuation rate of ETN was 68.3% in ADG and 100% in SG 18 months after the additional treatment (P<0.05). [Conclusion] We have to consider again with many cases, but surgical treatment might raise long-term continuous rate in BIO.

W70-3

Long-term retention of etanercept

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Conflict of interest: None

[Objectives] The purpose of this study is to investigate the factors that assoiciate with long-term retention of etanercept (ETN) for patients with rheumatoid arthritis. [Methods] The multi-center registry (Tsurumai Biologics Communication Registry; TBCR) consisted of 883 patients who used ETN as first biologics. 209 patients that continued ETN for more than 4 years and 232 patients that discontinued ETN within 4 years were included in the study. We investigated the demographic data of patients at baseline and the factors that associated with discontinuation of ETN due to adverse events (AE) and loss of efficacy (LOC) by Cox hazard regression model. [Results] In the continuation group, mean of age and disease duration was 56.0 years old and 12.0 years. The rate of concomitant MTX use was 61.4%. The factors that influenced discontinuation of ETN due to AE were age and no use of MTX(HR 1.038,1.557,95%CI 1.019-1.058, 1.011-2.396). The factors that influenced discontinuation due to LOC was no use of MTX(HR 1.814, 95%CI 1.187-2.772). [Conclusion] It was suggested that discontinuation rate due to AE was high in elderly patients without use of MTX. We showed that no use of MTX influenced discontinuation due to LOC, therefore concomitant MTX was needed for long-term retention of ETN.

W70-4

Predictor of long-term administration of infliximab for rheumatoid arthritis patients

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Conflict of interest: None

Introduction: Although there is strong evidence supporting the efficacy of infliximab (IFX), few studies have examined the predictor of long-term use of IFX. We evaluated the long term continuation of IFX in patients with rheumatoid arthritis (RA). **Method:** Among the initial 131 patients included in the study, 36 were continued receiving IFX treatment during at least 5 years (Continue "C" group) and 95 patients were discontinued less than 5 years (Discontinue "D" group). **Result:** The median time of receiving IFX was 6 years in C group and 1.6 years in D group, respectively. Compared with two groups, disease activity scores (DAS) 28 and CRP measured at first initiation was higher in D group (DAS: 5.4 VS 4.7; p=0.006, CRP: 2.9 VS 1.9 mg/dL; p=0.03) than in C group. Patients in D group were thinner than patients in C groups (body mass index: 21 VS 23 kg/m^2, p=0.04). Furthermore, patients in C group had experimented of more rapid improvement of DAS 28 during the first 14 to 22 weeks of therapy than in D group (14 week, 2.1 VS 1.2, p=0.006, 22 week, 1.7 VS 1.0; p=0.009). **Conclusion:** High DAS28 scores and CRP measured at first initiation and rapid improvement after receiving IFX were found to predict subsequent long-term continuation.

W70-5

Serum levels of MMP-3 correlate to changes in joint space narrowing score in patients with rheumatoid arthritis treated with TNF inhibitors

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Conflict of interest: None

We assessed relevance of joint-related markers including MMP-3 to changes in modified TSS, joint erosion (JE) and joint space narrowing (JSN) in RA patients treated with a TNF inhibitor (TNFi). 147 active RA patients were enrolled in the study and joint-related markers and radiographic changes were assessed at week 0 and 52 after the treatment with TNFi (IFX 49, ETN 49, ADA 49).. Baseline characters(mean±SD) were as the followings; age 58±14 yr, duration 107±124 mo, DAS28 5.7±1.1, MMP-3 285±282 ng/ml, NTx-Cr 62±39 nmol-BCE/nmol-Cr, mTSS 73±109, $\Delta mTSS_{0\text{-}52w}$ 8.4±11.5/y, JE 42±65, JSN 31±45. 70.9% fulfilled $\Delta mTSS_{0\text{-}52w} \leqq 0.5$, structural remission at 1 year after the TNFi therapy. Among multiple joint-related markers, MMP-3 at 52 weeks was most highly correlated to $\Delta mTSS_{0\text{-}52w}$ (r^2=0.085, p=0.0005), but BAP, NTx-Cr and others was not. MMP-3 at week 0 and 52 after TNFi was also highly correlated to $\Delta JSN_{0\text{-}52w}$ (week 0: r^2=.0504, p=.0005, week 52: r^2=.1386, p<.0001), but not to $\Delta JE_{0\text{-}52w}$. In conclusion, serum MMP-3 was highly correlated to changes in JSN but not that in JE after the treatment with TNFi, indicating that the inhibition of cartilage damage could be brought about by the reduction of MMP-3 from inflamed synovium by the treatment with TNF-inhibitors in patients with active RA.

W70-6

Study on joint destruction and repair of biological agents for rheumatoid arthritis

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Conflict of interest: None

[Objectives] To analyze the status of joint destruction/repair process and to identify its related factors on individuals with rheumatoid arthritis treated by biological agents. [Methods] Radiological evaluation was performed using joint X-ray images for 61 cases and classified into 4 groups as follows; Group D: progressive destruction of joints showing decreased joint space, erosions, Group R: joint repair showing increased joint space and disappear of erosion, Group N: no obvious changes, and Group M: different changes between joints. We also compared the age, disease duration, treating duration,part of the evaluated joints, CRP,MMP-3, DAS, and mHAQ between the groups of D and R. [Results] The number of cases in each group was D:21 (34.4%), R:7 (11.5%), N:30 (49.2%), and M:3 (4.9%). MMP-3 showed significant difference between the groups D and R(D:114.2ng/ml, R:47.6ng/ml, p=0.009), and mHAQ(D: 0.812, R:0.197, p=0.002) on the final follow-up. Joints in lower limbs were included in the group D (76.2%), whereas that in R was only 16.7%. [Conclusion] To decrease serum MMP-3 levels within normal range is an important factor for effective repair of joint structures and following improvement of mHAQ. However,joint destruction in lower limbs may be difficult to repair.

W71-1

Difference between responsive and unresponsive patients to the intensified infliximab treatment by dose escalation or interval reduction

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Conflict of interest: None

[Objectives] To evaluate the efficacy of intensified infliximab (IFX) treatment in RA patients resistant to standard regimen. [Methods] We analyzed 32 patients received intensified IFX therapy by dose escalation or interval reduction, because of primary or secondary treatment failure. [Results] Sixteen patients were successfully treated by the intensified therapy (Group A), although 16 patients were discontinued IFX (Group B). The number of primary and secondary failure was 7 and 9 in Group A, and 5 and 11 in Group B, respectively. In Group B, 14 patients received other biologics. The second biologics were tocilizumab (TCZ) in 9 patients, abatacept (ABT) in 3, adalimumab (ADA) in 1, and etanercept in 1. An ABT-treated patient and an ADA-treated patient were refractory to the therapy, necessitating switches to TCZ. Compared to Group B, Group A had a younger age (51.8±12.1 vs. 65.3±8.9 years) and a lower ESR (37.3±26.3 vs. 56.1±32.2 mm/hr) at the start of initial IFX therapy. Group A had a lower MMP-3 level at the start of the intensified IFX therapy (139.1±105.6 vs. 228.1±222.4 ng/mL). [Conclusion] The response to the intensified IFX therapy could be predicted by age and ESR at the start of IFX, and MMP-3 level at IFX treatment failure. TCZ seems to be useful for patients unresponsive to IFX.

W71-2

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

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Conflict of interest: None

[Objectives] We studied the efficacy of half dose etanercept (ETN) on 21 biologics naive rheumatoid arthritis (RA) patients with moderate disease activity. [Methods] The women constituted 90.5% and median age was 58.7 years. The patients with RA received subcutaneous injection of 25mg ETN every week. Clinical response through week 52 was assessed using DAS28-ESR and SDAI. [Results] DAS28-ESR and SDAI were 4.31±0.43 and 15.95±5.26 at enrollment, 2.99±1.08 and 8.41±6.09 at week 4, and 2.64±1.17 and 7.36±7.49 at week 52, respectively. The patients achieved DAS28-ESR remission (score<2.6) in 45.0% at week 4, and in 80.0% at week 52. Seventy seven percent of enrolled patients continued this treatment through week 52. Evaluation of effects of concomitant methotrexate (MTX) revealed the higher remission rate in group with MTX than in those without MTX. [Conclusion] In RA patients with moderate disease activity, 25mg dose of ETN every week yielded sustained improvement in signs/symptoms with safety, although in RA patients with high disease activity, the effects was not enough to tolerate.

W71-3

Modification of the infliximab infusion regimen for improving of RA patients' content - Review of 64 cases receiving 1-hour infusion and results of patient questionnaires -

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Conflict of interest: Yes

[**Objective**] To assess infliximab (IFX) infusion regimens for better infusion experience in RA patients. [**Methods**] The effect of reducing the IFX infusion duration from 2 to 1 h was assessed in 64 patients since January 2012. The duration was 2 h each for the first 5 doses and then reduced gradually by raising the infusion rate while monitoring vital signs (VS). It was reduced from the sixth dose onward. From June onward, the 1-h infusion rate was constant with VS monitoring. Safety evaluation was based on infusion reactions (IRs) and questionnaires. [**Results**] No patient exhibited IRs on accelerated infusion. A patient with moderate IR tolerated continuous treatment (2 h) with premedication. Questionnaires re-

vealed that 2-h infusion was “too long” in 60% and “just enough” in 30% patients; it was “satisfactory” in 70% cases, and 40% received the infusion with “anxiety.” Sixty percent of such patients consulted their friends/family members but <10% consulted hospital staff. [**Discussion**] The reduced IFX infusion duration was safe, and thus, this regimen is worth attempting. The reduced duration decreased the workload of nursing staff. Forty percent patients felt anxious while receiving the infusion. Thus, healthcare staff should try to relieve such feelings.

W71-4

Dosage intensification and dosing interval adjustment of infliximab in RA patients: Update of a multicenter IFX study2

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Conflict of interest: Yes

[Objectives] In July 2009, dosage intensification and dosing interval adjustment of infliximab (IFX) was approved for RA. We aim to evaluate the safety, efficacy, persistence rate of treatment and the frequency of dosing adjustment in quantity or interval for 2 years in patients who started IFX treatment after July 2009. [Methods] One hundred thirty patients were registered prospectively. Most were biologics naïve. The mean age was 54.6 years, with a mean disease duration of 7.0 years. [Results] The mean dosage at 2 years was 4.25 mg/kg and mean DAS28(ESR) was significant reduction from 5.29 at baseline to 3.43 ($p < 0.001$). Remission rate was 42.9% by DAS28 criteria and 25.6% by the Boolean criteria after 2 years. Of 130 patients, 29.1% received dose escalation after obtained the consent. No increase of adverse events was observed. At 2 years, the persistence rate on IFX was 71.1%. [Conclusion] Dosage intensification and dosing interval adjustment of IFX resulted in a drastic improvement of outcome with no increase of adverse events. Patients in this study have an excellent 2-year drug survival rate.

W71-5

Tolerability of shortened infliximab infusion times: a study of six-year experience

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Conflict of interest: Yes

[Objectives] Accelerated infliximab (IFX) infusions are officially approved by Health and Labor Ministry of Japan in May 2012. Since May 2006, we have shortened IFX infusion times in patients who have not experienced any adverse infusion reactions (IR) in 120-minute infusion time. In this study, we investigate the tolerability of shortened IFX infusion times from our six-year experiences. [Methods] The patients who completed IFX infusion without any IR at least 5 times in 120-minute infusion time were allowed to shorten. Infusion time was gradually shortened to 90, 60, and finally to 30 minutes with a primary goal of 60 minutes. Anti-allergy medication was not used routinely. All the infusions were conducted in the outpatient cancer treatment facility. [Results] Among 71 outpatients (69 RA, 1 PsA, 1 AS) treated with IFX, 13 patients were treated with 90-minute infusion, 29 with 60-minute, and 11 with 30-minute. A few patients experienced minor IR when infusion time was shortened or dose was increased, but could complete infusion by extending infusion time and/or using anti-allergy medication. [Conclusion] Infusion time of IFX can be safely shorted following proper procedures under close observation in the outpatient cancer treatment facility.

W71-6

Evaluation of Effectiveness and Safety of Etanercept (ETN) Treatment in Rheumatoid Arthritis (RA) Patients Aged 70 Years and Older

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Conflict of interest: None

[Objectives] Study the actual clinical effectiveness/safety of ETN in RA pts ≥70yo. [Methods] Data of RA pts who started ETN at ≥70yo; drug survival/clinical remission rates were retrospectively analyzed. [Results] Drug survival rate was analyzed for 95pts ≥70yo who started ETN by Jun. 2012; mean age 74.3yo; disease duration 9.1yr; MTX use 35.8%; and mean MTX dose 5.15mg/w; many pts could not tolerate MTX due to complications. Six-yr drug survival rate was 37.3% w/ no significant difference between pts with/without MTX. Adverse events (AEs) were main reason for discontinuation, being more apparent in pts w/out MTX. DAS28 remission rate was analyzed for 76 pts followed for ≥2yr. Remission rate at Week24, Years1 and 2 was 42.1, 32.9 and 35.5%, respectively. There was no significant difference in remission rate between pts with/without MTX; same trend was seen for mean DAS in pts continuing treatment. Compared to pts on 2yr treatment, those withdrawn due to AEs were significantly older and on less concomitant MTX. [Conclusion] ETN provided relatively high drug survival/remission rates in RA pts≥70yo. Aggressive treatment with biologicals may be indicated even for the elderly as needed. However, data suggested increased risk of dropout due to AEs in pts w/out MTX, requiring close monitoring.

W72-1

Prediction of efficacy of each biologics based on changes in rheumatoid factor

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Conflict of interest: Yes

[Objectives] Change in rheumatoid factor (RF) is known as one of parameters for immune abnormality in rheumatoid arthritis (RA), suggesting that the efficacy of different biologics may be predictable. [Methods] Seropositive RA patients who have started Infliximab (IFX), Etanercept (ETN), Tocilizumab (TCZ) or Abatacept (ABT) and have assessed DAS28 after 6months of treatment were included; IFX 35, ETN 97, TCZ 64 and ABT 31 pts. The change rate of RF at therapy initiation from 3months before was categorized into 3groups; >=20% decrease(RF↓), <20%(RF→) and >=20% increase(RF↑). Rate achieving remission/low disease activity at 6months after initiating therapy was compared. [Results] Above rate in each group was IFX(RF↓:RF→:RF↑(%)) 80.0:42.9:27.3, ETN 56.3:46.2:26.2, TCZ 56.3:74.1:66.7 and ABT 66.7:50.0:26.7. Compared to others, decrease in efficacy was not shown in patients treated with TCZ, even in the RF↑ group. [Discussions] IL-6, a differential proliferation factor of B cell, is believed to be strongly involved in patients with increasing RF. Therefore, an anti-IL-6R antibody, TCZ, should be considered as the first line treatment in patients with increasing RF. When treated with other Biologics, sufficient dose of MTX must be used in combination for enhancing effectiveness.

W72-2

Analysis of predictive biomarker which reflects the efficacy of Tocilizumab treatment for RA patient

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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. On the other hand, there is little report about good predictive biomarker for the efficacy of biologics before administration. (Objectives) We focused on serum cytokines expression to identify the predictive markers for TCZ. (Methods) We analyzed several cytokines from RA patients treated with TCZ. Serum cytokines were measured using MILLIPLEX MAP Human Cytokine/Chemokine before TCZ administration. In these cytokines, several cytokines were extracted as candidates for predictive biomarker. We investigated these cytokines in further many RA patients treated with TCZ using ELISA kit. (Results) Among serum cytokines measured by MILIPLEX MAP, IL-10 was high in good responders ($P<0.05$). Conversely, IL-13 and IP-10 level were high in poor responders ($P>0.05$). With the analysis of ELISA, IL-17A was high in poor responders ($P<0.05$). In addition, IP-10 tended to make high level in poor responders ($P>0.05$). (Conclusion) In this study, the levels of IL-10, IL-13, IL-17A and IP-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.

W72-3

Evaluation of disease activity and functional disability by the Routine Assessment of Patient Index Data 3(RAPID3)in patients with rheumatoid arthritis (RA) receiving Tocilizumab (TCZ)

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Conflict of interest: Yes

[Objectives] To investigate the usefulness of RAPID3 in evaluation of disease activity and functional disability in patients with RA receiving TCZ. [Methods] Seventeen patients with RA were enrolled in this prospective study. All patients received TCZ and were followed up to week 52. The primary outcome was DAS28-ESR, CDAI, SDAI, HAQ, RAPID3 at week 52. Secondary outcomes included proportion of patients in remission of RAPID3. [Results] The mean age of patients was 55 years, 65% of patients were females, the mean duration of disease was 12 years, 76 % of patients had received prior treatment of other biologics, 65% were MTX users and 82% were corticosteroid users. Significant reduction of DAS28-ESR, CDAI and SDAI was observed at week 24 and 52 compared to baseline. RAPID3 was significantly reduced at week 52 (mean 2.82, $P<0.05$ vs. baseline) but not at week 24 (3.21) compared with baseline (4.23). Remission rate of DAS28-ESR, CDAI, SDAI, HAQ, RAPID3 was 47, 18, 24, 35 and 24% in patients receiving TCZ after 52 weeks. RAPID3 correlated significantly with DAS28, CDAI, SDAI and HAQ. [Conclusion] RAPID3 is useful for evaluation of disease activity and functional disability in RA patients receiving TCZ. Improvement of RAPID3 was slower than that of other indices for disease activity.

W72-4

Evaluation of the Clinical/Functional Remission and MMP-3 Normalization, and its Contributing Factors by Long-term Treatment with Tocilizumab in Rheumatoid Arthritis Patients

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Conflict of interest: None

[Objectives] To examine the achievement rate and contributing factors of clinical/functional remission and MMP-3 normalization at 52 weeks after introducing tocilizumab (TCZ). [Methods] We evaluate 52 RA patients at our hospital who observed over 52 weeks after introducing TCZ. Mean age was 63.1 years old, disease duration was 11.5 years, CDAI before starting TCZ was 20.0±12.1, m-HAQ was 0.6±0.6, MMP-3 was 217.8±250.2ng/mL, ACPA was 227.2±298.1ng/mL (positive rate:89.7%), MTX dose was 7.5±2.4mg/week (combination rate:67.3%).Bioligics had uesd in 23 patients (44.2%) previously. Changes in CDAI, m-HAQ and MMP-3 were evaluated by LOCF method, and factors were extracted statisically. [Results] Mean CDAI after 52 weeks was significantly improved at 4.7±6.8 (remission rate 51.9%). Mean m-HAQ was also improved at 0.3±0.5 (remission rate 75.0%). Clinical/functional remission with normalized MMP-3 rate was 38.5%, and the contributing factors extracted were starting administration at a younger age,low m-HAQ,and low disease activity. CDAI and Boolean remission at 12 and 24 weeks also extracted. TCZ continuation rate at 52 weeks was 80.8%. [Conclusion] Earlier intervention and CDAI/Boolean remission at 12 and 24 weeks are possible indices for acieving a strictly good outcome 52 weeks after introducing TCZ.

W72-5

Positive anti SS-A antibody(SSA+) is associated with poor clinical response to tumour necrosis factor inhibitor(TNF-i) therapies in rheumatoid arthritis(RA) compared to tocilizumab(TCZ)

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Conflict of interest: None

[Objectives] Predictors of response to biologic therapy in RA are needed to achieve a more individualized therapy, however only a few objective predictors have been identified yet. In this retrospective study, we investigated whether SSA+ is related to clinical response in patients with RA treated with TNF-i or TCZ. [Methods] One hundred eighteen cases with RA treated with TNF-i or TCZ are enrolled. In the SSA+ group 37 cases were treated with TNF-i(n=17) and TCZ(n=10). All cases have been evaluated clinically at 3, 6, 12, and 24 months. [Results] In comparison with the SSA+ and negative SSA(SSA-) groups, TNF-i treatment brought about more effective outcome in the SSA- group(DAS28(4) ESR 3.14 vs 3.78 at 6months : $p=0.0207$, 2.89 vs 3.74 at 12 months : $p<0.001$, 3.14 vs 3.70 at 24 months : $p=0.0461$). TCZ didn't show any statistical differences of the clinical outcome between in the both groups. TCZ showed 80% persistency rate in 24 months whereas TNF-i did 64.8%. [Conclusion] According to the clinical response, it is suggested that SSA+ is one of the predictors of clinical efficacy in the TNF-i therapy. These data support the effectiveness of TCZ treatment among RA patients with SSA+.

W72-6

Optimal timing of tocilizumab administration in patients with rheumatoid arthritis: a cost evaluation study using the IORRA database

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Conflict of interest: Yes

[Objectives] To investigate the optimal timing of tocilizumab (TCZ) administration for RA patients from the perspective of cost-effectiveness. [Methods] We investigated the cost-effectiveness of TCZ (TCZ group) compared with methotrexate alone (MTX group) using a Markov model. Incremental cost-effective ratios (ICER) were estimated in six hypothetical populations, which differed in physical dysfunction severity based on the J-HAQ score (<0.6, 0.6-1.1, 1.1-1.6, 1.6-2.1, 2.1-2.6, and >2.6) at the start of treatment (initial J-HAQ score). All model parameters such as utilities and medical costs were based on clinical data extracted by the matching method from the IORRA cohort. A lifetime horizon and a discount rate of 3% per year for both health benefits and costs were assumed. [Results] Clinical data from two groups of 104 patients each were used for calculating parameters in the model. ICER was 2.59 million JPY for patients with initial J-HAQ scores of 0.6-1.1 and increased to 13.5 million JPY for patients with initial J-HAQ scores of over 2.6. [Conclusion] TCZ might be used most cost-effectively in RA patients whose initial J-HAQ is 0.6-1.1, suggesting that early administration of TCZ before the development of irreversible physical disability in RA patients is useful.

W73-1

Efficacy and safety of long-term subcutaneous injection of tocilizumab (TCZ-SC) monotherapy and after switching from intravenous infusion of tocilizumab (TCZ-IV) monotherapy to TCZ-SC in patients with rheumatoid arthritis (RA)

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Conflict of interest: Yes

[Objectives] To investigate efficacy and safety in long-term TCZ-SC and after switching from TCZ-IV to TCZ-SC in patients with RA. [Methods] Patients with inadequate response to synthetic/biologic DMARDs, received TCZ-SC (162 mg/2w) or TCZ-IV (8 mg/kg/4w) under double-blind conditions after which all patients received TCZ-SC. With a data cut-off date of March 2012, efficacy data up to Week 60 and all safety data were analyzed. [Results] DAS28 and CDAI remission rates were kept at same levels between before and after switching to TCZ-SC and no new safety issue was reported in 160 patients with switched to TCZ-SC. The continuation rate of TCZ-SC was 87.3%, and ACR20/50/70 response rates were 86.9%, 69.3% and 52.3% at Week 60, respectively in 158 patients who had continued TCZ-SC from double-blind period. The rates of AEs, SAEs and serious infections were 546.2 events/100 PYs, 17.9 events/100 PYs and 5.5 events/100 PYs, respectively. One death and 3 cases of malignancy were reported. Injection site reactions were reported in 56 cases out of 44 patients, but all events were mild. [Conclusion] The continuation rate of TCZ-SC was excellent, and the efficacy and tolerability of long-term TCZ-SC was seen. Efficacy was maintained after switching to TCZ-SC and no new safety concerns was observed.

W73-2

Safety of tocilizumab and TNF inhibitors in patients with rheumatoid arthritis in clinical practice: analyses from the REAL database

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Conflict of interest: Yes

Objective: To compare safety of tocilizumab (TCZ) and TNF inhibitors (TNFI) in clinical practice. **Methods**: Patients with rheumatoid arthritis (RA) starting TCZ [TCZ group, n=302, 238.5 patient-years (PY)] or TNFI [TNFI group, n=304, 241.4 PY] from 2008 to 2011 in the REAL database were included. We assessed types and incidence rates of serious adverse events (SAEs) and serious infections (SIs) duringfirst year of the treatment. **Results**: In the TCZ group, patients had longer disease duration, higher frequency of renal diseases and concomitantcorticosteroids usecompared with the TNFI group. The incidence rates (/100PY) of SAEs and SIs in theTCZgroup were higher than those in the TNFI group (SAEs, 20.1 vs. 14.1; SIs, 10.1 vs. 2.9). The incidence rate of non-respiratory infection, but not for respiratory infection, was conspicuously higher in the TCZ group compared with the TNFI group (7.1 vs. 1.7). However, after adjusting for confounding factors using the Cox proportional hazard analysis, treatment with TCZ was not associated with higher risk for SAEs or SIs. **Conclusions**: Tocilizumab was prescribed for RA patients with a higher risk for SAE, but the adjusted risks for SAEs and SIs were not significantly different between TCZ and TNFI treatment.

W73-3

Influence of history of anti-TNF therapy on the efficacy of tocilizumab in RA patients -Examination from Tsurumai Biologics Communication Registry-

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Conflict of interest: None

[Objectives] To investigate the relationship between the efficacy of tocilizumab (TCZ) and history of anti-TNF therapy. [Methods] This study included 137 patients who received TCZ treatment with history of anti-TNF therapy in Tsurumai Biologics Communication Registry (TBCR). DAS28-ESR at 1 year was compared between group A (94 patients with history of one anti-TNF therapy) and group B (43 patients with history of two or more anti-TNF therapy). In addition, effects of previous anti-TNF agents were assessed by comparing between two groups on each drug; the one with the use of a certain anti-TNF agent and the other without the agent. [Results] Change in mean DAS28-ESR from baseline to 1

year was 5.7 to 3.0 in group A, and 5.8 to 3.2 in group B; no significance was shown between the two groups. DAS28-ESR at 1 year of the group with previous use of etanercept (ETN) was significantly higher than the group without ETN (3.3 vs 2.6). Moreover, among the patients with previous use of ETN, patients who were switched from ETN just before TCZ were not liable to be remission than switched from other anti-TNF agents. [Conclusion] The efficacy of TCZ switched from anti-TNF agents is not influenced by the number of anti-TNF agents which used previously but by the previous use of ETN.

W73-4

Importance of concomitant MTX use during treatment with tocilizumab in patients with rheumatoid arthritis

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Conflict of interest: Yes

[Objectives] Any Information to predict outcome is important for the choice of biologics. The aim of this study is to identify the baseline factors that contribute to the remission in treatment with tocilizumab (TCZ). [Methods] This study included 223 patients who received TCZ treatment in Tsurumai Biologics Communication Registry (TBCR). We analyzed the baseline factors predicting DAS28-ESR remission rate at week 52. In addition, we formulated a matrix model using the key factors associated with DAS28-ESR remission in order to compare TCZ effectiveness by subgroups. [Results] The multivariate logistic regression analysis showed a significant positive association between DAS28-ESR remission at week 52 and the following baseline factors: no previous use of biologics [OR2.35 (1.26-4.43)], and lower half of DAS28-ESR(<5.6) [OR3.70 (2.07-6.76)]. Interestingly, in the patients with higher disease activity (DAS28-ESR(>5.6), concomitant MTX had a significant impact on achievement of remission [OR3.08(1.24-8.18)]. [Conclusion] Concomitant MTX should be important for the achievement of remission in the patients who need more aggressive intervention with poor prognostic factors such as higher disease activity, previous biologics use, and with shorter disease duration.

W73-5

Determination of clinical characteristics by patient background in RA patients treated with tocilizumab at 6 week intervals

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Conflict of interest: None

[Objectives] We performed a retrospective analysis to determine clinical characteristics of the RA patients who could be maintained remission with tocilizumab (TCZ) every 6 week. **[Methods]** 84 RA patients treated with TCZ in our institute from July, 2008 to August, 2011.We compard the background of 10 patients who have been in remission for more than 24 weeks and the infusion interval of TCZ was extended to every 6 week, and the other 74 patients who had received TCZ every 4 week. **[Results]** DAS28-ESR (at week 0, week 12 and week 24) of the 6 week interval group were 1.96/2.33/2.01. Patients background data in each (6 week interval/4 week interval) group were as follows; mean age: 60.8/58.5, no. of female patients: 9/64, mean duration of RA: 99.6/127.8, maen DAS28-ESR: 5.66/5.5, and MTX combination: 50/65%), all were not significant. **[Conclusion]** TCZ at the 6 week interval could maintain remissionin some patients who achieved remisison for more than 24 weeks. Those patients were tend to have slightly shorter disease duration and lower incidence of MTX use, but not significant.

W73-6

Efficacy of tocilizumab in patients with rheumatoid arthritis in our department – Possibility of a first biologic agent -

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Conflict of interest: None

[Objectives] To clarify the efficacy and safety of tocilizumab (TCZ) in the patients with rheumatoid arthritis (RA) in our institute. [Methods] A total of 55 RA patients treated with TCZ in our department after 2008, were included in this retrospective study. Clinical status and safety were evaluated for 24 weeks. [Results] Mean age was 54.1 years old and mean duration of the disease was 3.5 years. Use of MTX was found in 81.8% of the patients, and 45.4% of the patients were previously treated with other biologics. Mean DAS-28 was 5.28. Clinical remission was obtained in 51.9% (66.7% vs. 32.0% in biologic naïve patients vs. in others), 27.5% (36.7% vs. 12.0%), 29.4% (40.0% vs. 12.0%) and 12.7% (20.6% vs. 4.3%) by DAS-28, CDAI, SDAI and Boolean definitions, respectively. Non-concomitant MTX before starting TCZ was identified as an independent factor for DAS-28 remission and CDAI at the start of TCZ was identified for CDAI remission in multivariate logistic regression analysis. Clinical remission by DAS-28 was obtained in 54.5% in the patients with MTX and 45.5% in those without. The persistence rate of TCZ was 94.5% at 24 weeks. [Conclusion] TCZ exhibited good efficacy and safety profiles also as a first Bio and almost equal effectiveness regardless of concomitant use of MTX.

W74-1

Inhibition of Joint Destruction by Tocilizumab - Evaluation at Baseline and After Two Years of Treatment -

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Conflict of interest: None

[Objectives] Joint destruction inhibition in rheumatoid arthritis (RA) patients treated with tocilizumab (TCZ) in clinical practice was verified. [Methods] The subjects were 118 patients in our hospital treated with TCZ until October 2012 in whom X-ray evaluations could be performed after 1 year of TCZ treatment, and 39 patients could be performed after 2 years. The Total Sharp Score (TSS) was used in the evaluation. [Results] The patient characteristics included a mean age of 58.0 years, mean disease duration of 10.3 years, MTX concomitant rate of 63.6%, history of use of TNF inhibitors of 61.0% and initial TSS of 94.4. The yearly progression

of joint destruction (ΔTSS/year) was 12.5 at baseline and 0.5 after 1 year, showing inhibition of 96.0%. The achievement rate of ΔTSS ≤ 0.5 for structural remission was 74.5% and 66.7% at after 1year and 2years, respectively. In patients with insufficient response to TNF inhibitors, ΔTSS was 0.5 at baseline and -0.1 after TCZ treatment in an investigation of 17 patients in whom X-ray evaluation from 1 year before TCZ treatment was possible. [Conclusion] TCZ showed clear inhibition of joint destruction in RA patients and it appears necessary to consider switch to TCZ in patients with insufficient response to TNF inhibitors.

W74-2

Treatment with tocilizumab (TCZ) improved rheumatoid arthritis (RA) patients clinically and structurally regardless of the prior use of anti-tumor necrosis factor (TNF) biologics in daily clinical practice

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Conflict of interest: None

Aim: To explore the radiographic efficacy of TCZ in RA patients with or without the prior use of TNF inhibitors in daily clinical practice. **Methods:** Of a total of consecutive 115 RA patients initiating TCZ treatment in Keio university hospital from July 2008 to March 2011, 46 patients who had x-rays of the both hands and feet were assessed stratified by the use of prior biologics (BIO+) and no use of them (BIO-). They were observed for 52 weeks to evaluate the clinical and structural outcomes. **Results:** Baseline characteristics (BIO+, BIO-) were as follows: mean age of 54.8±11.2 years, 52.5±12.5 years; mean disease duration of 6.8±6.5 years, 4.0±3.4 years; concomitant use of MTX in 76.9%, 48.5%. Baseline patients' characteristics were comparable between BIO+ and BIO- groups except for ESR (65.9±32.3 in BIO+ vs 42.4±35.3 in BIO-). In BIO+ and BIO- patients, DAS28 remission was achieved in 61.5% and 81.8%, CDAI remission 38.5% and 51.5%, respectively. Radiographic remission (ΔTSS ≦ 0.5) was 46.2% (6/13) in BIO+ patients and 66.7% (22/33) in BIO- patients. There were no significant differences in clinical and structural remission rates between the two groups. **Conclusion:** The treatment with TCZ improved RA patients clinically and structurally regardless of the prior use of anti-TNF biologics.

W74-3

Efficacy and Safety including Bone and Joint Evaluation in Long-term Observational Investigation of Rheumatoid Arthritis Patients Receiving Tocilizumab (Interim Report)

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Conflict of interest: Yes

[Objectives] To verify the efficacy and safety of tocilizumab (TCZ) for rheumatoid arthritis (RA). [Methods] Subjects were 612 patients (including 498 women) 1 year after starting TCZ administration. Mean age was 59.6±13.6 years and mean disease duration was 9.7±9.1 years. Disease activity was evaluated in 465 patients by DAS28-ESR and Boolean-based remission criteria, and bone and joint evaluation was conducted using modified total sharp score (mTSS) in 114 patients. [Results] Mean DAS28-ESR was 5.1±1.3 before administration and 2.5±1.6 at the final observation. Mean time until attaining DAS28-ESR remission was 18.6±10.8 weeks. One year after starting the continuation rate was good at 81.8%. The bone erosion score at start was 55.1±55.0, joint space narrowing (JSN) score at start was 40.2±37.4, and mTSS at start was 94.5±91.6. Bone erosion score/year was 6.58±0.72 at start and 0.17±0.72 after 1 year, JSN score/year was 5.07±0.59 at start and 1.05±0.55 after 1 year, mTSS/year was 11.65±1.28 and decreased to 1.22±1.28 after 1 year, and 64.8% of subjects attained ΔmTSS≦ 0.5. Adverse events were no more numerous than in post-marketing surveillance. [Conclusion] TCZ showed good tolerability, and is an effective method of suppressing bone destruction, leading to rapid remission.

W74-4

A Study of tocilizumab (TCZ) treatment for patients with rheumatoid arthritis (RA) about achievement and maintenance of remission, and prevention of joint destruction

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Conflict of interest: None

[Objective] We examined the effectiveness of TCZ treatment for RA patients about the achievement and the maintenance of remission from the viewpoint of Treat to Target (T2T). [Method] For 116 RA patients who introduced TCZ treatment in our hospital from 2008 to 2011, we analyzed the change of disease activity (DAS28-ESR, Boolean standard), MMP-3 at 52 weeks, a period until the achievement of the remission and the duration of its maintenance. [Result] Remission rate at 52 weeks was 47.4% and 21.6%, respectively. The first remission achievement time was 15.2±11.4 and 19.3±14.3 weeks. Remission state continued for 23.3±14.8 and 12.9±14.7 weeks. Remission state continued in forty-six(39.7%) and Thirteen(11.2%) patients over 24 weeks. Serum MMP-3 level fell to 120±106 from 358±379 ng/ml at the last observation, and 42 cases(36.5%) showed normal value. 27 patients showed normalized serum MMP-3 level over 24 weeks. Between the remission of DAS-ESR and the normalization of serum MMP-3 level at the time of the last evaluation significant relationship was seen ($p<0.0346$, χ^2 test). [Conclusion] Achievement of clinical remission and its maintenance of RA patient were possible by TCZ treatment. TCZ therapy suggested the effect of prevention of joint destruction and its maintenance.

W74-5

Radiographic progression of cervical lesions in patients with rheumatoid arthritis receiving infliximab and tocilizumab treatment from TBCR

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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 par-

ticular, 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 of IFX and TCZ for inhibiting the radiographic progression of RA cervical lesions at this time. [Methods] We used IFX and TCZ for treating Japanese patients with active RA. The final study cohort of each 126 and 38 patients received continuous IFX and TCZ treatment for at least 1 year. For evaluation of cervical lesions, ADI, SAC and Ranawat value were measured by plain lateral radiographs in the flexion position, at initiation and 1 year. [Results] The number who was able to suppress progression in all three parameters were each 89 cases (71%) receiving IFX and 26 cases (68%) receiving TCZ (p=0.839). Significantly higher suppression of cervical lesion progression was found in the good responders than moderate responders receiving both IFX and TCZ. [Conclusion] IFX and TCZ treatment can be used to suppress the progression of RA cervical lesions, as well as hand and foot joints lesions.

W74-6

Long term observation of RA patients who have High Disease Activity after 6months treatment with Tocilizumab - from Tsurumai Biologics Communication Registry

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Conflict of interest: None

[Objectives] Tocilizumab (TCZ) often shows satisfactory response in the TNF-IR patients. Some patients have slow response with TCZ switched from TNF-inhibitor. Long-term TCZ response in the patients who have High Disease Activity (HDA) in 24th week is investigated. [Methods] 229 RA patients who have used TCZ over 24weeks is investigated from Tsurumai Biologics Communication Registry (TBCR) [Results] At 24th week, 13 patients(6.1%) were in HDA(group H) and 195 patients(84.7%) were in Moderate disease activity or lower (group M). In the baseline data, before TCZ is injected, MTX use was significantly lower in the group H(15.4%) than group M(51.8%). Mean DAS28ESR was also significantly higher in the group H(6.7) than group M(5.6) at the baseline. When patients were in HDA at 24th week, 60% of the patients became MDA, and some patients became LDA or remission at 52th week. In the 4th year of TCZ injection with LOCF analysis, 40% is ceased, 45% is in MDA, 15% is in LDA. [Conclusion] TCZ often become lethal weapon in the patients who are TNF-IR. If TCZ is continued in TNF-IR patients who are in HDA at 24th week of TCZ, 60% might become MDA at 52th week. We need more information about whether switching from TCZ to another biologics is better than continuing TCZ over 24weeks or not.

W75-1

Neutrophil CD64 level to rule out infectious diseases in elderly patients

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Conflict of interest: None

[Objectives] In elderly patients, it is difficult to diagnose febrile disease because they sometimes suffer from infectious diseases without any specific sign or manifestation. We examined the utility of neutrophil CD64 level as a diagnostic marker for ruling out infectious diseases in aged patients. [Methods] The expression level of CD64 molecule per neutrophil was quantitatively measured by flow cytometry using a QuantiBRITE kit (Beckton-Dickinson) in febrile aged (>65 y.o.) patients. Information having infectious disease or not was obtained from each patient's medical record in which attending physicians were obliged to write down a synthetic diagnosis following resolution of manifestations. [Results] Among 175 febrile patients, 59 patients were diagnosed as infectious disease, and 116 patients as non-infectious diseases. A cutoff level of neutrophil CD64 was determined 2,000 molecules per cell by the receiver operating characteristics analysis. The sensitivity and specificity of the determination of neutrophil CD64 level were 87% and 88% each. The positive likelihood ratio (LR) was 7.3, and the negative LR was 0.13. [Conclusion] Considering frequent infectious diseases in elderly patients, the determination of neutrophil CD64 level may help us to rule out infectious diseases.

W75-2

CD64 and CD35/CD64 on neutrophils are useful for Epstein-Barr virus (EBV) screening for methotrexate-related lymphoproliferative disorders (MTX-LPD) in patients with rheumatoid arthritis (RA)

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Conflict of interest: None

[Objectives] RA patients sometimes suffer from MTX-LPD, half of which are EBV-related. We had previously reported the CD35/CD64 ratio on neutrophils was useful to distinguish between bacterial and viral infections in RA patients. [Case 1] A 44-year-old male with RA was suffering from fever and weight loss. A bone marrow biopsy showed lymphoma cells around the trabecula, which were LMP1 negative. EBV-DNA in whole blood was undetectable with real-time PCR. The CD64 level and CD35/CD64 ratio were 1428 molecules/cell and 13.56. [Case 2] A 65-year-old female with RA was suffering from fever and left supraclavicular region swelling. A biopsy of the supraclavicular lymph node showed Hodgkin's lymphoma that was LMP1 positive. The EBV-DNA in whole blood was 320 copies per 10^6 WBC. The CD64 level and CD35/CD64 ratio were 11776 molecules/cell and 0.69. [Case 3] A 64-year-old female with RA was suffering from fever, night sweats and weight loss. The PET-CT showed accumulations in several areas of the bone marrow. The EBV-DNA in whole blood was 1000 copies per 10^6 WBC. The CD64 level and CD35/CD64 ratio were 15468 molecules/cell and 0.70. After MTX treatment was stopped, her symptoms disappeared. [Conclusions] EBV-related MTX-LPD were found to exhibit a viral pattern (CD64>2000, CD35/CD64<2.8).

W75-3

Measurement of neutrophil CD64 expression in RA patients with nontuberculous mycobacterial diseases

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Conflict of interest: None

[Objectives] In rheumatoid arthritis (RA), infection is not only one of the major complications but also one of the frequent causes of death. Quantitative measurement of CD64 expression on neutrophils can be used as an infection marker in RA patients. We measured the expression level of CD64 per neutrophil in RA patients with nontuberculous mycobacterial diseases (NTM) to examine the relationship of disease activity and expression of CD64 on neutrophils. [Methods] We measured the expression level of CD64 per neutrophil in 13 RA patients with NTM(11: *M.avium-intracellulare complex,* 2*: M.nonchromogenicum*) quantitatively by flow cytometry. The cut-off point was 2000 molecules/cell. [Results] Neutrophil CD64 expression was usually below the cut-off level in patients with non-active lung disease; the expression level tended to elevate above the cut-off level in patients with fever and/or productive cough, and significantly higher among patients with high disease activity, such as pleuritis, persistent high fever due to NTM. The level of CD64 expression downregulated after these patients were treated by antimycobacterial drugs. [Conclusion] The expression of CD64 on neutrophils tended to reflect disease activity in patients with NTM. Further studies are needed.

W75-4

Usefullness of Serum Procalcitonin Measurement in the Diagnosis of Infection in Patients with Rheumatic Diseases and Connective Tissue Diseases

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Conflict of interest: None

[Objectives] Procalcitonin (PCT), a precursor for calcitonin, has been reported as a useful marker in diagnosis bacterial infection. We investigated the usefullness of serum procalcitonin measurement in the diagnosis in the diagnosis of various infection in patients with rheumatic diseases and connective tissue diseases. [Methods] We measured serum PCT level in 142 patients(male46, female96) with rheumatic diseases and connective tissue disease, who were fulfilled the criteria of systemic inflammatory response syndrome (SIRS). After collecting blood samples, they were all admitted to our hospital and started the treatemend. [Results] 77patients were considered having infectons and the other 65patients were considered having disease flare of their autoimmune disease and onset of new diseases. Serum PCT level was higher in the infection group than in the other group(average 8.3/0.4, $p<0.001$). With a PCT cutoff value of 0.50 ng/ml, sensitivity and specificity for the detection of infection were 57.1%, and 86.2%.Positive Predictive Value (PPV) was 83.0% and Negative Predictive Value (NPV) was 62.9%. [Conclusion] PCT is useful in the diagnosis of infections in patients with autoimmune diseases. BUt we should pay attention to the possibility of PCT elevation without systemic infections.

W75-5

Analysis of factors associated with development of sepsis in patients with collagen diseases

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Conflict of interest: None

[Objectives] The current study was undertaken to clarify background factors developing sepsis in patients with collagen diseases (CDs). **[Methods]** Forty patients with CDs complicated with sepsis who admitted to our hospital from 1996 to 2012 were studied. In all cases, pathogen was detected from blood culture. The relationships of primary disease with patient's characteristics including prognosis, laboratory date and pathogenic agent were explored. **[Results]** Of 40 patients, 12 patients were RA, 16 were SLE, 4 were systemic vasculitis syndrome and 2 were MCTD, dermatomyositis, SSc or the other rheumatic diseases, respectively. The total number of pathogenic agent was 41 strains [gram negative bucilli (GNB): 58.5%, gram positive cocci: 34.4%, fungi: 4.8%]. Most of the bacterial translocation came from urinary tract, in which *Eshericia coli* was most frequently detected in 16 patients. In patients with RA, the rate of GNB sepsis was significantly increased, compared to those with CDs other than RA ($p=0.0158$). Furthermore, the mortality rate was significantly higher in RA patients ($p=0.0223$). **[Conclusion]** These data indicate that high mortality rate of sepsis in RA patients might result from some causes specific to RA, such as decreased activity of daily life.

W75-6

A case of rheumatoid arthritis (RA) complicated with Listeria monocytogenes infection during infliximab (IFX) therapy

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Conflict of interest: None

A 73-year-old woman was diagnosed as having RA in 1992 based on her joint symptom in the feet. Since her symptom developed gradually, she was treated with methotrexate and prednisolone. Despite this, her disease activity was not well controlled, and IFX was started in March 2012. After receiving third administration of IFX, she noticed black stool from the middle of May 2012 and developed anemia. Upper endoscopic examination revealed multiple gastric ulcers, and then she stopped receiving NSAIDs and PPI was initiated. However, her anemia progressed further, and she was admitted to our hospital on May 31. After admission, her anemia due to multiple NSAIDs ulcers was improved by transfusion. On the other hand, she presented with fever at the time of admission, and blood cultures later showed positive for Listeria monocytogenes. Since no abscess or meningitis were observed, she was diagnosed as having Listeria sepsis and was successfully treated with ampicillin (12g/day). Listeria infection associated with anti-TNF agents, which was issued as a boxed warning from FDA in

2011, is a rare complication, but we need to consider the possibility of this complication when we found febrile patients under treatment with anti-TNF agents.

W76-1

Investigation of the factors inducing infection in rheumatic connective tissue disease

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Conflict of interest: None

Objective To isolate the factors inducing infection in rheumatic connective tissue disease. Methods The subjects were 63 patients with rheumatic connective tissue disease, and were divided into 2 groups for analysis according to whether they developed infections before the conclusion of steroid therapy for the underlying condition: those who developed infections (n = 28) and those who did not develop infections (n = 35). Results Multivariate logistic regression analysis of the factors considered as associated with inducing infection before and after steroid therapy between the 2 groups enabled isolating 3 factors, namely, cumulative steroid dose, post-treatment lymphocyte count, and post-treatment IgG minus pre-treatment IgG (ΔIgG). Conclusions The effects of cumulative steroid dose, lymphocyte count, and ΔIgG, which were identified as the factors inducing infection, interact with each other, and hence, they could not be used to predict infections. Nevertheless, patients in whom all these isolated factors are present may be at a high risk of developing infections.

W76-2

Clinical features of patients with collagen diseases complicated by infection

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Conflict of interest: None

[Objectives] We studied clinical backgrounds of patients with infections complicated with immunosuppressive therapies for collagen diseases. [Methods] We studied 265 patients under immunosuppressive therapy, out of 329 patients admitted to our department of Kyoto University Hospital from April 2010 to March 2011. [Results] 108 patients experienced infections and 25 patients needed treatments for several infections. Lymphopenia and low serum IgG level were observed in the infection group, the several infection group and the cytomegalovirus (CMV) reactivation group. The infection group is older and more frequently treated with immunosuppressants compared with the control group. The several infection group was treated with higher dose of corticosteroids (CS) and intravenous CS pulse therapy (IVCS). The bacterial infection group was older, complicated with lung diseases. The pneumocystis pneumonia (PCP) group was older and treated with MTX. The CMV group was treated with higher dose of CS, IVCS, and intravenous cyclophosphamide therapy. [Conclusion] Lymphopenia and low serum IgG level were risk factors of infections in patients with collagen diseases. Before immunosuppressive therapy, we should estimate these risk factors of each infection to prevent the opportunistic infections.

W76-3

The impact of serious infection on the treatment and the disease activity of rheumatoid arthritis

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Conflict of interest: Yes

[Objectives] We studied whether the serious infection accompanied by the treatment for RA (rheumatoid arthritis) cause difficulty in subsequent RA treatment and deteriorate disease activity. [Methods] We enrolled 298 RA patients in KURAMA cohort (Kyoto University Rheumatoid Arthritis Management Alliance) and analyzed the correlation between the past history of hospitalized infection and the present medication and disease activity. [Results] Forty patients experienced hospitalized infection. (Bacterial pneumonia;12, Cellulitie;10 etc.) Before and after infections, the number of patients who use MTX decreased, while the use of oral corticosteroid did not change. The use of biologics decreased from 13 to 6 patients, but 6 patients were newly introduced for biologics at least 3 years after infections. At present, compared with the non-infected group, the infected group had longer disease duration, treated with lesser doses of MTX and higher dose of oral corticosteroids. The use of biologics and the present disease activity were similar in both groups. Hospitalized infection did not impact on the present the disease activity by multivariate analysis. [Conclusion] It was indicated that serious infection may impact on subsequent RA treatment but not on the final disease activity.

W76-4

Comparative analysis of hepatitis B virus reactivation between rheumatic diseases and hematologic diseases

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Conflict of interest: None

[Objectives] Recently, it is notable about HBV reactivation in patients treated with immunosuppressive agents. We compared HBV reactivation between patients with rheumatic diseases (RD) and with hematologic disorders (HD). [Methods] The following two groups were retrospectively compared: 380 RD cases with immunosuppressive therapy; and 151 HD cases with rituximab. [Results] The frequency of HBV carriers in RD and HD were 1.3% and 6.6%, respectively. The frequency of patients with HBsAg (-) and HBsAb (+) and/or HBcAb (+) in RD and HD were 16.1% and 32.5%, respectively. Of these, more women possessed in RD (RD vs HD, 64.8% vs 34.7%, respectively; $p<0.001$) and HBsAb-positive patients in HD were lower (RD vs HD, 86.5% vs 64.3%, respectively; $P= 0.017$). Of patients with previous HBV infection, HBV reactivation in HD was higher than that in RD (4/23 cases (17.4%) vs 1/61 cases (1.5%), respectively; $P=0.041$). Hematologic patients with reactivation were significantly more HBsAb-negative

patients than those without reactivation ($p<0.005$). [Conclusion] The frequency of HBV reactivation in HD treated with rituximab was similar, while that in RD was lower, in comparison to other reports. This may be due to low number of men and HBs-negative patients in RD, which were recognized as risk factors.

W76-5

Clinical Profiles of Rheumatoid Arthritis with Pre-Existing Hepatitis B Virus Infection

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Conflict of interest: None

[Objectives] We reviewed the differences in clinical profile of rheumatoid arthritis (RA) patients whther they have pre-existing hepatitis B virus (HBV) infection or not. [Methods] RA patients without HBsAg were divided into two groups according to anti-HBc positivity. We reviewed serum levels of rheumatoid factor (RF) and anti-cyclic citrullinated peptide (CCP) antibodies, measured RA activity. [Results] Three hundred and seventeen patients were the anti-HBc-negative group and 96 patients were in the anti-HBc-positive group. In comparison to negative, mean onset age was significantly older in HBc positive group (51.9 and 59.3 year's old, $p<0.001$). Titers of Rheumatoid factor were significantly higher in HBc positive group, while anti-CCP antibody titers did not show significant difference. Rates in patients who had been given methotrexate (MTX) and biologic DMARDs were 78.9% and 31.2% in the anti-HBc-negative group, and 65.6% and 29.2% in the anti-HBc-positive group, and p-value was respectively 0.01 and 0.8. Disease activity and clinical response were almost identical among those two groups. [Conclusion] These data suggested HBV seems to play a role in the pathogenesis of RA.

W76-6

Study of 16 adult cases of human parvovirus B19 infection

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Conflict of interest: None

[Objectives] To investigate the characteristics of human parvovirus B19 (HPV B19) infection in adults. [Methods] We retrospectively reviewed 16 patients (all case were female, age 44.9 ± 12.0 years) of adult HPV B19 infection who visited our outpatient department. Diagnosis of adult HPV B19 infection was based on positive anti-HPV B19 IgM antibody in serum. [Results] The predominant signs and symptoms of the patients were as follows: fever (87.5%), edema (68.8%), skin rash (62.5%) and arthralgia/myalgia (50.0%). 6 patients had the following underlying diseases or complications: 3 cases of rheumatoid arthritis, 2 cases of anti-phospholipid antibody syndrome. The following abnormal laboratory findings were observed: positive of ANA (75.0%), leukopenia (50.0%), hypocomplementemia (43.8%), anemia (31.2%), positive rheumatoid factor or anti-CCP antibody (31.3%), positive anti-DNA antibody(6.3%), positive anti SS-A antibody (6.3%). [Conclusion] HPV B19 infection is well known as a cause of erythema infectiosum in children. HPV B19 can infect adults and cause more diverse signs and symptoms compared to children. Adult HPV B19 infection can be suspected from family history and clinical findings. Accordingly, more attention should be paid to adult HPV B19 infection.

W77-1

Analysis of cytomegalovirus (CMV) infection in patients with collagen diseases (CD): a single center retrospective study

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Conflict of interest: None

[Objectives] To study the clinical manifestation of CMV infection in patients with CD. [Methods] We retrospectively reviewed the patients who had CMV infection among 450 CD patients who admitted in our department from 2005 to 2012. CMV infection was defined as positive results of CMV pp65 antigenemia assay. [Results] CMV infection was identified in 39 patients (M 8, F 31; 52±14 years old). Primary diseases were SLE (n=20), ANCA-associated vasculitis (n=7), myositis (n=5), AOSD (n=3), MCTD (n=2), and RA (n=1). The mean WBC and lymphocyte counts were 8192±5505/μl and 596±486/μl, respectively. The mean maximum level of CMV antigenemia was 113±364 cells. All patients had received steroids (44±16 mg/day of PSL). Immunosuppressants were used in 54% patients. Serious organ damages were observed in some patients; bowel perforation due to CMV colitis (n=2), CMV-associated gastric ulcer (n=1), and CMV pneumonia combined with pneumocystis pneumonia (PCP) (n=1). The death due to CMV infection was observed in 1 patient with CMV+PCP pneumonia. [Conclusion] Although the death due to CMV infection was rare, serious complications, such as development of CMV pneumonia and bowel perforation caused by CMV colitis, should be taken into consideration in the treatment of CD.

W77-2

Influence of immunosuppressive therapy on cytomegalovirus infection in patients with systemic autoimmune disease

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Conflict of interest: None

[Objectives] Cytomegalovirus (CMV) infection is commonly associated with immunosuppressive therapy, however, the incidence has not been well documented, and standardization of management has not been established. The purpose of this study is to identify the incidence of CMV infection in the daily practice of autoimmune diseases. [Methods] Among autoimmune patients who have hospitalized in Tokyo Women's Medical University Hospital from April 2011 to March 2011, incidence of cytomegalovirus infection defined by C7-HRP was retrospectively investigated according to the therapy of massive corticosteroid (≧40mg/day), corticosteroid pulse or intravenous cyclophosphamide pulse therapy. [Results] Among 157 patients who received above mentioned therapy, C7-HRP was measured in 135 patients after the immunosuppressive therapy. C7-HRP was positive in 17/46 (36.9%) with massive corticosteroid, 7/20 (35.0%) with corticosteroid pulse, and 27/69 (39.1%) cases with intravenous cyclophosphamide pulse therapy, and ganciclovir was infused in 8 (47.1%), 3 (42.9%) and 8 (29.6%) cases, respectively. [Conclusion] CMV infection was identified among 37.8% of patients with autoimmune diseases who

received immunosuppressive therapy. Careful monitoring and appropriate management is necessary in these patients.

W77-3

Clinical analysis of patients with connective tissue diseases who developed Pneumocystis pneumonia

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Conflict of interest: None

[Objectives] To clarify the clinical features of Pneumocystis pneumonia (PCP) in patients (Pts) with connective tissue diseases (CTD). [Methods] We compared 1) background, 2) treatments for CTD, 3) clinical findings, 4) treatments for pneumonia, 5) prognosis between 15 Pts with PCP and 36 Pts with bacterial pneumonia (BP) who were admitted to our hospital from Apr 2009 to Oct 2012, retrospectively. [Results] 1) Mean age was 68±10 y in PCP, 66±14 y in BP (NS). 10 PCP Pts and 15 BP Pts had lung complications (NS). 2) The dose of prednisolone (PSL) was 21±17 mg/d in PCP, 12±11 mg/d in BP ($P<0.05$). 8 PCP Pts and 10 BP Pts were treated with immunosuppressants and/or biologics (NS). 3) At onset of PCP, βD glucan 230±359 pg/ml, LDH 394±115 U/ml, they were significantly higher than BP ($P<0.05$). In PCP, PCR for P. jirovecii was positive in 14 Pts, Grocott's stain was positive in 2 Pts. All PCP Pts had progressive hypoxemia and GGO in CT. 4) All PCP Pts were treated with TMP/SMX, because of side effects, it was changed to pentamidine in 2 Pts. PSL was increased in 11 Pts, 9 of them took pulse therapy. All BP Pts took antibiotics, 2 Pts took pulse therapy. 5) 4 Pts died in both PCP and BP (NS). [Conclusion] This study showed that aged CTD Pts treated with higher dose of PSL had a high risk for PCP.

W77-4

Clinical investigation of Pneumocystis jiroveci DNA concentration in respiratory truct specimens and serum βD-glucan value in patients with PCP complicating collagen vascular disease – not detectable pneumocystis jiroveci DNA by conventional PCR method in some patients with PCP complicating collagen vascular disease –

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Conflict of interest: None

[Objectives] To clarify the clinical significance of Pneumocystis jiroveci DNA concentration (Pj-DNA conc) in respiratory truct specimens and serum βD-glucan value (βD) in patients with PCP complicating collagen vascular disease (CVD-PCP). [Methods] BAL or sputum from 9 CVD-PCP were used for DNA extraction. Pj-DNA was investigated by conventional-, nested- and real time-PCR method. Pj-DNA conc and βD were evaluated with several clinical parameters. [Results] Pj-DNA conc and βD were not significant correlation to A-aDO2 values. Pj-DNA could be not detected in 2 patients by conventional PCR, while they were detectable by nested PCR and one of them had below the threshold limit by real time PCR. For mild three cases whose blood gas showed above pO_2 70 mmHg at room air, βD (pg/ml) increased slightly such as 56.5, 38.1, 31.8 respectively however Pj-DNA conc (pg/ml) were 0.87, 61.0, below the threshold limit in far different values. βD was not interrelated to Pj-DNA conc, while it was significant correlation to serum IgG value ($r = 0.71$, $P < 0.05$). [Conclusion] Nested PCR is useful for the diagnosis of CVD-PCP. βD was excellent marker for CVD patients treated with immunosuppressive therapy because it might inform us early stage of CVD-PCP. βD may be affected by an immunity of host.

W77-5

A case of reactive arthritis due to active tuberculosis (TB) infection(Poncet's disease) with high titer of rheumatoid factor(RF) and anticitrullinated protein antibodies (ACPA)

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Conflict of interest: None

A 69-year-old man with childhood history of chronic left knee arthritis experienced difficulty in walking owing to right knee pain since 2009. He also had left gonitis; however, it spontaneously improved with pus drainage. He visited our hospital with suspected rheumatoid arthritis (RA) because of elevated C-reactive protein and high titers of rheumatoid factor and anti-CCP antibody (ACPA). His right knee was swollen; his left leg was atrophic and showed bony ankylosis without inflammation. The QuantiFERON-Tb Gold test was positive, and computed tomography scan showed a calcified pulmonary nodule, suggestive of right knee joint tuberculosis (TB) infection; however, his synovial fluid culture was negative and synovial biopsy revealed only neutrophil infiltration and blood vessel proliferation. A small sample of his left-knee fluid was cultured, which tested positive for TB; hence, we diagnosed him with right knee reactive arthritis accompanied with left knee gonitis tuberculosa. His symptoms improved after anti-TB therapy commencement. In addition to being a useful marker for RA diagnosis, ACPA is thought to be associated with its etiology. However, ACPA is occasionally positive in TB patients, and hence, differential diagnosis is important in ACPA-positive arthritic patients.

W77-6

Clinical features of rheumatoid arthritis patients positive for *Aspergillus* serological tests

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Conflict of interest: None

[Objectives] To clarify the clinical features of *Aspergillus* (Asp) infection in rheumatoid arthritis (RA) patients. **[Methods]** We investigated Asp antigen and antibody in the serum and chest CT in 144 RA patients (Female; 93, Male; 51). **[Results]** 32 RA patients (22%) were seropositive (Female; 21, Male; 11). The mean age was higher and average duration of RA was longer in seropositive patients than in seronegative patients (70.5 vs. 65.0 years old, 10.2 vs. 6.1 years, respectively). There was no significant difference in gender. Regardng RA treatments, the mean dosage of prednisolone was not different between seropositive and seronegative patients (4.8mg vs. 4.3mg a day, respectively). 57 RA patients (40%) were complicated with interstitial pneumonia (IP), and the IP complication was not associated with serological test results. As for CT imaging, the presence of any pulmonary diseases or bronchiectasis did not make any significant difference in serological results. **[Conclusion]** Elderly RA patients and patients with long duration of RA may be susceptible to Asp infection. Our results suggest that Asp serological tests should be performed frequently in these patients.

W78-1

Plasma levels of fibrin/fibrinogen degradation products are a useful indicator of disease activity and nephritis complications in antineutrophil cytoplasmic antibody-associated vasculitis

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Conflict of interest: None

[Objectives] To study whether plasma FDP levels could be an indicator of disease status in AAV. [Methods] Patients with AAV who were admitted and had their plasma FDP levels checked in the active state were retrospectively included. Plasma FDP levels were compared between the active and inactive states. Among patients in the active state, FDP levels were evaluated for differences in each disease and organ damage. Laboratory markers and BVAS were examined to determine their correlations with FDP levels in the active state. [Results] Four EGPA, 32 MPA and 6 GPA patients were included. Plasma FDP levels were high in the active state and decreased significantly after therapy ($p<0.001$). Among patients in the active state, plasma FDP levels were significantly higher in patients with MPA than in patients with GPA ($p<0.05$). Plasma FDP levels were significantly higher in patients with nephritis than in patients without nephritis ($p<0.001$). Plasma FDP levels significantly correlated with Neutrophil counts, serum CRP levels, BVAS, serum Cr levels, and eGFR ($p<0.05$). Plasma FDP levels were significantly higher in the patients with proteinuria and hematuria ($p<0.05$). [Conclusion] Plasma FDP levels are a useful indicator of disease activity and nephritis complications in patients with AAV.

W78-2

Associations between complement and ANCA-associated vasculitis

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Conflict of interest: None

[Objectives] The etiology of ANCA-associated vasculitis (AAV) has not been fully elucidated yet. Recently some studies suggested that complement activation via the alternative pathway has an important role in the development of AAV. Nevertheless, it is not well known about the relationship between the serum complement level and clinical features of AAV. The objective of this study is to investigate the relationship between the initial serum complement level and the clinical features. [Methods] We retrospectively analyzed medical records for the newly diagnosed from 2007 to 2010 in Okayama university hospital. [Results] A total of 33 patients were divided into two groups by the serum complement level. 6 women (46%) was included in the high CH50 group (n=13) and 3 (15%) in the normal group (n=20). Though there were no differences in age and BVAS, serum levels of CRP was lower and relapse rates were higher in the high CH50 group than the normal group. Although the glomerular depositions of complement and immunoglobulin tended to be more frequent in the high CH50 group (n=7) than the normal group (n=8), the proportion of damaged glomeruli didn't differ among two groups. [Conclusion] The elevation of initial complement level may be one of the indicators of activity in AAV patients.

W78-3

A case of granulomatosis with polyangitis, in which PR3-ANCA measurement by capture ELISA was useful for disease activity evaluation

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Conflict of interest: None

A 23-year-old man was admitted to our hospital with purpura on his lower legs and acute kidney dysfunction in March 2010. He was diagnosed as Granulomatosis with polyangitis, based on the presence of a high titer of proteinase-3 antineutrophil cytoplasmic antibody (PR3-ANCA), leukocytoclastic vasculitis, crescentic glomerulonephritis, and pulmonary nodules. He was treated with steroid therapy (mPSL pulse + PSL 60 mg/day) and IVCY therapy (750 mg/ m^2/ 4 weeks). His clinical symptoms became improved once, but the disease activities relapsed with growing lung nodules in January and July 2011. By using intravenous infusion of low-dose rituximab, the disease activity was controlled. When his disease recurred, a titer of PR3-ANCA obtained by direct ELISA was low grade, which showed a discrepancy between clinical disease activity and PR3-ANCA serum level. Whereas, PR3-ANCA level measured by capture ELISA was consistent with it. It is known that a titer of PR3-ANCA and disease activity does not always correspond. This case report suggests that capture ELISA is a more valuable PR3-ANCA detection tool than direct ELISA for evaluating the clinical disease activity of ANCA-related angitis.

W78-4

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 guidelines for the rapidly progressive glomerulonephritis (RPGN) were published in 2002, in Japan, the RPGN with anti-GBM antibodies remains poor prognosis.【Methods】We investigated clinicopathological characteristics of four patients who diagnosed as RPGN with anti-GBM antibodies at Kanazawa University Hospital and an affiliated hospital after 2002.【Results】Two patients were female and two were men. Mean age; 56±17 years old, follow-up duration; 1651±1319 days, urine protein; 1.4±0.8 g/g·Cr, serum Cr; 3.0±2.0 mg/dL, CRP; 14.9±8.5 mg/dL, the titer of anti-GBM antibodies 168.8±152.8 EU. Three out of four cases were under dialysis. Predonisolone (Starting dose was 30 – 60 mg/day) was used in all cases, and the titer of anti-GBM antibodies decreased to 29.0±30.0 EU by the end of one to nine times of plasma exchange, and two to three cycles of methylprednisolone pulse therapy. One case with 22% crescent formation released from hemodialysis. One case with 90% cellular crescent formation did not need hemodialysis.【Conclusion】Renal biopsy would give us clinical information in possibilities of recovery of renal function.

W78-5

Clinical characteristics and predictors for serious infection during the first six months of remission induction treatment: a report from Remission Induction Therapy in Japanese Patients with ANCA-associated Vasculitis (RemIT-JAV)

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Conflict of interest: None

[Objectives] The purpose of this study was to identify clinical characteristics and predictors of serious infections (SIs) in ANCA-associated vasculitis (AAV) patients in the RemIT-JAV. [Methods] We analyzed SIs which developed during the first six months of remission induction therapy in 156 patients who were enrolled in the RemIT-JAV from April 2009 to December 2010. We used the COX proportional hazard model to identify predictors for SIs. [Results] Sixty-three SIs developed in 42 patients during the first six months. The median length of time to the onset of SIs was 57 days. Baseline characteristics of patients who developed SIs were as follows: median age, 73 years; male, 48%; pulmonary comorbidities, 48%; severe type of clinical subgroups, 26%; median initial dosages of prednisolone (PSL), 0.9 mg/kg/day; use of cyclophosphamide, 48%. Based on the results of the multivariable analysis, male (HR 2.1, p=0.024), severe type (HR 2.2, p=0.025), and initial PSL dosages ≥0.8mg/kg/day (HR 2.7, p=0.002) were identified as predictors for SIs. [Conclusion] From a point of view of benefit-risk balance, further investigation is required about initial corticosteroid dosages and necessity for immunosuppressants in the remission induction therapy, especially for male patients with severe type.

W78-6

Incidence Rate and Risk Factors of Venous Thromboembolism among Churg-Strauss Syndrome Patients

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Conflict of interest: None

[Objectives] We evaluated the incidence rate and risk factors of Venous thromboembolism (VTE) associated with Churg-Strauss syndrome (EGPA). [Methods] A total of 24 EGPA patients were enrolled in this study; 11 males and 13 females. In the retrospective components, we compared the incidence rate of VTE between EGPA patients and general population. We also assessed the risk factors of VTE at the time of EGPA diagnosis. [Results] The patients' ages were 62.3±11.6 years old. Among the 24 EGPA patients, 4 had VTE while 20 did not. The incidence rate of VTE among EGPA patients was significantly higher than among the general population; 1.61% per person-year (95% Confidence Interval 0.44-4.10%) versus 0.012% per person-year (0.00-0.21%), respectively. Females had a tendency to be afflicted with VTE (p=0.0673). In the VTE group, they had a tendency of lower eosinophil counts (9064.8±2786.4/μl)(p=0.10) and higher antinuclear antibody titer at the time of EGPA diagnosis (320 times for 2 patients, 160 and 40 times for the remaining patients)(p=0.075). [Conclusion] The incidence rate of VTE in EGPA patients is significantly higher than in the general population. Female sex, lower eosinophil counts, and higher antinuclear antibody titer at the time of EGPA diagnosis can be risk factors of VTE.

W79-1

Three new amino acid polymorphisms associated with the susceptibility of Takayasu arteritis

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Conflict of interest: None

[Objectives] Takayasu arteritis (TA) is one of refractory vasculitis syndromes. It is very interesting that some HLA types correlate with TA-susceptibility, when we consider the autoimmune mechanisms in TA's pathophysiology. We searched HLA-B protein's amino acid polymorphisms associated with TA-susceptibility. [Methods] We collected samples from 100 TA patients and 1,000 healthy controls and analyzed their HLA-B types. [Results] We replicated a TA-susceptibility of B52*01. Next, we replicated B67*01's association with TA-susceptibility that was reported previously, and confirmed the susceptibility of B67*01 is independent from that of B52*01 by the combined analysis with the previous study. When we examined HLA-B's amino acid variations that are correlated with TA-susceptibility by a step-up multiple logistic regression analysis, we found three amino acid polymorphisms associated with TA (171His, 67Phe and 325Ser). A 3-dimensional structure analysis revealed that 171His and 67Phe sit on the important positions in the groove of HLA protein. [Conclusion] We replicated B67*01's susceptibility with TA, and found that 3 amino acid variants are correlated with TA-susceptibility. These findings suggest that TA occurs on the backgrounds of immunological disorders.

W79-2

Role of midkine in pathogenesis of vasculitis syndrome

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Conflict of interest: None

[Objective] To evaluate the role of midkine (MK) in patients with vasculitis syndrome, we measured serum level of MK in these patient. [Method] Our study included 31 patients with ANCA-associated vasculitis: AAV (n=22, age 70.5±11.6 years old, 13 females) and other vasculitis disease (n=9, age 70.5±11.6 years old, 7 females). Midkine levels in sera of the patients were measured by ELISA. [Result] Mean (±SD) vasculitis activity score (BVAS) in AAV patients was 16.5±9.1 and mean vasculitis damage index (VDI) was 1.8±1.3. Serum levels of MK (2014±1839 pg/ml) in all the patients with vasculitis were significantly higher than that of healthy control. Mean serum MK level (2528±3221 pg/ml) in AAV patients was significantly higher than that (1433±433 pg/ml) of other vasculitis syndrome. BVAS, VDI, CRP ans ESR showed no significant correlations with serum MK level, respectively. [Conclusion] These data suggested that serum level of MK might be an important marker of AAV.

W79-3

Abundant neutrophil extracellular traps (NETs) in thrombus of patient with microscopic polyangiitis (MPA)

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Conflict of interest: None

[Objectives] Patients with MPA have an increased risk of deep vein thrombosis (DVT); however, the mechanism remains elusive. Recently, NETs is reported to be related with the pathogenesis of MPA. On the other hand, NETs can induce thrombosis. In this study, the association of NETs and DVT in the patient with MPA was examined. [Methods] NETs in the thrombus of the patient with MPA was examined by immunofluorescent staining. The quantity of NETs was compared to thrombi from patients with sepsis and pulmonary embolism using immunohistochemistry for citrullinated histone, which is essential for NETs formation. [Results] MPO/DNA containing-NETs was identified in the thrombus of the patient with MPA. When compared to other thrombi unrelated to MPA, the amount of NETs was significantly greater in the MPA patient. [Conclusion] It is reported that MPO-ANCA can induce NETs, and that NETs can induce thrombosis. This study suggests the possibility that the pathogenesis of thrombosis in MPA could be critically associated with MPO-ANCA and NETs.

W79-4

Clinical and biochemical analysis for PMR patients diagnosed in this hospital

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Conflict of interest: None

[Objectives] We are expecting the increased incidence of PMR under the progress of the aging society. In this regards, to gain the insight for better management, we've analyzed all PMR cases diagnosed during the last 5 years in our hospital. [Methods] 47 PMR cases were analyzed for (1) Clinical features (2) Laboratory data such as CRP, ESR, MMP-3 and sIL-2R (3) Outcome following the initial treatment with PSL (4) Further analysis for the cases showing PSL resistance or subsequent complications. [Results] Mean age of the patients was 75.9 y.o (range; 55-94) with 72% female. Average CRP was 8.3 mg/dL(0-28.2) and ESR of 81 mm/h (range; 6-140). Characteristically most patients showed the increased level of MMP-3 (male; 249.2 ng/mL, female; 197.7) as well as sIL-2R (1002 U/mL; 221-2770). Initial dose of PSL was 17 mg/day on average (range; 5-50). While 36 cases were successfully treated with initial dose of PSL, 6 patients exhibited resistance to PSL, and 6 subsequently developed RA. In addition, 3 and 2 patients subsequently developed vasculitis and malignancies respectively. [Conclusion] It would be advised to carefully monitor the development of PSL resistance particularly for the patients with elevated CRP, together with the onset of other rheumatoid disorders as well as the malignancies.

W79-5

Fibromuscular dysplasia with annular ulcer and multiple aneurysms masquerading as polyarthritis nodosa

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Conflict of interest: None

【Case】A 23-year-old female was referred to our hospital because of annular ulcer of small intestine and hypertension. In July 2012, she suddenly suffered from bleeding due to the rupture of a hepatic artery aneurysm. The ruptured lesion was embolized endovascularly by coiling. Angiography findings revealed that she had multiple aneurysms of visceral arteries and a coronary artery. Although the clinical findings raised concern for polyarthritis nodosa, it was hard to make definite diagnosis at that time. Partial resection of small intestine was performed for the purpose of treatment for the stenosis and to take pathological findings, which revealed intimal fibroplasia and hyperplasia of muscular tissue without vasculitis. So, she was diagnosed with fibromuscular dysplasia (FMD) and treated with antihypertensive agents intensively.【Discussion】The diagnosis of systemic vasculitis is sometimes difficult without the organ involvements which are approachable with less invasive biopsy. The characteristic angiographic findings of FMD are indistinguishable from those of vasculitis, and the correct diagnosis can be made only after histopathologic evaluation of the arterial lesions. Therefore, we should not hesitate to perform an aggressive biopsy in such a case.

W79-6

3 patients with systemic sclerosis(SSc) who developed ANCA-associated vasculitis(AAV)

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Conflict of interest: None

We describe 3 patients with systemic sclerosis (SSc), who developed ANCA-associated vasculitis (AAV). Case 1. A 57-year-old woman had a 20-year history of SSc and a 3-year history of rheumatoid arthritis. In 2007, she was admitted to the hospital with alveolar hemorrhage and acute kidney injury. MPO-ANCA was positive. She was treated with methylprednisolone pulse therapy, intravenous cyclophosphamide and plasma exchange that resulted in resolution of her disease. Case 2. A 59-year-old woman with a 10-year history of SSc was diagnosed with AAV because of fever, multiple mononeuritis, and positive MPO-ANCA. She was treated with prednisone 28.5 mg daily that induced remission of her disease. Case3. A 43-year-man showed interstitial pneumonia, refractory arrhythmia and myocardial fibrosis in 2005 and has been followed-up thereafter. He showed the fever and renal damage in 2012 and was diagnosed with AAV because of positive MPO-ANCA and the biopsy-proved crescentic glomerulonephritis. He was also diagnosed with systemic sclerosis sine scleroderma with lung, heart, and esophageal involvement. His AAV remitted by the treatment of 60mg prednisone.

W80-1

Effects of teriparatide (Forteo®) in osteoporosis of patients with rheumatoid arthritis for one year ~ Should activated vitamine D3 be combined with teriparatide?~

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Conflict of interest: None

[Objectives] To evaluate the effects of teriparatide (TPTD) in

osteoporosis of RA patients for one year and to compare effects and rate of hypercalcemia between activated vitamine D3 combined group (VD-G) and non-combined group (N-G). [Methods] 28 cases were used for analysis of effectiveness of TPTD and 40 cased were used for analysis of hypercalcemia. [Results] Lumbar spine (LS)-BMD was incresed with time (0.824 at baseline, 0.868 at 6m, 0.899 at 12m). Proximal femur (PF)-BMD was also incresed with time (0.564 at baseline, 0.569 at 6m, 0.586 at 12m). P1NP were incresed mostly among four bone turnover markers (BAP, P1NP, NTX, TRACP). Mean age in VD-G(68.9) were significantly younger than that in N-G(74.2). Although there was no significant difference in increase rate of LS-BMD between VD-G and NG, the increse rate in PF-BMD in VD-G at 6m(2.7%) and 12m(5.0%) were significantly better than that in N-G(-1.4% at 6m, 0.4% at 12m). Hypercalcemia occurred in 25.0% of V-G and 16.7% of N-G (not significant). [Conclusion] TPTP were effective in osteoporosis of RA patients, especially in LS-BMD. P1NP were most sensitive marker among four bone turnover markers. Combination of TPTD and VD increased PF-BMD compared with N-G. These results suggest that some patients need the combination TPTD and VD.

W80-2

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] Both biological agents (Bio) and teriparatide (TPTD) strongly influenced bone metabolism. We investigated the influence of the combination Bio and TPTD on osteoporosis and change of bone turnover markers in RA patients. [Methods] 13 cases (BioG) treated with both Bio and TPTD and 25 cases (non-BioG) treated with only TPTD were included in this study. Patients characteristics and the change of both bone mineral density (BMD) of lumbar spine (LS) and bone turnover markers (BAP, P1NP, NTX, TRACP-5b) from baseline to 6 months were compared between two groups. [Results] All were female. Mean age was 70yo in BioG and 71yo in non-BioG. RA duration was 17y in BioG and 20y in non-BioG. The rate of concomitant prednisolone was 69% in BioG and 60% in non-BioG. Although LS-BMD in non-BioG were increased significantly (0.831g/cm2 at baseline, 0.894g/cm2 at 6m), LS-BMD in Bio-G were not increased significantly (0.872g/cm2 at baseline, 0.900g/cm2 at 6m). The change of bone turnover markers in BioG was more compared with that in non-BioG. [Conclusion] Although bone turnover markers in BioG increased more than that in non-BioG, BMD in non-BioG increased more than that in BioG.

W80-3

Comparison of the effect of 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 Teriparatide (TPTD) on RA osteoporosis patients (RA) by comparing with that of postmenopausal osteoporosis patients (Porosis). [Methods] 50 female RA (mean age 67.7 years old, DAS28-CRP 2.9, 74% taking prednisolone (PSL) with average dose 4.6mg, 18% taking biologics, lumbar T-score -2.6, femoral neck T-score -2.7, previous vertebral fracture 2.4) and 51 Porosis (mean age 72.6 years old, lumbar T-score -3.1, femoral neck T-score -2.4, previous vertebral fracture 2.7) were enrolled. Daily subcutaneous injection of 20μg TPTD was administered for 12 months. Lumbar spine and total hip BMD measured by DXA. [Results] BMD change from baseline→6 months→12 months was as follows. Lumbar spine(RA:0.46→9.03→11.68%/Porosis:-0.35→8.79→12.80%) Femoral neck(RA:-3.45→-2.58→4.88%/Porosis:-1.82→-3.95→0.28%). There were no significant difference of lumbar spine BMD change between two groups, but femoral neck BMD of RA group increased significantly compared to that of porosis group(P<0.05). Incidence of new fracture was 2% in RA and 3.9% in Porosis (P=0.57). [Conclusion] Our findings indicate that 12 months administration of daily TPTD increases BMD and prevent fracture equal or more in RA compared to Porosis.

W80-4

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 19 CD patients (male 2, female 17) receiving steroid therapy and were prescribed TP from March 2011 to October 2011. [Results] Mean age was 68.4 years old. RA 16 (overlap of scleroderma 3), scleroderma 1, Sjogren 1, adult Still's disease 1. Seventeen patients had a history of fragile fracture. Clinical features at starting TP; the mean period of steroid therapy 137 months, the mean steroid (prednisolone) dose 4.5 mg/day, the mean YAM value of lumbar BMD 68.3% (n=16). Previous therapy for osteoporosis; bisphosphonate 14 (with vitamine D, 6), vitamine D alone 8, SERM 1. New vertebral fracture developed in 2 cases, but non-vertebral fractures were not seen. Mean YAM value of lumbar BMD significantly elevated to 72.7% (n=7) after one year. Two cases stopped TP due to adverse reactions (myalgia). [Conclusion] In elderly patients with CDs receiving steroids, lumbar BMD significantly elevated by treatment with TP.

W80-5

Retrospective cohort study of osteonecrosis of the jaw(ONJ) and bisphosphonate-related osteonecrosis of the jaw(BRONJ)in patients with rheumatoid arthritis - Extracted from NinJa database-

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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] 1890 RA patients(311 male 1579 female, median age 63.7y, mean RA duration18.0y) of our hospital 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] 9 cases of ONJ were identified (all female,median age 76.7y, mean RA duration14.2y) and the frequencies of ONJ were 7.48/100000 person-years(p-y) after birth and,28.7/100000 p-y from the onset of RA. 8 among 9 ONJ candidates were BRONJ candidates (all female, median age 78.0y, mean RA duration 15.0y.) Recent prescriptions of BP were 7 candidates with Alendronate and 1 candidate with Risedronate. Mean duration of BP medication was 65.1months. The frequencies of BRONJ were 72.8/100000 p-y from the onset of RA and 208/100000 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.

W80-6

The evaluation of efficacy and safety of combination therapy with alendronate and eldecalcitol on glucocorticoid-induced osteoporosis compared to alendronate and alfacalcidol combination therapy: a retrospective study

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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] Twenty five patients on oral glucocorticoid therapy (≧1mg/ day of prednisolone) with autoimmune disease such as SLE and rheumatoid arthritis were treated with ALF(1.0μg/day) and ALN(35mg/week) were enrolled. The responses of subjects switching from ALF to ELD (n=8: group EA) were compared to those of subjects who continued ALF (n=17: group AA). After 24-week treatment, we retrospectively evaluated the bone mineral density (BMD) change in lumbar spine for efficacy, and serum calcium (Ca) for 24 weeks. [Results] In group EA, lumbar spine BMD increased significantly from baseline (p=0.008), while group AA showed a decrease. The difference in BMD change between the two groups was significant (2.6% vs. -1.3%: p<0.01). The titers of bone specific alkaline phosphatase in neither group markedly changed from baseline. There were no significance in the change of adjusted serum Ca and urine Ca/creatinine between two groups. [Conclusion] The switching treatment from ALF to ELD is effective and well tolerated in patients who were treated with ALN for GIOP.

W81-1

Risk factors associated with the occurrence of distal radius fracture in Japanese patients with rheumatoid arthritis: a prospective observational cohort study

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Conflict of interest: None

[Objectives] To evaluate the association between potential risk factors and the occurrence of distal radius fractures in Japanese RA patients. [Methods] A total of 11,907 patients (82% female; mean age, 56 years) with RA were enrolled in a prospective observational study from 2000 to 2012. Self-reported distal radius fractures were verified using patient medical records. [Results] A total of 140 distal radius fractures were reported. Among these patients, 85 distal radius fractures (right: 35 fractures, left 43 fractures, bilateral one fracture, unknown 6 fractures) were verified with medical records. Cox proportional hazards models are now used to analyze independent contributions of various risk factors to distal radius fracture occurrence. [Conclusion] Risk factors associated with the occurrence of distal radius fracture in Japanese patients with rheumatoid arthritis may be apparent from this study.

W81-2

Juxtaarticular osteoporosis exists in the wrist joint from the early stage of rheumatoid arthritis

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Conflict of interest: Yes

[Objectives] To investigate from when juxtaarticular osteoporosis exists in the wrist joint in patients with rheumatoid arthritis. [Methods] In 177 patients, 24 were male, and 153 were female. The averages of age and the duration of the disease were 62.2 and 16.3 years. The DAS28 was 3.18 in average, and the HAQ value was 0.89 in average. Dual-energy X-ray absorptiometry was performed in the patients at the left sides of the distal radius and the proximal femur and was evaluated by the young adult mean (YAM) value. Only the data of female patients was analyzed. [Results] The total value of the distal radius was 71.5±18.3 in average, relatively lower than that of the proximal femur (79.8±13.6). The average values of UD (71.1±19.5) and MID (70.0±19.8) of the distal radius were relatively lower than that of 1/3 (77.6±21.3). The value of MID and 1/3 were negatively correlated with the duration of the disease, respectively (p<0.01), while that of UD was not. Significant difference was not observed between the values of UD of the early stage (less than 3 years after the onset of the disease) and the late stage (more than 15 years) of the patients. [Conclusion] Juxtaarticular osteoporosis in the wrist joint exists from the early stage of the disease.

W81-3

Investigation of effects on bone metabolism of anti-TNF-α biologics 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 among patients with rheumatoid

arthritis (RA). [Methods] We selected patients with RA who have Alendronates (AL group) 26 cases and those who receive AL and anti-TNF-α Biologics 19 cases (AL+anti-TNF-α group). We investigated NTX and TRACP5b as bone resorption markers, BAP, osteocalcin as bone formation markers and COMP as cartilage metabolic markers. We examined the incidence of spinal compression fracture and bone mineral density with X-ray and inflammatory situation with DAS28-ESR and DAS28-CRP. [Results] COMP is significantly higher in AL groups (952.8±291ng/ml) than AL+anti-TNF-α group (760.2±235.6) ($P<0.05$). Bone mineral density (%YAM) of the femoral neck in AL+anti-TNF-α group (75.7±12.7%) is significantly higher than that of AL groups (68.5±8.5%) ($P<0.05$). CRP of AL group (0.7±0.9 mg/dl) is significantly higher than that of AL+anti-TNF-α group (0.5±1.0) ($P<0.05$) and there are no difference among other parameters. There was significantly positive correlation between NTX and TRACP (rho= 0.44, $P<0.01$). [Conclusion] Our data indicated that anti-TNF-α Biologics treatment for patients with RA has a potential for suppression of cartilage destruction and maintenance of bone mineral density.

W81-4

Prevalence of and factors associated with vitamin D deficiency in 4,793 Japanese patients with rheumatoid arthritis

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Conflict of interest: Yes

[Objectives] To determine the prevalence of vitamin D deficiency and associations with clinical characteristics in Japanese patients with rheumatoid arthritis (RA). [Methods] Serum 25(OH) D levels and data were obtained from 4,793 patients with RA who participated in the IORRA observational cohort study in April and May of 2011. We defined vitamin D deficiency as < 20 ng/mL and severe deficiency as < 10 ng/mL. [Results] Among all patients, the mean (SD) serum 25(OH) D level was 16.9 (6.1) ng/mL and the prevalence of vitamin D deficiency and severe deficiency were 72% and 12%, respectively. In multivariate analysis, female gender, younger age, high J-HAQ disability score, and low serum total cholesterol and high serum alkaline phosphate (ALP) levels were significantly associated with both vitamin D deficiency and severe deficiency ($P < 0.01$). Low serum total protein levels and NSAID use were significantly correlated with vitamin D deficiency ($P < 0.01$). [Conclusion] 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 cholesterol and total protein, high serum ALP levels, and NSAID use appear to be associated with vitamin D deficiency in Japanese patients with RA.

W81-5

Patients with rheumatoid arthritis have multiple falls compared to healthy individuals – The TOMORROW Study-

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Conflict of interest: None

Background: Patients with rheumatoid arthritis (RA) who have muscle weakness and stiff or painful joints might be at increased risk of falling. The present study prospectively determines the incidence of falls 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 for a period of two years in 202 patients with RA (58 years) and 202 age- and sex-matched healthy volunteers (controls, 57 years). **Results:** There is no difference in incidence of falls between RA patients (30%) and controls (27%) during two years. RA patients had significantly more frequent number of falls (2.4 times) than that of controls (1.6 times) ($p=0.03$). After adjusting for risk factors of falls, multiple regression analysis identified that walking times (>30 m/day) were associated with incidence of falls in RA (odds 3.12, 95%CI: 1.23-7.75 $p=0.014$). In RA patients, use of prednisolone (PLS) appeared to be related to number of falls after adjusting for risk factors. (PLS: $\beta=0.188$, $P=0.010$). **Conclusions**: In conclusion, multiple fallers in RA patients were higher than in controls during two years. In RA patients, walking times and PLS appeared to be related to falls.

W81-6

Factors influencing flexion angle before and after PS-TKA

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Conflict of interest: Yes

[Objectives] Factors influencing flexion angle before and after PS-TKA were assessed. [Methods] This study consisted of 71 males and 297 females and the mean age was 74.1 years old. In 368 PS-TKA cases with Stryker NRG system were analyzed. Multi-variance analysis was performed and factors influencing flexion angles were assessed. [Results] Factors that influenced the flexion angle before TKA were BMI (standard regression coefficient, -0.166), standing FTA (-0.140), external rotation angle of the femoral component relative to the posterior condylar line (0.220) and resurfacing the patella (-0.225). Factors that influenced the flexion angle after TKA were flexion angle before TKA (0.491), medial soft tissue releases (-0.116) and patellar lateral release (-0.130). In cases with heavy weight, severe deformity and patella damage, flexion angle before TKA was bad. In cases in that medial soft tissues release and/or patella lateral release were necessary, flexion angle after TKA was not good. [Conclusion] In cases with contractures and deformities, flexion angle before TKA was bad and it is hard to obtain deep flexion angle after TKA.

W82-1

HAQ analysis using NinJa 2011 data base

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Conflict of interest: None

[Objectives] To clarify the characteristics of MHAQ and its items from the point of view of disease duration and disease activity of RA [Methods] Analysis was performed using NinJa 2011 data base. [Results] (1) MHAQ was getting worse in correlation with disease duration and activity of RA. (2) at the early stage of RA, the score of some typical items (#1 Dressing #2 Rising #7Grip) would be worsened, while disability had progressed generally in the late stage(>10y). (3) to keep HAQ remission status, the items #3 (Eating) #6(Reach) seemed to be key activities. (4) MHAQ has a close relation with patient' global assessment. [Discussion & Conclusion] MHAQ might be consist of activity HAQ(ACT-HAQ) and damage related HAQ(DAM-HAQ). The former seemed to be

related with disease activity and the latter with disease duration. Taking into consideration patient's concern about their disabilities, we should be asserted the importance of patients' activity level as well as disease activity control.

W82-2

Cost-effectiveness analysis of DMARDs and biolosics therapy (annual report from NinJa 2011) -The beginning of improvement is confirmed-

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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 2002-2011 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 2011. That was increasing year by year. ([The rate of the number of low activity patients to that of high activity patients] / cost) decreased in 2004-2006 and was almost constant in 2006-2009. But not until 2010 did it increase over the level in 2004. (Decrease of mHAQ from previous year)/(increase of cost from previous year) tends to increase. [Conclusion] The improvement of cost-effectiveness in recent anti-rheumatic treatment has begun in 2010 and was continuing in 2011.

W82-3

Anual change of the costs of anti-rheumatic drugs in NinJa -analysis among ages, disease durations, hospitals and biologics -

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Conflict of interest: None

[Objectives] To evaluate annual change of the cost of anti-rheumatic drugs. [Method] The Data from RA patients registered in the large multi-center cohort database (NinJa) in 2002-2011 was analyzed. They included age, disease duration, anti-rheumatic drugs (biologics and others) and those dosage. The annual costs of drugs were calculated from dosage and dose interval. [Results] The annual cost was about 430,000 yen / patient in 2011. That was increasing year by year. The younger the patients were, the higher their costs were.The costs were almost same among patients with each disease duration and increasing constantly, but only the costs of the patients with disease duration of less than 2 years stopped to increase since 2008. Those have become about a half of the costs of patients with more than 2 years disease duration. The average cost of ETN and ADA decreased year by year. That of IFX increased rapidly in 2009. That of GLM was the highest and twice of that of ETN. [Conclusion] It is adequate that more cost was invested in younger patients. But it does not match to T2T and Bio-free Era that less cost was invested in early RA patients. Also it is inadequate that average costs were greatly different among biologics, and standard prices of biologics may need to be validated.

W82-4

Discrepancies Between Patients and Physicians in Their Perceptions of Rheumatoid Arthritis Disease Activity

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Conflict of interest: None

[Objectives] Patients and physicians often differ in their perception of rheumatoid arthritis (RA) disease activity. The purpose of this study is to explore the reasons for this discrepancy. [Methods] 385 patients were RA patients who visited our hospital outpatient. Numbers of painful and tender joint counts by patients, tender and swollen joint counts by physicians, patient's global assessment (P-VAS), evaluator's global assessment (Dr-VAS) were recorded. [Results] The correlation coefficient between PJC self-assessed by patients and TJC by physicians was 0.48. P-VAS and Dr-VAS were divided into 3 groups, 10 or less, 11 to 50, and 51 or more, and multiplied by them to make nine groups. Comparing three groups that match Dr-VAS and P-VAS, with three groups that P-VAS is above the Dr-VAS, the average of the difference between TJC and PJC the former is 2.22, the latter is 4.40.. Cases following CRP1, SJC and TJC by an physician is less than 1, the group of P-VAS was 10 or less and the group of P-VAS was 11 or more, the average of the PJC was a significant difference in 1.01,3.88, respectively. [Conclusion] Discrepancy between painful joint count by patients and tender joint count by physicians affects the discrepancy between patient's global assessment and, evaluator's global assessment.

W82-5

Analysis of patients with rheumatoid arthritis not fulfilling the 2010 ACR/EULAR classification criteria

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Conflict of interest: None

[Objectives] The 2010 ACR/EULAR classification criteria has been used in Japan. The aim of this study was to analyze patients with rheumatoid arthritis (RA) not fulfilling the 2010 criteria. [Methods] The study included 42 patients with RA between April 2011 and March 2012. Disease activity score (DAS)28 and requirements for methotrexate (MTX) therapy were compared patients not fulfilling the 2010 criteria with patients fulfilling the 2010 criteria. [Results] Thirty RA patients fulfilled the 2010 criteria and twelve RA patients did not fulfill the 2010 criteria. Seven patients not fulfilling the 2010 criteria were diagnosed as RA using MRI. Mean DAS28 of the patients fulfilling the 2010 criteria was 4.1. Mean DAS28 of the patients not fulfilling the 2010 criteria was 4.3. Seventy five percent of the patients fulfilling the 2010 criteria were required MTX therapy and 63.6% of the patients not fulfilling the 2010 criteria were required MTX therapy. [Conclusion] MRI is useful for patients not fulfilling the 2010 criteria as

diagnosis of RA. Many patients with RA not fulfilling the 2010 criteria were required MTX therapy.

W82-6

To collect comprehensive adverse effects of DMARDs by pharmacy specialist will secure the safety and enhance the efficacy of medications at private clinic

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Conflict of interest: None

【Objectives】The adverse event (AE) in our clinic were intensively collected. Rheumatoid arthritis (RA) patients with DMARDs treatments were 1390. According to Common Terminology Criteria for Adverse Events (CTCAE) Grade2 are reported to PMDA and pharmaceutical manufacturers (PM). Among AEs, the liver dysfunction (LD) with methotrexate (MTX) are mentioned. 【Methods】We screened the records and clinical data of 1,390 RA patients, at each visit, from Nov.2011 to Oct. 2012, and picking up the SEs, got informations from Doctors through intra-net at clinic. 【Results】We reported 6-9 AEs to PM, simultaneously 26 cases CTCAE grade3 or higher to PMDA of Ministry of Health.We evaluated MTX related LD monitored by GPT. In the total of 1,390 RA patients, include 1,173 treated with MTX, 7 deaths, 7 malignant neoplasms were claimed to PMDA as the severe cases. Among infections parts of AE, 75 patients need for antibiotics. Patients on MTX treatment, 76 cases of elevated GPT were monitored, but AE related discontinuation were 3, reduction 12 cases. 【Conclusion】The patient death 0.5%, and malignancies for 0.5% of our all RA patients, claimed to PMDA were1.8%. The LDwere 7.1%, but only 1.4% required dosage reduction. To collect comprehensive AE is important to establish sound medical institution.

W83-1

Disease activity predictive algorithm of rheumatoid arthritis by using a smartphone

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Conflict of interest: Yes

[Objectives] The aim of the present study was to develop a novel algorithm to predict the disease activity of RA by a smartphone. [Methods] This study included 65 patients with RA, age 63.1 ± 11.9 years. The 28-joint disease activity score (DAS28-CRP) was measured for all participants at each clinic visit. The patients assessed their status with the modified health assessment questionnaire (mHAQ), a self-assessed tender joint count (sTJC), and a self-assessed swollen joint count (sSJC) in a smartphone application. The patients' their trunk acceleration while walking was also measured with the application. The peak frequency, auto correlation peak (AC), and coefficient of variance of the acceleration peak intervals were calculated as the gait parameters. [Results] In a stepwise linear regression analysis, mHAQ (β=0.26, $p<0.05$), sTJC (β=0.58, $p<0.001$), and AC (β=−0.16, $p<0.05$) were significantly associated with DAS28-CRP in the final model (R^2=0.67). This predictive model was significantly and strongly correlated with DAS28-CRP (ρ=0.82, $p<0.001$). [Conclusion] The results suggest that self-assessment of a combination of joint symptoms, limitations of daily activities, and walking ability can adequately predict daily disease activity of RA with a smartphone application.

W83-2

Paraffin hyperthermia therapy did not affect synovial vascularity and improved function of finger joints rheumatoid arthritis

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Conflict of interest: None

[Objective] Paraffin hyperthermia therapy (PHT) has been used to improve joint mobility in RA, however it had less in scientific evidence. In the study, we investigated therapeutic mechanism of PHT. [Methods] Patients with RA were investigated; 14 patients with positive synovial vascularity (SV) in finger joints and 8 with negative SV. PHT were performed as follow, bilateral hands were immersed in warm paraffin liquid by ten times and kept them comfortable position for 15 minites. Function of finger joints were estimated by grip strength and visual analogue scale (VAS).Examination were performed at baseline and 2nd week. Statical significance was assessed by paired student-*t* test and *p* value<0.05 was decided as significant. [Results] Grip strength, lateral pinch strength and VAS were significanty improve in all patients. In the group with positive SV, SV significantly decreased from baseline to 2nd week. [Conclusion] PHT have potential to improve function of finger joints via anti-inflammatory mechanism. PHT could be useful therapy for RA.

W83-3

The relationship between clinical evaluation score and functional outcome and joint damage in rheumatoid arhtirits

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Conflict of interest: None

[Objectives] To evaluate the relationship between disease activity, radiographic joint damage and physical dysfunction. [Methods] We assessed disease activity (DAS28-ESR), radiographic damage (TSS : Total Sharp Score) and physical functions (mHAQ, 10m gait time, TUG : Timed Up and Go, DASH : Disabilities of Arm shoulder and Hand, FIM : Functional Independence Measure) in 77 rheumatoid arthritis patients prior to initiating biologic agents. Correlations between these scores were analyzed by Speaman's rank correlation coefficient. [Results] Significant correlation was observed between DAS28-ESR and mHAQ (Rs=0.52). But DAS28-ESR showed only weak correlations to other functional scores while mHAQ and FIM showed significant correlation with all other functional measures. TSS also showed significant correlations to these scores but not to mHAQ and DAS28-ESR in this study. [Conclusion] To treat rheumatoid arthritis, aiming at radio-

graphic and functional remission with tight control of disease activity has become realistic goals in recent years. Physical dysfunction related to established joint damage should be an important target of RA therapy to achieve the functional remission.

W83-4

Study of music therapy using musical instruments for 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 usability of playing music instruments in addition to singing songs in music therapy. [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 was 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 STAI. [Results] Twenty-nine patients with RA (27 females and 2 males) were participated the survey. mHAQ of the attendee was 0.56±0.62. VAS was improved from 2.9±2.9 to 2.5±2.6, face scale was improved from 6.3±5.0 to 4.3±4.2, and state anxiety of STAI was improved from 39.1±10.1 to 32.1±10.5 by music therapy. One patient could not play the instrument by physical disability and another patient had a joint pain by playing. However, almost all the participants were in favor of playing music. [Conclusion] Music therapy using musical instruments improves physical and psychological conditions of patients with RA.

W84-1

A semiquantitative evaluation of the synovitis of finger IP joint using ring gauge

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Conflict of interest: None

[Objectives] Disorders of the finger IP joints are often observed in patients with rheumatoid arthritis (RA). A presence of synovial joint swelling is included in the evaluation of the disease activity. However, Boolean datatype of evaluation for the synovial swelling cannot be always true.The purpose of this study was to evaluate the synovitis of thumb IP and finger PIP joint using ring gauge semiquantitatively. [Methods] Three patients with RA, all female, age averaged 61 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 (P) IP joints decreased significantly (15.5 to 14.3, 18.7 to 17.5 and 15.7 to 15.0 in average gauge) soon after the first induction of biologics. [Conclusion] Semiquantitative evaluation of the synovitis of finger (P) IP joint using ring gauge is easy to achieve, reliable and economical tool for the treatment of RA.

W84-2

Overall of pulmonary hypertension in Department of Rheumatic diseases of Tokyo Metropolitan Tama Medical Center

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Conflict of interest: None

[Objectives] To check the characteristics of cases with pulmonary hypertension (PH) in our department. [Methods] A: 1913 cases with collagen vascular disease in our department at the time of April 2012. B: 17 cases with PH in our department in the fiscal year of 2011. C: 68 cases with PH in our hospital from September 12, 2011 to September 11, 2012. D: 189 cases who we performed echocardiogram in the fiscal year of 2011. We extracted cases with PH from above four (A-D) data set and assessed our service for pulmonary hypertension. [Results] In 31 cases with PH, 17 cases (55%) had collagen vascular disease. Of the 17 cases, 8 cases(47%) had interstitial pneumonia, 3 cases(8%) died in 13 months follow-up. Right heart catheterization study performed only in 6 patients of the 17. [Conclusion] Early screening and diagnosis of PH is desirable because of possibility of improvement of prognosis. In this overview, we found that the ratio of collagen vascular disease cases is high in PH patients. But more than half of them were not performed right heart catheterization study. It is necessary to reinforce connections between our department and the departments practicing echocardiogram or right heart catheterization study to execute systematic screening, diagnosis and treatment in early phase of PH.

W84-3

Anti-cyclic citrullinated peptide (anti-CCP) antibody positivity at comprehensive health screening of asymptomatic individuals with prospective observations for up to five years

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Conflict of interest: Yes

[Objectives] There has been no prospective follow-up of anti-CCP in asymptomatic persons. Serum anti-CCP was measured as part of the comprehensive health screening to determine positivity in individuals without joint symptoms. The development of arthritic symptoms and rheumatoid arthritis (RA) in this cohort was prospectively followed up to 5 years. [Methods] Commercial anti-CCP assay (SRL, Inc.) was included as part of comprehensive health screening. Subjects with a history of RA or with active joint symptoms were excluded. [Results] Among the 499 male and 814 female individuals (n=1313; mean age 50.4yrs) with at least one screening visit, 20 (1.5%) were anti-CCP positive at first visit, with 2 out of the 20 (10%) becoming symptomatic and meeting the 2010 ACR/EULAR Classification Criteria for RA. Six individuals (0.46%) additionally developed anti-CCP positivity at a subsequent visit. [Conclusion] Asymptomatic individuals have low anti-CCP positivity. However, symptom onset and development of RA seem to occur at relatively high rates in those who are anti-CCP positive. The utility of anti-CCP as a screening modality needs further evaluation in larger populations.

W84-4

Three β-D-glucan-positive rheumatoid arthritis patients treated with a TNF inhibitor

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Conflict of interest: None

[Objectives] β-D-glucan is useful in the diagnosis of deep-seated mycosis and *Pneumocystis jiroveci* pneumonia. Guidelines for TNF inhibitor treatment in rheumatoid arthritis (RA) recommend screening for deep-seated mycosis by serum β-D-glucan. We report three β-D-glucan-positive RA patients treated with a TNF inhibitor. [Methods] After getting informed consent, we treated three RA patients with a TNF inhibitor who were positive for serum β-D-glucan and negative for deep-seated mycosis infection. Adalimumab was used to treat two patients, and etanercept was used for the third patient. [Results] The simplified disease activity index (SDAI) of the patients at baseline and at weeks 12, 24, and 48 after the TNF inhibitor treatment were 13.9 ± 12.7, 5.2 ± 5.1, 1.7 ± 0.8, and 1.1 ± 0.8 (mean ± SD), respectively. The serum β-D-glucan levels of the patients at baseline and at weeks 12, 24, and 48 were 66.5 ± 59.8, 40.8 ± 32.3, 35.7 ±1 9.0, and 16.8 ± 2.6 (mean ± SD (pg/ml)), respectively. There were no cases of deep-seated mycosis after the TNF-inhibitor treatment. [Conclusion] Serum β-D-glucan levels can be increased by a variety of factors in addition to fungal components. In our three patients, the serum β-D-glucan levels decreased with the improvement of RA after the TNF inhibitor treatment.

W84-5

Study on renal dysfunction of gout arthritis or hyperuricemic patients and effect on renal function by uric acid-lowering therapy

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Conflict of interest: None

[Objectives] Renal dysfunction is an important complication of hyperuricemia, we examined the renal dysfunction in patients with gout arthritis or hyperuricemia. We also studied the effect of lowering serum uric acid (UA) on the renal dysfunction. [Methods] We investigated eGFR of 316 male patients and examined the changes in eGFR after 6 months with UA-lowering therapy. [Results] In the patient group, eGFR reduced by 0.7 a year.On the other hand, eGFR reduced by 0.4 a years in patients without gout and hyperuricemia. Because there are a lot of obese patients, eGFR was corrected by body surface area. Corrected eGFR of gout or hyperuricemia reduced 1.1 a year. EGFR was significantly increased to 78±16 from 75± 16 at 6 months after the treatment with UA-lowering drugs. In the patients eGFR was less than 70, eGFR significantly increased to 63± 8 from 59±8. Especially in the patients serum UA level was less than or equal 6.0 mg/dL, eGFR was significantly increased to 65±9 from 59±8 after the treatment, but there was no significant eGFR change in patients serum UAlevel was more than 6.1 mg/dL. [Conclusion] Renal function in patients was reduced 2-3 fold compared to normal subjects and the improvement of renal function was observed in lowering serum UA levels sufficiently.

W84-6

The diagnostic performance of anti-CCP antibody in undiagnosed rheumatoid factor positive population

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Conflict of interest: None

[Objectives] To evaluate the diagnostic performance of anti-CCP antibody (ACPA) in rheumatoid factor (RF) positive population without previous diagnosis of rheumatoid arthritis (RA). [Methods] Among 105778 patients who had been checked RF as screening test in health check, we retrospectively extracted all the 7876 patients who had shown elevated RF level more than upper limit of normal at least once. After excluding patients who had already have diagnosed of RA, a retrospective review of medical records was performed to evaluate the diagnostic utility of ACPA in RF positive population. [Results] ACPA was checked in 629 RF positive patients, and 74 patients showed ACPA positivity. The diagnosis of RA was made significantly frequent in ACPA positive group (35.1%) than in ACPA negative group (3.4%, $p<0.001$). The sensitivity and specificity of ACPA in this population were 57.8% and 90.2%, respectively. [Conclusion] ACPA showed high specificity for diagnosing RA in RF positive population. The combination of RF and ACPA screening in health check is useful for detecting undiagnosed RA.

W85-1

Comparative study between etanercept and cyclophosphamide as treatment of patients with amylopid A amyloidosis secondary to rheumatoid arthritis

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Conflict of interest: None

Objectives. To compare the effectiveness of an alkylating agent with that of a biological agent in treatment of patients with amyloid A (AA) amyloidosis secondary to rheumatoid arthritis (RA). ***Methods.*** Cyclophosphamide (CYC) and etanercept (ETN) were administered to 62 and 24 RA patients, respectively. We evaluated whether the SAA1.3 allele, being influencing treatments and retrospectively analysed the effectiveness of both agents via statistical methods. ***Results.*** Patients given ETN had somewhat worse renal function, i.e. 24-hour proteinuria (P=0.02), at the initiation of treatment. ETN demonstrated greater effectiveness than CYC, as evidenced by significantly improved levels of serum C-reactive protein and serum albumin (both P<0.01) and estimated glomerular filtration rate (eGFR) (P=0.032). ETN improved survival (P=0.025) and the hazard ratios for the risk of death endpoint with eGFR and 24-hour proteinuria were significant by P=0.024 and P=0.025, respectively. The SAA1.3 allele did not affect the response to medications in AA amyloidosis secondary to RA. ***Conclusions.*** ETN treatment was more effective than CYC treatment, and C-reactive protein, albumin, and eGFR may be valuable biomarkers for analysis. The SAA1.3 allele was not a factor affecting treatment.

W85-2

Treatment with biologic agents did not improve survival of the patients with rheumatoid arthritis and amyloidosis treated with hemodialysis

Takeshi Kuroda[1], Mihoko Yamazaki[2], Hiroe Sato[2], Takeshi

Nakatsue[2], Yoko Wada[2], Shuichi Murakami[2], Masaaki Nakano[3], Ichiei Narita[2]
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Conflict of interest: None

[Objectives] Our purpose was to examine the safety and effects of the therapy with biologics on prognosis in RA patients with reactive AA amyloidosis with hemodialysis (HD). [Methods] Twenty patients with an established diagnosis of reactive AA amyloidosis participated in the study. Survival was calculated from the date of HD initiation until the time of death, or up to end of November 2011 for the patients who were still alive. [Results] HD initiation was according to the program of HD initiation for systemic amyloidosis patients associated with RA. Eight patients had been treated with biologics before HD initiation for 18 month in average (biologic group) and 12 had not (non-biologic group). Although there were no statistical significance, biologic group showed higher mortality rate in a Kaplan-Meier analysis (p=0.279) and associated with higher risk of death in age-adjusted Cox proportional hazards model (hazard ratio 1.35, p=0.550). Infections are significantly more frequent case of death in the biologic group than in the biologic group (p=0.001). [Conclusion] The use of biologics might increase the risk of infectious complications, which may affect the survival of RA patients with AA amyloidosis with HD.

W85-3

Detection of AA76, the most common species of AA amyloid

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Conflict of interest: None

[Objectives] In AA amyloidosis, carboxyl terminus-truncated serum amyloid A (SAA), AAs, deposit in tissues. Since the most common AA is 76 residue-length, specific detection of that AA species (AA76) would be useful for diagnosing AA amyloidosis. However, the currently utilized antibodies cannot distinguish AA76 from non-amyloidotic SAA and other AA specieses. Thus,we tried to develop antibodies specific to the AA76. [Methods] Rat was immunized with the peptide corresponding to carboxyl terminus of AA76 and monoclonal antibodies were developed by the conventional methods. [Results] Two clones (CF1 and CF6) were obtained by the initial screening as negative reactions with longer peptides than AA76. In immunohistochemistry, both antibodies reacted with AA amyloid deposits well, not with SAA leaked from vessels. Reactivity of both to AA fibrils were reduced largely by degenerative treatments such as SDS or guanidine. [Conclusion] AA76 may be a species appeared specifically during amyloidogenesis. The present antibodies can specifically detect, though in the limited, AA76. The antibodies should seek usefulness for diagnosis and investigative studies.

W85-4

Rheumatoid Arthritis with AA amyloidosis

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Conflict of interest: None

[Objectives] To clarify prognosis and prognostic factor of rheumatoid arthritis (RA) patients with AA amyloidosis. [Methods] All RA patients with AA amyloidosis who were referred to our hospital from 1985 to 2012 were analyzed retrospectively. [Results] 25 patients were enrolled in this study. (3 men and 22 women, mean age at diagnosis of AA amyloidosis; 60.5±9.5 years old, serum Cr 2.7±2.1 mg/dl.) All 25 patients had renal involvement and 13 patients had gastrointestinal involvement of AA amyloidosis. 16 patients were induced dialysis: 11 patients died, 5 patients are still alive and still receiving bio-DMARD. Among 9 non-dialysis patients, 5 patients died, 4 patients has received bio-DMARD and their renal function has not worsened. Infection was most common cause of death both in dialysis and non-dialysis patients. All 25 patients had received treatment with steroids and never had received continued MTx or bio-DMARD before diagnosis of AA amyloidosis. The number of new occurrence of AA amyloidosis has been only four cases since 2006. Use of bio-DMARD was only significant variable for overall survival and renal survival of patients with AA amyloidosis. [Conclusion] Bio-DMARD has improved prognosis of patients with AA amyloidosis significantly.

W86-1

Infliximab (IFX) differentially regulates bone erosion and cartilage resorption in patients with rheumatoid arthritis (RA)

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Conflict of interest: Yes

Background: Several clinical studies demonstrate efficacy of IFX to inhibit structural damage, however, some rapid radiographic progression in RA exist even after IFX treatment. Objective: To investigate predictor of CRRP in IFX therapy. Methods: Modified Total Sharp Score (mTSS), Joint Erosion (JE) and Joint Space Narrowing (JSN) were evaluated in 89 RA patients treated with IFX in our institution. We studied patient background, disease activity and biomarkers in structural remission (REM;ΔmTSS≤0.5) and clinical rapid radiographic progression group (CRRP;ΔmTSS>3). Results: No difference in age, disease duration, MTX dose and DAS28 was observed between groups. CRP and MMP-3 at week 54 in CRRP were significantly higher than in REM ($p<0.0001$). The result of multiple logistic regression analysis showed only CRP was significantly associated with CRRP (p=0.0433). Same analysis made in ΔJE and ΔJSN (REM;≤0,CRRP;>3) showed JE tended to correlate with CRRP (p=0.0643). The result of multiple regression analysis on ΔmTSS, ΔJE and ΔJSN by CRP and MMP-3 found significant association between MMP-3 and ΔJSN (p=0.0360). Conclusion: CRP and MMP-3 correlate with CRRP of mTSS. Especially impact of CRP on JE and MMP-3 on JSN was shown. Bone and cartilage destruction may occur by different mechanism.

W86-2

Clinical and radiographic results of single 25mg etanercept therapy a week for patients with rheumatoid arthritis

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Conflict of interest: None

[Objectives] To evaluate the clinical and radiographic results of

25mg etanercept therapy once a week for patients with rheumatoid arthritis (RA). [Methods] We enrolled 25 patients with RA who were administered etanercept 25mg/week and could have observation periods for 2 years. We measured CRP, ESR, MMP-3 and each parameter of DAS28-ESR. Treatment response was determined by EULAR response criteria. Progression of joint destruction was evaluated using a modified total Sharp score (mTSS). [Results] The mean DAS28-ESR was 5.31 at baseline and improved to 3.64 at one year, and to 3.39 at 2 years after 25mg etanercept administration. Good or moderate response rate according to EULAR improvement criteria was 68% at one year and 72% at 2 years. Eight patients resulted in poor response with weekly 25mg etanercept therapy were then switched to 50mg etanercept. Mean change in mTSS from baseline was the 0.83 at one year and 1.37 at 2 years after 25mg etanercept administration. During the two years, 53% of the patients showed no radiographic progression. [Conclusion] Etanercept therapy of 25mg a week showed good efficacy to inhibit the progression of joint damage in RA patients.

W86-3

Evaluation of the cost effectiveness of biological agents for the treatment of rheumatoid arthritis using the IORRA cohort database

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Conflict of interest: Yes

[Objectives] To evaluate the cost-effectiveness of selecting biological agents (BAs) using the real-world RA cohort database. [Methods] We investigated the cost-effectiveness of BAs (BA group) compared with methotrexate alone (MTX group) using a Markov model-based probabilistic simulation. BA group started either one of four BAs (adalimumab, etanercept, infliximab, and tocilizumab) between April 2007 and April 2011. MTX group were extracted using the pair matching method. Markov states were defined based on the J-HAQ score. Model parameters were determined using clinical data from the IORRA. Lifetime costs, quality-adjusted life years (QALY), and incremental cost-effectiveness ratio (ICER) were calculated. A lifetime horizon and a discount rate of 3% per year for both health benefits and costs were assumed. [Results] Clinical data from two groups of 454 patients were used. Lifetime costs in the BA and MTX groups were 34.8 and 24.1 million JPY and QALYs were 11.4 and 9.3, respectively. The ICER was 5.04 million JPY, indicating that BA is cost-effective in Japan based on the reported threshold (5.0-6.0 million JPY per QALY). [Conclusion] BAs are cost-effective for RA patients based on data from an observational cohort representing daily clinical practice in Japan.

W86-4

AIMS-2-Based Evaluation of Long-Term QOL in Patients with Rheumatoid Arthritis- Outcome of 2 Years on Etanercept Treatment -

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Conflict of interest: None

Objective: The achievement of remission at an early period and its long-lasting maintenance is important in the course of rheumatoid arthritis (RA) treatment. We examined whether or not patients who maintained remission or low disease activity (DA) could also have their scores of AIMS-2, a measure of QOL, controlled. **Methods:** RA patients showing sustained remission or low DA achieved by etanercept (ETN) treatment were evaluated by AIMS-2 for 2 years. **Results:** The study included 66 patients; 61 continuing ETN and 5 switched to other medications, including 2 to adalimumab and 3 to abatacept. Those continuing ETN had no great change in each AIMS-2 subscale for 2 years, showing that QOL was maintained. In contrast, the switched patients appeared to have poorer scores for "social activity," "support" and "walking" subscales, and better scores for "pain," "hand and finger function" and "level of tension" subscales. **Conclusion:** The sustained remission or low DA for long term with ETN treatment was associated with the maintenance of QOL. Immediate response to abnormalities and change in therapeutic effects that can be detected early through QOL surveys such as AIMS-2 administered by nurses and positive contact to RA patients may also contribute to maintaining QOL for a long term

W86-5

Satisfaction of RA patients using biologics correlates with changes in disease activity from the start of administration

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Conflict of interest: None

(Objectives) We evaluated BIO patients' satisfaction to use it as an index of goal achievement and studied if the results correlated with changes in disease activity. (Method) As subjects, 204 BIO outpatients (infliximab:53, etanercept:98, adalimumab:15, tocilizumab:35 and abatacept:3) answered questions about pain/anxiety and satisfaction with treatment. Also they were evaluated before treatment and at the time of the survey with DAS28, SDAI, HAQ, and FACE to see if their satisfaction correlates with those values or/and changes of the values. (Results) Among patients, 29% were satisfied, 57% somewhat satisfied, 11% somewhat dissatisfied and 3% dissatisfied and there were no major differences in DAS28, SDAI, HAQ, FACE before treatment, but at the survey there was a tendency of increasing values of each method as the satisfaction decreased, which was more prominent with greater significance in the amount of changes of values than the values itself, particularly in HAQ and FACE. Not much difference was seen in satisfaction among each treatment. In the analysis, FACE showed the highest satisfaction level. (Conclusion) Patients' satisfaction with treatment depends on disease activity levels at the onset of treatment but FACE is suggested as a useful index of goal achievement in T2T.

W86-6

Biologics therapy which rheumatoid arthritis patients expect

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Conflict of interest: None

[Objectives] To clarify the expected biologic therapy by RA patients and the present problems in daily clinical practice [Methods] The questionnaire investigation was done from July to September in 2012 for RA patients who received any of 6 biological agents. [Results] Impression of biologics; expensive 48.7%, high frequency of adverse effect (AE) 8.7%, permanent use 14.0%. Worry before starting biologics; AE 40.8%, effectiveness 26.7%, economical 23.3%. Worry after receiving biologics; AE 37.9%, ef-

fectiveness 38.9%, economical 20.0%. How do you overcome your worry; explanation by the attending doctor 48.0%, study by themselves 12.2%, explanation by nurses 2.0%. Expecting anti-rheumatic agents; oral 52.6%, subcutaneous 24.0%, drip infusion 23.4%. Among subcutaneous biologics, patients want less frequent injection and prefer less frequent visit with self-injection (66.7%) than monthly injection (33.3%) at the hospital. Preferred visit interval for drip infsion was every 8 week. Most patients (86.3%) want to continue biologics despite high cost. [Conclusion] Oral agents are the most expected therapy. Among 6 biologics our patients prefer the agent which does not need frequent visit to the hopital. The explanation by the attending doctor is important for relieving patients' worry.

W87-1

Long-term efficacy of tocilizumab in patients with rheumatoid arthritis

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Conflict of interest: None

[Objectives] To evaluate the long-term efficacy and continuous rate of tocilizumab (TCZ) in RA. [Patients & Methods] Clinical efficacy of TCZ was evaluated on 50 patients (16 males, 34 females) treated with TCZ in our hospital since January 2001 to November 2011. The numbers of patients treated with TCZ in 3 years was 27. [Results] The mean age of RA patients who started to use TCZ was 56.5±10.4 years old and the mean duration of RA was 11.1±12.7 years. The average DAS28(4)-ESR before treatment was 5.70±1.46, It improved to 2.83±1.50 in one year, 2.40±1.15 in 3 years. Continuous rate of tocilizumab in one year or 3 years were 71.6% or 62.1%. [Conclusion] Our study suggest that TCZ was effective and continuous rate as same as TNF-inhibitors. We need to know the protective effect of bone distraction by TCZ in long-term.

W87-2

A study of the persistency ratio of tocilizumab for the second biologic in patients with rheumatoid arthritis

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Conflict of interest: None

[Objectives and Methods] In this study, we analysed the persistency ratio in 64 patients with rheumatoid arthritis with inadequate response to anti-TNF therapy for first biologic from July 2008 to September 2011 in our hospital. 25 patients were treated with tocilizumab (an anti-IL-6 receptor antibody) and 39 patients treated with infliximab, etenercept and adalimumab (anti-TNF drugs) for second biologics. [Results] The persistency ratio for 2 years was 79.8% on the group with anti-IL-6 versus 50.0% on the group with anti-TNF. In addition, the persistency ratio for 2 years in patients with inadequate response to anti-TNF therapy for first biologic as secondary failure was 90.0% on the group with anti-IL-6 versus 25.0% on the group with anti-TNF. [Conclusion] After inadequate response to anti-TNF, particularly after secondary failure, the persistency ratio in patients treated with anti-IL-6 was higher than anti-TNF.

W87-3

Examination of Discontinuation Criteria for Tocilizumab in Rheumatoid Arthritis Patients (Multicenter Study)

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Conflict of interest: Yes

[Objectives] The appropriateness of the discontinuation criteria "three consecutive DAS28-ESR <2.6 and MMP-3 levels below standard value" was assessed in rheumatoid arthritis (RA) patients during tocilizumab (TCZ) treatment. [Methods] A retrospective study of RA patients who were introduced to TCZ was conducted at 3 facilities. The primary endpoint was the discontinuation rate 24 weeks after TCZ discontinuation. Patients with DAS28-ESR >3.2 twice consecutively who resumed TCZ were considered to have relapsed. [Results] Among 230 patients administered TCZ, 34 of them met the discontinuation criteria and were able to discontinue TCZ. Of the 32 patients who could be observed for at least 24 weeks after TCZ discontinuation, 17 of them met the discontinuation achievement assessment criteria and could maintain discontinuation for 24 weeks. [Conclusion] The discontinuation criteria are appropriate because results were good with a 53% discontinuation rate at 24 weeks after TCZ discontinuation. Factors which might affect the discontinuation rate include the stage and combined use of DMARDs during discontinuation. Regarding DMARDs, the ratio of MTX administration in the relapse group was higher than in the discontinuation atonement group.

W87-4

Progress After Dropout Tocilizumab Therapy in Rheumatoid Arthritis

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Conflict of interest: None

[Objectives] Tocolizumab (TCZ) shows the effect even in rheumatoid arthritis (RA) of inadequate response TNF inhibitors. There are few reports that clinical course of patients dropped out TCZ. In this study, we report clinical courses of RA dropped out TCZ. [Methods] The subjects were 21 patients whom clinical data could be performed after 1 year of dropout TCZ therapy. We defined dropouts due to insufficient as A group [12, number of patient], and the other as B group [9]. We investigated treatment progresses at induction TCZ, dropout TCZ, and one year after dropout TCZ. [Results] In group B, the reasons of dropout TCZ were adverse event [3], clinical remission [2] and other [4]. Treatments of RA after TCZ are TNF inhibitors [8] and abatacept [3] in group A, TNF inhibitors [3], golimumab [1], methotorexate [4] and tacrolimus [1] in group B. The mean of CDAI points were 27.7→33.6→12.7, CDAI score were improved by switching another biologics in group A. In group B, the mean of CDAI points were 26.2→7.4→3.5. Especially, 4 patients treated with DMARDs after TCZ kept low disease activity (LDA, CDAI≤10). [Conclusion] Our results suggest that switching other biologics from TCZ has some effects, and we can stop TCZ therapy and keep LDA with DMARDs concomitant after TCZ in RA.

W87-5

Discontinuation of tocilizumab after attaining remission in patients with rheumatoid arthritis

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Conflict of interest: None

[Backgrounds] Efficacy and safety of biologic agents against refractory rheumatoid arthritis (RA) patients have been proved, however expensive cost is still a problem. Biologic free study about infliximab and adalimumab were reported, but about tocilizumab (TCZ) is none. [Objectives] To investigate the maintenance ratio of biologic free, low disease activity (LDA), remission (REM) after discontinuation of TCZ in RA patients achieved REM [Methods] Ten RA patients were included who discontinued TCZ after induction of DAS-REM. The ratio of biologic free, LDA, REM were calculated by Kaplan Meier method. Related factor between arthritis flare group and disease activity maintenance group were analyzed by logistic regression test. [Results] Four patients were flared. The maintenance ratio of biologic free was 100% (24wk), 53.3% (52wk). Two patients restarted TCZ and clinical REM could be achieved. The maintenance ratio of LDA, and REM was 85.7%, 67.5% (24wk), and 45.7%, 33.8% (52wk) respectively. Significant related factor between flare group and maintenance group was not recognized. [Conclusion] The maintenance ratio of LDA and REM after discontinuation of TCZ was relatively high. This study was retrospective and number was small, further investigation will be needed.

W87-6

Prospective study on the possibility of MTX cessation in RA patients who have remained remission with combination of MTX plus tocilizumab

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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 + tocilizumab (TCZ) **[Methods]**9 RA patients who were in remission with combination of MTX + TCZ were randomly assigned to the MTX cessation (= TCZ mono-therapy) group and MTX continuation (= combination of MTX + TCZ) group and we evaluated the efficacy of these 2 treatment strategies prospectively at week 20.Clinical features of the patients at the initiation of TCZ were as follows; average age 57.7 years old (M;2, F;7), mean MTX dose was 6.8 mg/w, mean disease duration was 10.8 years, mean DAS28-ESR was 4.48. **[Results]**3 were assigned to the MTX cessation group(=M-group), and 6 were to the MTX continuation group(=C-group). Patients' background characteristics at the randomization, average age was 65.3 and 56.0 years old, disease duration was 8.5 years and 11.1 years, the mean MTX dose was 6.3 and 7.0 mg/w, DAS28-ESR was 1.35 and 1.36,respectively. DAS28-ESR after 20 weeks was 1.68 in the M-group, and 1.16 in the C-group. The number of the patients in remission at week 20 was 2 in the M-group, and 4 of 6 in the C-group.Adverse event was seen in only one case of the C-group, which was leukopenia. **[Conclusion]**DAS28-ESR was worsened in the M-group but not significantly.

W88-1

The significance of the combination of MTX in clinical efficacy of biologic therapy to RA patients

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Conflict of interest: None

[Objectives] To detect the difference of the clinical efficacy by MTX combined application for biologic therapy to RA patients. [Methods] DAS28 of the patients with MTX combination 'abbreviated to (+)' were compared with that of the patients without MTX use 'abbreviated to (-)' before and 1 year after treatment in 23 ADA patients, 44 ETN patients, 53 TCZ patients and 29 ABA patients. MTX combination rates were 60.9%, 72.7%, 71.7%, and 51.7%. [Results] DAS28 after one year, the achievement rate of DAS28<3.2, DAS28 improvement, the achievement rate of DAS28 improvement>0.6 were 3.67±1.09, 35.7%, 1.86±1.24, 85.7% in ADA(+) group, 5.15±1.48, 11.1%, 0.45±1.22, 33.3% in ADA(-) group, 4.17±1.25, 21.9%, 2.62±1.49, 90.6% in ETN(+) group, 4.27±1.13, 25.0%, 2.12±1.24, 91.7% in ETN(-) group, 2.33±1.02, 73.7%, 2.83±1.19, 100% in TCZ(+) group, 2.71±1.15, 66.7%, 2.59±1.00, 100% in TCZ(-) group, 4.01±1.43, 20.0%, 1.03±1.36, 66.7% in ABA(+) group 4.34±1.57, 28.6%, 0.87±1.77, 50.0% in ABA(-) group. [Conclusion] Combination use of MTX should be needed in ADA treatment to obtain sufficient clinical response and to achieve the therapeutic goal, but the clinical response could de similar in ETN, TCZ and ABA treatment with or without MTX use.

W88-2

Comparison of treatment response, drug adherence and prednisolone and MTX reduction in patients with rheumatoid arthritis treated with infliximab, etanercept, adalimumab, tocilizmab or abatacept. Results from ten years of surveillance of clinical practice in Department of Hematology and Rheumatology, Tohoku University Hospital

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Conflict of interest: None

[Objectives] To compare the efficacy of five biologics directly in patients with rheumatoid arthritis (RA) and to identify clinical prognostic factors for response. [Methods] For the present study, we included 128 patients who had RA and biologic treatment (infliximab:IFX, etanercept:ETN, adalimumab:ADA, tocilizmab: TCZ, or abatacept:ABT) was initiated. Baseline predictors of treatment response were identified and clinical responses, remission rate, drug withdrawal, Disease Activity Score in 28 joints (DAS28) and dose of methotrexate (MTX) and prednisolone was calculated. [Results] Seventy percent improvement according to the American College of Rheumatology criteria (an ACR70 response) was achieved in 39.6% and Boolean remission in 17.9% of patients after 12 months. Average DAS28 score was decreased from 5.1 to 3.2. Average daily dose of prednisolone was 6.3mg and significantly reduced to 4.2mg after biologics treatment especially in patient treated with ADA and TCZ. Moreover weekly administration of MTX was reduced from 6.4mg to 5.7mg. Average 12 months drug withdrawal rate was 73.8%, IFX:63.7%, ETN:70.0%, ADA:65.8%, TCZ: 88.2% and ABT:71.4%, respectively. [Conclusion] Tocilizmab showed the highest treatment response, drug adherence and prednisolone and MTX reduction.

W88-3

Adherence to Second Biologics Agents at 52nd Week in Rheumatoid Arthritis Patients: Comparison of Anti TNF-alpha Inhibitors, an Anti-IL-6-receptor Inhibitor, and a T-cell Selective Costimulatory Regulator

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Conflict of interest: None

[Objectives] The object of this study is to examined correlation between adherence to second biologics for RA patients who chose either of three biologics with different mechanisms of action and characteristics of the RA patients. [Methods] Between June 2008 and November 2011, a retrospective study was conducted on 768 RA patients who were administrated first biologic agents at Tsurumai Biologics Communication Registry. We investigated the patient characteristics at the time of administration, the survival rate at week 52 and the reason for discontinuous. [Results] Of the 768 patients, 599 were administered anti TNF-alpha inhibitors, 98 were used TCZ, and 71 were used ABT. As for the patient characteristics, the ABT group was older, contained a higher percentage of men compared to the anti-TNF-alpha and TCZ group. The adherence to each medication at the 52nd week was 69.7% for the anti-TNF-alpha group, 85.7% for the TCZ group, and 83.1% for the ABT group (P=0.0004). The percentage of adverse events was 9.5% for the anti TNF-alpha group, 5.1% for the TCZ group and 2.8% for the ABT group. [Conclusion] While every group having different patient characteristics, The TCZ group exhibited the highest adherence and the ABT group experienced the lowest percentage of adverse events.

W88-4

The efficacy and safety of abatacept (ABT) in combination therapy with tacrolimus (TAC) and methotrexate (MTX) for patients with rheumatoid arthritis (RA)

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Conflict of interest: None

[Objectives] The efficacy and safety of ABT on RA was evaluated by comparing patients receiving ABT plusTAC (TAC group), ABT plus MTX (MTX group), and ABT only (non-combination group: NC group: including combination with DMARDs other than TAC/MTX) in a multicenter study (Tsurumai Biologics Communication: TBC). [Methods] Of 217 patients who started treatment with ABT after marketing and received ABT for 24 weeks, 211 patients, excluding 6 patients who received TAC and MTX, were assigned to TAC group (22 patients), MTX group (102 patients), or NC group (87 patients) to evaluate disease activity, retention status, and reasons for discontinuation. [Results] SDAI scores reduced from 31.3, 24.3, and 26.1 at baseline to 12.6, 14.5, and 17.0 at Week 24 in TAC, MTX, and NC groups, respectively. There was a statistically significant difference between TAC group and MTX and NC groups. The retention rate was 86.4%, 86.3%, and 81.6% in TAC, MTX, and NC groups, respectively. No difference was found between TAC and MTX groups. Treatment was discontinued in 3 patients in TAC group. None was due to adverse events. [Conclusion] A combination of ABT and TAC would appear to be as effective and safe as the ABT/MTX combination. This suggests that the ABT/TAC combination is a useful option.

W88-5

Interval extension and dose reduction of biologics in patients with rheumatoid arthritis (data from NinJa2011)

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Conflict of interest: None

[Objectives & Methods] To reveal the actual situation of interval extension (IE) and dose reduction of biologics in NinJa2011 (including 940 by ETN, 459 by TCZ, 352 by IFX, 258 by ADA, and 206 by ABT). [Results] In ETN, IE (<once a week) was seen in 6.8%, and the dose (/w) of 25mg in 30.7% and <25mg in 6.5%, respectively. Compared with the patients group treated with 50mg/w, that with <50mg/w had significantly lower DAS28, Pain VAS and usage rate of MTX, and higher rate of remission by DAS28-ESR and by Boolean, age at onset and usage rate of 2 or more DMARDs. In TCZ, IE (>4w) was seen in 9.6% and the dose of <7mg/kg in 11.8%. Compared with the patients group whose interval of 4w, that >4w have significantly lower disease activity by composite measures, TJCs, Pt &Dr VASs, usage rate of NSAID and steroid, and higher remission rates. In ABT, IE (>4w) was seen in 0.5%, and the dose of 500mg in 6.3% in the group whose BW was <60kg and that of 500mg in 44.4% and of <500mg in 4.4% in the group whose BW was ≥60kg, respectively. IE in ADA (>2w) and IFX (>8w) were 5.1%, respectively. [Conclusions] In daily practice, IE and dose reduction were being tried in many ways. Further studies were needed to verify the influence of these trials on the joint destruction and ADL of patients.

W88-6

Efficacy and Safety of Mavrilimumab (an Anti-GM-CSFRα Monoclonal Antibody) in Japanese Subjects with Rheumatoid Arthritis: Results of Phase 2A Randomized-Controlled Trial

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Conflict of interest: Yes

Objective: Mavrilimumab (MAV) was evaluated in an international phase 2 study of 284 (MAV n=192; placebo [PBO] n=92) moderate/severe RA subjects; 51 were Japanese (MAV n=34; PBO n=17). Methods: Subjects were randomized 2:1 to subcutaneous MAV (10mg/30mg/50mg/100mg) or PBO in this ascending dose study. The primary endpoint was % subjects achieving DAS28-CRP decrease >1.2 from baseline at wk 12. Results: The Japanese subset is presented. Most Japanese subjects (MAV 97%; PBO 88%) completed the study treatment; 1 (3%) MAV subject discontinued due to adverse events (AEs). The primary endpoint was

achieved by 50% of subjects in all MAV groups vs 24% in PBO (P=.081); 75% in MAV 100mg vs 24% in PBO achieved the primary endpoint (P =.028). Most secondary endpoints followed a similar trend: statistical significance was achieved in 75% MAV 100mg vs 24% PBO for ACR20 (P=.028) at wk 12. The efficacy data were consistent between Europe and Japan. One acute pneumonia event (MAV 50mg) was reported in a Japanese subject. Most common AEs in Japanese subjects were nasopharyngitis (15% MAV vs 18% PBO) and neutropenia-leukopenia (9% MAV vs 12% PBO). Conclusion: Safety data were consistent between Europe and Japan. The study results support further clinical development of MAV for the treatment of RA.

W89-1

Do anti-CCP antibody-negative RA become anti-CCP antibody-positive RA?

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Conflict of interest: None

[Objectives] The sensitivity of anti-CCP antibody (ACPA) in early RA has been reported to be as low as 50%, whereas that in established RA is ~80%. The discrepancy of these figures is believed to be explained by the seroconversion from ACPA(-) RA to ACPA(+) RA, but we felt that the seroconversion of ACPA was much low in the real world. Therefore, we investigated the precise proportion of seroconversion retrospectively. [Methods] The ACPA(-) RA patients (defined by the patients taking anti-rheumatic drugs) who were measured ACPA more than once with the interval of 3 months or longer were investigated the percentage of seroconversion of ACPA. [Results] The 241 patients (17.1%) out of 1,412 RA cases were negative for ACPA. In the 120 cases of ACPA(-) RA whose ACPA were measured more than once, only 6 patients (5.0%) showed seroconversion of ACPA. All the 6 cases were RF positive and had bone erosions by X-ray. [Conclusion] The proportion of conversion from ACPA(-) to ACPA(+) RA was ~5%. This result is similar to the previous report in an early arthritis cohort in Europe. These results imply that the low percentage of ACPA in early RA patients is not mainly due to that ACPA has not developed yet but rather due to that ACPA(-) RA contains non-RA arthritides.

W89-2

The characteristic of anti-citrullinated-glucose-6-phospate isomerase (GPI) antibodies in patients with RA

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Conflict of interest: None

[Objectives] To identify and characterize the antibodies (Abs) against citrullinated glucose-6-phosphate isomerase (GPI) peptides in patients with RA. [Methods]1) Nine GPI arginine-bearing peptides in human GPI protein were selected and cyclic citrullinated GPI peptides (CCG) 1-9 were constructed. Samples were obtained from patients with RA (n=208), SLE (n=101), Sjögren's syndrome (SS; n=101), and from healthy controls (HC; n=174). The Abs against CCG-1-9 were measured by ELISA. 2) Anti-citrullinated a enolase -1(CEP-1), anti-CCP Abs were also examined. 3) The levels of the Abs were compared before and after treatment with TNF antagonists in 58 patients with RA. [Results]1) Anti-CCG-2, 4 and 7 Abs were detected in 25.5%, 33.2% and 37.0% patients with RA, respectively. These Abs were very specific for RA (specificity, 98.1% - 99.7%). 2) Positivity of anti-CEP-1 and CCP Abs were 44.2% and 86.1% in RA sera, respectively. Anti-CCG-2, 4 and 7 Abs were correlated with anti-CCP and anti-CEP-1 Abs.3) Treatment with TNF antagonists significantly reduced the levels of anti-CCG-2 and 7 but not of anti-CEP-1 Abs. [Conclusion] We showed the presence of anti-CCG Abs specifically in patients with RA. Moreover, we showed that anti-CCG-2 and 7 Abs might be correlated with disease activity.

W89-3

Autoimmune reactivity of chromatine assembly factor-1 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. Therefore, we conducted this study to clarify autoimmune response of chromatine assembly factor-1(CAF-1), which belongs to PCNA multiprotein complexes existing ubiquitously in intracellular space, in patients with SLE. **[Methods]** Immunoreactivity against CAF-1 was measured by ELISA in sera with normal healthy control (NHC), SLE, and diseases controls (PM/DM, SSc, SjS, MCTD, and RA). The gene expression of CAF-1 and apoptotic related gene was evaluated by quantitative RT-PCR in peripheral mononuclear cell (PBMC) from patients with SLE and NHC. **[Results]** Increased autoimmune response was significantly observed in sera with SLE. Anti CAF-1 antibody positive sera were specifically recognized in SLE patients, who have a high disease activity such as active lupus nephritis. CAF-1 and apoptotic related gene expression was significantly upregulated in SLE. **[Conclusion]** Anti-CAF-1 antibody had disease specificity for SLE and could be useful against diagnosis of SLE. The increased expression of CAF-1 and apoptotic gene in SLE may concern a mechanism of autoantibody production due to exposure of excess antigens to immune system.

W89-4

Prevalence of inhibitory or non-inhibitory autoantibodies to angiotensin converting enzyme 2 (ACE2) in patients with SLE

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Conflict of interest: None

[Objectives]: We have reported serum autoantibodies to ACE2 in patients (Pts) with constrictive vasculopathy. This study describes inhibitory activity of anti-ACE2 antibodies in SLE Pts. [Methods]::Serum anti-ACE2 ELISA was estimated in35 non-vasculopathy Pts with active SLE, 3 SLE Pts with pulmonary arterial hypertension, 4 Pts with SLE-digital necrosis, and 74 control Pts. Inhibiton by serum IgG fraction against in vitro ACE2 activity was evaluated for all the vasculopathy Pts and 21 active SLE Pts having high serum anti-ACE2 ELISA titers. [Results]: Serum anti-ACE2 ELISA titers was higher in 35 nonvasculopathy Pts with ac-

tive SLE (0.81±0.51) and 7 SLE vasculopathy Pts (0.69±0.31) compared with 30 remitted SLE Pts (0.15±0.12), 44 RA Pts (0.06±0.05), P≦0.0001. In vitro ACE2 activity in the presence of 1 μg purified IgG from healthy subject-sera was defined as reference activity. The assay using IgG from SLE patients was determined as relative % value of reference ACE2 activity. Significant inhibition in triplicate assays was shown in 6 of 7 vasculopathy Pts and 4 of 21 nonvasculopathy SLE Pts (p=0.0033). [Conclusion] : Most patients with active SLE or vasculopathy had serum anti-ACE2 antibodies, and inhibitory antibodies were associated with vasculopathy, but not with active SLE.

W89-5

Antiribosormal P protein antibodies enhance the in vitro IL-8 production of human peripheral blood mononuclear cells (PBMC)

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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 IL-8 levels of cerebrospinal fluid were significantly elevated in patients with NPSLE. The current study was undertaken to explore the effects of anti-P on the production of IL-8 in PBMC. [Methods] IgG anti-P were affinity-purified from sera of anti-P positive lupus patients. PBMC were obtained from healthy adult volunteers by centrifugation of heparinized venous blood over sodium diatrizoate-Ficoll gradients. PBMC were cultured with anti-P or control IgG for 5 days. The concentrations of IL-8 in the culture supernatants were measured using ELISA. [Results] Anti-P significantly enhanced the production of IL-8 in PBMC, compared to normal IgG. [Conclusion] These results indicate that anti-P might play an important role in the pathogenesis of SLE through promotion of the production of IL-8 in mononuclear cells at the site of inflammation.

W89-6

Proteomic analysis of the autoantibodies in idiopathic non-specific interstitial pneumonia

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Conflict of interest: None

[Objectives] Involvement of autoimmunity has been suggested in the pathogenesis of idiopathic non-specific interstitial pneumonia (NSIP). Seeking for the minimally invasive diagnostic marker, we performed proteomic analysis of the autoantibodies in idiopathic NSIP. [Methods] Sera were collected from patients of idiopathic NSIP (N=8), idiopathic pulmonary fibrosis (IPF, N=10), autoimmune pulmonary alveolar proteinosis (N=10), sarcoidosis (N=10) and healthy controls (N=10). Proteomic analysis of the autoantibodies was performed using ProtoArrayâ (Invitrogen). Immunohistochemistry was performed on the surgical lung biopsy specimens from idiopathic NSIP and IPF patients. [Results] By scoring autoantibodies based on ProtoArrayâ data, we found 51 disease-specific autoantibodies in idiopathic NSIP. Especially, the titer of anti-myxovirus resistance protein 1 (MxA) antibody was significantly elevated among idiopathic NSIP patients compared to patients with other diseases and healthy controls (p=0.005, ANOVA). Immunohistochemistry revealed that MxA is highly expressed in hyperplastic alveolar epithelial cells and macrophages, which are accumulated in the air space. [Conclusion] Anti-MxA antibody is one of the candidates for the diagnostic marker of Idiopathic NSIP.

International Workshop

IW1-1

miR-451 suppresses autoimmune arthritis via downregulating neutrophil chemotaxis

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Conflict of interest: None

[Objectives] The objective of this study was to identify the role of miR-451 in autoimmune arthritis and to examine the compensation of miR-451 could modulate the autoimmune arthritis. [Methods] We used SKG mice as an autoimmune arthritis model by injecting mannan. Double-strand miR-451 mixed with atelocollagen was administered to mice from tail vein. We evaluated neutrophil chemotaxis by air pouch model and under agarose assay. Phosphorylation of p38 mitogen-activated protein kinase (MAPK) was quantified with western blot, ELISA and flow cytometory. Arthritis score for SKG mice were measured in a time-dependent manner. [Results] The concentration of plasma miR-451 from mice with arthritis was significantly lower than that from control mice. miR-451 was expressed high in blood cell and miR-451 was released most abundantly by neutrophil. Chemotaxis of neutrophils from miR-451 overexpressed mice was significantly disturbed. We newly identified two targets of miR-451. miR-451 suppressed the phosphorylation of p38 MAPK via these targets. Arthritis scores were low in SKG mice with treatment of miR-451 compared with control mice. [Conclusion] miR-451 suppressed autoimmune arthritis via suppressing neutrophil chemotaxis and has a therapeutic potential for rheumatoid arthritis.

IW1-2

Downregulation of miR-193b in systemic sclerosis regulates the proliferative vasculopathy by urokinase-type plasminogen activator (uPA) expression

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Conflict of interest: None

Objectives To investigate the association of miRNA with SSc. Methods To investigate differentially expressed miRNAs in SSc and normal healthy (NH) skin fibroblasts, we performed miRNA array analysis. MiR-193b in SSc skin fibroblasts and SSc skin sections were analyzed by Real-time PCR.Transfection of miR-193b precursor/inhibitor were used to identify target of miR-193b. Expression and localisation of uPA were examined by Real-time PCR, WB and IHC. Human pulmonary artery smooth muscle cells (HPASMC) were treated with uPA and proliferative effect was determined by WST-1 assay and annexin V staining. Results 31 miRNAs showed differentially expression. MiR-193b was significantly down regulated in SSc fibroblasts. MiR-193b was also reduced in SSc skin sections. Induction of miR-193b in SSc and NH fibroblasts suppressed the expression of uPA. Conversely, the knockdown of miR-193b increased the level of uPA. The basal expression of uPA was up regulated in SSc. uPA expressed almost all in vessel in SSc skin section. Interestingly, uPA induced cell proliferation and inhibited apoptosis on HPASMC. Conclusion In SSc, down regulation of miR-193b induces the expression of uPA, which leads to proliferation of vascular smooth muscle cells and thereby contributes to the proliferative vasculopathy.

IW1-3

Aberrant Expression of Autophagy Markers During Osteoarthritis

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OBJECTIVES: Recent studies suggest that the process of autophagy, a form of programmed cell survival, is impaired during osteoarthritis (OA) and may contribute towards decreased chondroprotection in the articular cartilage associated with OA pathophysiology. To further explore the role of autophagy in OA, we determined the expression of known autophagy genes in human OA, mouse and dog model of OA. **METHODS:** Human normal and OA cartilage was subjected to human autophagy PCR array and Heatmap was generated. The expression of key autophagy markers was further investigated by quantitative PCR (qPCR) and immunohistochemistry and compared with mouse and dog OA model. The effect of major OA pro-inflammatory cytokine (IL-1β) on the expression of autophagy markers was also determined. **RESULTS:** The Heatmap and GEDI images obtained from human autophagy PCR array demonstrated a down-regulation of 16 and up-regulation of 17 autophagy genes in human OA cartilage versus normal cartilage, with a fold change of <-1.5 or >1.5 respectively. Data further demonstrated a significant up-regulation in the expression of autophagy master regulator mTOR, and significant reduction in the expression of key autophagy markers including ULK1 (most up stream autophagy inducer), LC3B (critical factor for autophagy vacuole formation), ATG5 (required for autophagosome formation) and BNIP3 (interactor of LC3) in human OA compared to normal cartilage. Similarly, a significant up-regulation in the expression of mTOR and downregulation of autophagy-specific genes (LC3B and ATG5) was observed in mouse and dog experimental OA. Treatment of normal human cartilage explants with IL-1β resulted in a significant reduction in the expression of LC3B, ATG5 and BNIP3. **CONCLUSIONS:** This study is the first to provides a global view of dysregulation in the expression of mTOR and various autophagy-specific genes in human OA compared to experimentally-induced OA in mouse and dogs. Targeting autophagy could open up new therapeutic avenues for OA treatment or prevention.

IW1-4

PAD4 probably play an important role in rheumatoid arthritis by influncing histone H3R17/ H4R3 methylation

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Objective Peptidyl arginine deiminase 4 (PAD4) is a enzyme that catalyzes protein citrullination,which have a role in the pathogenesis of rheumatoid arthritis (RA). However, PAD4 also regulates histone arginine methylation levels via demethylimination especially in H3R2,H3R8, H3R17, H3R26and H4R3, which is considered to play an important role in the transcriptional regulation of proinflammatory genes. In this study,we detect the levels of PAD4 mRNA and histone arginine methylation levels in histone H3R17/H4R3 in RA. Methods Real-time quantitative PCR was used to determine the expression of PAD4 mRNA in PBMCs from 60 RA patients and 40 healthy individual,and the histone H3R17

asymmetric di-methylation and H4R3 symmetric di-methylation and mono-methylation was semi-quantified by Western blotting from 12 osteoarthritis (OA), 26 RA patients and 10 healthy individual. Results 1.The level of PAD4 mRNA in RA was significantly higher than healthy controls ([34.6(16.7,70.8)] vs 20.6 (11.1, 51.8)], P<0.05). The PADI4 level was positively related to anti-CCP antibodies (r=0.527, P<0.001),. 2.The level of histone H3R17 asymmetric di-methylation in RA was significantly higher than OA and healthy individual (71.34±25.65 vs 37.18±18.62 vs 50.67± 13.99, P<0.05), the level of histone H4R3 symmetric di-methylation was no different in RA, OA and healthy individual (75.02± 20.35 vs 57.92±22.77 vs 68.37±17.57, P>0.05). 3. The level of histone H4R3 mono-methylation in RA was significantly lower than OA and healthy individual (11.24±7.81 vs 32.77±30.77 vs 51.20± 47.14, P<0.05). The level of histone H4R3 mono-methylation in RA was negative related to PAD4 (r=-0.450, P=0.021). The level of histone H3R17 asymmetric di-methylation and H4R3symmetric di-methylation was not associated with PAD4 in RA. (r=-0.185, p=0.377; r=0.198, p=0.344). Conclusion PAD4 probably play an importent role in rheumatoid arthritis by influncing histone H3R17/ H4R3 methylation.

IW1-5

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) have potential for joint repair in rheumatoid arthritis (RA) due to its immunoregulatory ability and pluripotency. In order to develop an effective delivery system of MSCs, we utilized a scaffold made of nano-diameter poly-lactic-co-glycolic acid fiber (nano-fiber). [Methods] Human MSCs were seeded on nano-fiber and implanted into ankles (IMP) of collagen-induced arthritis (CIA) rats or simply injected intra-articularly (IA) or intra-peritoneally (IP). [Results] Treatment with MSC through IMP significantly suppressed the severity of arthritis evaluated by arthritis score, hind paw thickness and body weight compared to CIA control and treatment via IA and IP. X-ray, micro-CT revealed less bone destruction in IMP than IA or IP. Histological analysis showed less infiltration of inflammatory cells and bone erosion in IMP, compared to other treatment groups. Furthermore, the draining lymph nodes and spleen revealed smaller in size and reduced pro-inflammatory cytokine expression. [Conclusion] Implantation of MSCs with nano-fiber scaffold efficiently suppressed arthritis and bone destruction and systemic inflammation, suggesting a novel MSCs delivery system for future RA treatment.

IW1-6

Discovery of protein biomarkers in plasma from active systemic lupus erythematosus patients by gel-based proteomics

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Systemic lupus erythematosus (SLE) exhibits an aggressive clinical phenotype with severe complications and overall poor prognosis. The goal of this study was to identify candidate protein biomarkers to help to diagnose SLE patients from Taiwan. The SLE plasma samples were collected from Cathay General Hospital, Taipei, Taiwan. They, one male and eighteen female patients, were also diagnosed with renal involvement. The average age is 32.1±11.5. The patient protein profile in the plasma was randomly compared to that from twelve healthy controls from three male and nine female with average age at 41.9±12.2. The protein concentration in the plasma samples was quantified and the total protein was separated by one-dimensional and two-dimensional SDS-polyacrylamide gel electrophoresis. The up- and down-regulated proteins compared to healthy plasma ($p < 0.5$) were cut from the gels and digested with trypsin followed by the amino acid sequencing with mass spectrometry (MALDI-TOF/TOF and ESI-MS/MS). Five proteins are found to be up-regulated in patient plasma: apolipoprotein B-100, alpha-2-macroglobulin, haptoglobin, retinol-binding protein 4 and transthyretin. Transthyretin is a serum and cerebrospinal fluid carrier of the thyroid hormone thyroxine and retinol. The retinol-binding protein 4 was one of the subunits in retinol-binding protein-retinol complex, which interacts with transthyretin. The retinol-binding protein-retinol-transthyretin complex was known to prevent the loss of retinol in kidney. Transthyretin is also known to be associated with diseases such as amyloid, senile systemic amyloidosis, familial amyloid cardiomyopathy and familial amyloid polyneuropathy. It was proposed by Ranjana Minz's group in 2012 that the presence of this protein in SLE patients might develop secondary amyloidosis.

IW1-7

A common mechanism of gout/hyperuricemia with decreased urate excretion from intestine

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Conflict of interest: None

[Objectives] ABCG2 is a high-capacity urate exporter and the combination of its dysfunctional variants raises risk of gout/hyperuricemia. Hyperuricemia has been pathophysiologically classified into urate "overproduction type," "underexcretion type" and "combined type." We then investigated the association between ABCG2 variants and urate excretion. [Methods] We genotyped ABCG2 in 644 Japanese male patients of hyperuricemia with their urinary urate excretion (UUE). Urate excretion is also examined with Abcg2-knockout (KO) mice. [Results] Paradoxically, ABCG2 export dysfunction significantly increases UUE. ABCG2 dysfunction is found in 75.6% of patients and raises the risk of "overproduction" hyperuricemia (risk ratio=2.3 at the maximum). KO mice show increased serum uric acid (SUA) levels and renal urate excretion, and decreased intestinal urate excretion. [Conclusion] These findings indicate a novel common mechanism of hyperuricemia that the decrease in extra-renal urate excretion via dysfunctional ABCG2 increased SUA and UUE. Here we propose that current "overproduction type" be renamed "renal overload type" which consists of two subtypes, "extra-renal urate underexcretion" and genuine "urate overproduction," providing a new concept valuable for treatment of hyperuricemia and gout.

IW1-8

Members of the receptor for advanced glycation end products axis as potential therapeutic targets in patients with lupus nephritis

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Introduction: Innate immunity related receptor for advanced glycation end products (RAGE) and RAGE ligands together may play immunopathological roles in autoimmune diseases. In the present study, we assess the relationship between inflammation and the expression of full-length receptor for advanced glycation end products (flRAGE) on monocytes, plasma levels of high mobility group box protein 1 (HMGB1), soluble RAGE (sRAGE) and endogenous secretory RAGE (esRAGE), and to elucidate the effect of HMGB1/DNA/RAGE-mediated innate inflammatory responses in patients with lupus nephritis (LN). Methods: Expression of flRAGE, plasma levels of HMGB1, circulating sRAGE and esRAGE from 27 LN patients and 24 healthy volunteers were examined by flow cytometry or ELISA. Ex vivo effects of HMGB1/DNA/RAGE axis on lupus monocytes were assessed using flow cytometry. Results: Expression of flRAGE was increased in the monocytes of lupus patients, which correlated with the plasma HMGB1 levels. Plasma sRAGE level negatively correlated with systemic lupus erythematosus (SLE) disease activity as reflected by the SLEDAI. Plasma esRAGE level was significantly lower in SLE patients with flare while esRAGE/sRAGE ratio negatively correlated with C3 level. HMGB1 alone could moderately induce ex vivo IL-6 production, which resulted in transient activation of intracellular p38 MAPK, JNK and NF-κB in peripheral blood monocytes. Moreover, TLR9 ligand together with HMGB1 exhibited a synergistic effect on IL-6 and IL-12p70 secretions and also activated the phosphorylation of p38 MAPK and NF-κB in monocytes. Conclusions: Over-expression of flRAGE in lupus may lead to the amplification of RAGE ligands-mediated inflammatory responses through the activation of p38 MAPK and NF-κB. Plasma sRAGE may serve as a potential biomarker for disease activity as well as a future therapeutic target in SLE.

IW1-9

Lysophosphatidic acid receptor 1 (LPA_1) is essential for the development of arthritis

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Conflict of interest: None

[Objectives] Lysophosphatidic acid (LPA) is a bioactive lipid. In the previous JCR meeting, we showed lysophosphatidic acid receptor 1 (LPA_1) is highly expressed in rheumatoid arthritis (RA) synovium, LPA_1 antagonist inhibited murine collagen-induced arthritis (CIA), and macrophage migration into the synovium. In addition, LPA_1 antagonist inhibited osteoclast formation and Th17 differentiation. In this study, we analyzed the effects of LPA_1 on arthritis using LPA_1-deficient mice. [Methods] CIA was induced in $LPA_1^{-/-}$ or wild-type (WT) mice. Migrated fluorescence labeled-$CD11b^+$ splenocytes, which were transferred into CIA, into the synovium were counted. Bone marrow cells were incubated with RANKL+M-CSF, and osteoclast formation was analyzed by TRAP staining. $CD4^+$ naïve T cells were incubated with Th1-, Th2-, or Th17-polarizing condition and Th differentiation was analyzed by FACS. [Results] LPA_1 KO mice did not develop arthritis by the collagen immunization. Infiltration of $LPA_1^{-/-}$ $CD11b^+$ cells was suppressed compared with WT. Osteoclast formation and Th17 differentiation, but not Th1 and Th2, was also inhibited in $LPA_1^{-/-}$ cells. [Conclusion] LPA-LPA_1 signaling contributes to the development of arthritis by cellular infiltration, Th17 differentiation and osteoclastogenesis.

IW1-10

Apolipoprotein E-knockout mice show an autoimmune disease

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Apolipoprotein E-knockout ($ApoE^{-/-}$) mice, atherosclerosis-prone mice, show an abnormal immune response, but the pathogenesis is not fully understood. We investigated the pathogenesis in female and male $ApoE^{-/-}$ mice. The spleens and kidneys of all $ApoE^{-/-}$ and C57BL/6 (B6) mice were weighed. The area of glomeruli in $ApoE^{-/-}$ mice were compared with those in B6 mice by H&E staining. The serum IgG level and titers of anti-nuclear antibody (ANA) and anti-double-stranded DNA (anti-dsDNA) antibody were assayed by ELISA. The expressions of IgG and C3 and macrophage infiltration were detected in glomeruli by immunostaining followed by morphometric analysis in all mice. Apoptosis of spleen tissue was evaluated by TUNEL. TLR4 level in spleen tissue was tested by immunohistochemistry and western blot analysis. Levels of MyD88, p38, phosphorylated p38 (pp38), interferon regulatory factor 3 (IRF3) and Bcl-2-associated X protein (Bax) in spleen tissue were detected by western blot analysis. We also survey the changes of serum autoantibodies, spleen weight, splenocyte apoptosis and the expressions of TLR4, MyD88, pp38, IRF3 and Bax in spleen tissue in male $ApoE^{-/-}$ mice after 4 weeks of lipopolysaccharide (LPS), toll-like receptor4 ligand, administration. $ApoE^{-/-}$ mice showed splenomegaly and significantly increased serum level of IgG and titers of ANA and anti-dsDNA antibody as compared with B6 mice. Splenocyte apoptosis and the expression of TLR4, MyD88, pp38, IRF3 and Bax in spleen tissue were significantly lower in $ApoE^{-/-}$ than B6 mice. The expression of TLR4, MyD88, IRF3, pp38, and Bax differed by sex in $ApoE^{-/-}$ spleen tissue. The down-regulation of TLR4 signal molecules induced by LPS led to decreased expression of Bax and increased serum titers of ANA and anti-dsDNA antibody. Furthermore, $ApoE^{-/-}$ mice showed significantly increased kidney weight and glomerular area and expressions of IgG, C3 and infiltration of macrophage in glomeruli as compared with B6 mice. Therefore, $ApoE^{-/-}$ mice show an autoimmune disease, the TLR4 signal pathway may participate in maintaining the balance of splenocyte apoptosis and autoantibody production in $ApoE^{-/-}$ mice.

IW1-11

Protective roles of myeloid-derived suppressor cells in autoimmune arthritis murine models through inhibiting pro-inflammatory immune response of $CD4^+$ T cells

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Conflict of interest: None

[Objectives] Myeloid-derived suppressor cells (MDSCs) have a myeloid origin and an ability to suppress T cell responses. MDSCs in cancer have been studied in detail, but the roles of MDSCs in autoimmune disease remain controversial. Here we investigate the roles of MDSCs in autoimmune arthritis using collagen-induced arthritis (CIA) mouse models. [Methods] We first determined the number of MDSCs in CIA mice by flow cytometry. Next, we cultured MDSCs isolated by magnetic cell sorting with $CD4^+$ T cells. We investigated $CD4^+$ T cell proliferation and differentiation by flow cytometry, and cytokines by ELISA. Finally, we transferred MDSCs into CIA mice and evaluated the severity of arthritis. [Results] MDSCs significantly accumulated in the spleens of CIA mice at the peak of the disease. MDSCs inhibited $CD4^+$ T cell proliferation and differentiation into Th17 cells. Moreover, MDSCs inhibited the production of IFNγ, TNFα, and IL-6, whereas MDSCs promoted IL-10 production. Adoptive transfer of MDSCs significantly decreased the severity of the disease and the number of $CD4^+$ T cells and Th17 cells in the draining lymph nodes. [Conclusion] In CIA mouse models, MDSCs suppress the progression of arthritis. These observations suggest that MDSCs could be exploited for new cell-based therapies.

IW1-12

Identification of Biomarkers in Serum of Rheumatoid Arthritis by quantitative proteomics analysis

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Objective To discover serum biomarkers of rheumatoid arthritis (RA) by quantitative proteomics analysis. **Methods** Peripheral blood Samples were collected from10 active RA patients and 10 healthy controls. Samples were pooled, respectively. Low-abundance proteins were enriched using the ProteominerTM enrichment kits. Subsequently, the enriched proteins were eluted from the column and separated on 1D SDS-PAGE. The gel bands were excised, reduced and alkylated, followed by in-gel trypsin digestion. The digestion products were labeled with the TMT 6-plex reagents according to the manufacturer's instructions. The labeled peptides were desalted by a C18 stage tip column and analyzed by LC-MS/MS with nano-LC combined with orbitrap Q Exective mass spectrometer. Three times of analysis were tried for different specimens. ELISA assay was performed in order to confirm the the differentially exepressed proteins identified by quantitative proteomics analysis. **Results** We identified the 16 differentially expressed proteins. Expression levels of Thrombospondin-1(TSP-1), Isoform 2 of Ficolin-2(FCN-2), isoform 1 of FN1 protein, Apolipoprotein E, Isoform 1 of Clusterin, Antithrombin-III et al were higher in RA patients than that in healthy controls, while Transthyretin, Angiotensinogen, paraoxonase, Isoform 1 of Alpha-1-antitrypsin, Plasminogen were lower in RA patients than those in the healthy controls. Furthremore, By ELISA assay, we found that Levels of TSP-1 and FCN-2 were significantly higher in RA patients than in healthy controls ($P<0.05$). Level of TSP-1 was correlated to number of swelling joints, DAS28 score, and rheumatoid factor($P<0.05$);.meanwhile, level of FCN-2 was correlated to number of tender joints, number of swelling joints,DAS28 score, levels of rheumatoid factor and IgM ($P<0.05$). **Conclusion**: Quantitative proteomics analysis coupled with ELISA may be useful way in screening biomarkers of autoimmune disease.

IW1-13

Elevated levels of CD4+CD25+FoxP3+ T cells in systemic sclerosis patients contribute to the secretion of IL-17 and immunosuppression dysfunction

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Background: Immune imbalance between Th17 and regulatory T cells (Treg) is a characteristic of systemic sclerosis (SSc). The functional heterogeneity and differentiation can be shown by separating Treg cells into three subsets based on the expression of $FoxP_3$ and CD45RA. **Objective:** To investigate subsets of Treg from SSc and assess their roles in the immune balance between Treg and Th17. **Methods:** PBMCs were collected from 31 SSc and 33 health controls, analyzed for the expression of CD4, CD25, CD45RA, CTLA-4, FoxP3 and IL-17 with flow cytometry. Measuring Treg suppressive capacity against proliferation of $CD4^+CD25^-$ T cells in coculture experiments. The expressions of mRNA were studied with real-time PCR. **Results:** (1) In SSc, the frequency of $CD4^+CD25^+FoxP_3^+$ Treg cells were significantly elevated (3.62±1.14 vs 1.97±0.75, $P<0.001$), the expression of CTLA-4 and $FoxP_3$ mRNA were lower in Treg cells ($P<0.05$, respectively), the immunosuppressive capacity of Treg cells were diminished ($P=0.034$). (2) In SSc, the frequency of $CD45RA^-FoxP_3^{high}$ cells (aTreg, FrII) were lower (0.25±0.16 vs 0.66±0.41, $P<0.001$), $CD45RA^-FoxP3^{lo}$ T cell (FrIII) were higher (6.23±2.29 vs 2.90±0.91, $P<0.001$), there were no difference in two groups with $CD45RA^+FoxP3^{lo}$ cells (rTreg, FrI). (3) Immunosuppressive capacity of FrII cells were greater than FrI cells ($P=0.025$) in control; but there were no difference between FrII cells and FrI cells of SSc, which were both lower than control; FrIII cells had no suppressive capacity neither in SSc nor control; in SSc, the expression of CTLA-4 and its mRNA in FrII and FrIII cells were decreased significantly; (4) The expression of IL-17 were higher in FrIII cells than FrI and FrII cells significantly in both group, but there were no difference of FrIII between these two groups; Th17 cells were increased in SSc ($P<0.001$); in SSc, $CD25^+FoxP_3^+IL17^+$cells were increased (0.075±0.032 vs 0.049±0.027, $P=0.029$), but no difference of $CD25^+FoxP3^+IL17^-$ with control; the expression of IL-17A and RORC mRNA were increased in the FrIII cells of SSc ($P<0.001$, respectively). **Conclusion:** Decreased aTreg with functional deficiency and increased $CD45RA^-FoxP_3^{lo}$ T cells were the reason of unbalance of Treg and Th17 cells in SSc.

IW1-14

Novel IL-10 induction pathway mediated by Egr-2 in IL-27-stimulated T cells

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Conflict of interest: None

IL-10 producing T cells play a role in the regulation of autoimmune diseases. IL-27 is one of the IL-12 family cytokines suppressing immune responses through induction of IL-10 production. We have previously shown that forced expression of Egr-2, a transcription factor required for T cell anergy induction, induces IL-10 and LAG-3 expression and confers regulatory activity *in vivo* on naïve $CD4^+$ T cells. Among various IL-10 inducing factors, only IL-27 induced high levels of Egr-2 and LAG-3 expression. Other

IL-12 family cytokines, such as IL-12 and IL-23 could not efficiently induce Egr-2 and LAG-3 expression. Intriguingly, IL-27 failed to induce IL-10 in Egr-2-deficient naïve $CD4^+$ T cells. Moreover, IL-27-mediated induction of Blimp-1, a transcriptional repressor important for IL-10 production in $CD4^+$ T cells, was also impaired in the absence of Egr-2. Luciferase assay and ChIP assay revealed Egr-2-mediated control of Blimp-1 expression. This Egr-2 induction by IL-27 was abrogated by STAT3-deficiency, not by STAT1-deficiency. IL-6 could also induce $Egr\text{-}2^+LAG3^+$ T cells, but IL-10 mRNA induction by IL-6 was lower than that by IL-27. These results suggest that STAT3-dependent IL-27 signal transduction through Egr-2 and Blimp-1 cascade plays an important role for IL-10 production.

IW1-15

Monoclonally expanded human CD4+ Th17 cells are phenotypically stable against direct and DC-derived cytokine-mediated modulation

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Background: Th17 cells are key players in autoimmunity. Their low freqencies in peripheral blood, as well as differences in phenotype and function between mouse and human Th17 cells pose major challenges to their investigation. We previoulsy showed Tolerogenic Dendritic Cell (TDC)-mediated Th17 contraction in polyclonal CD4+ memory T cells. Here we aimed to investigate TDC potential for modulation of Th17 plasticity at the single cell level. In order to facilitate these studies, we sought to monoclonally expand human Th17 cells, and to test potential direct and DC-mediated cytokine effects on Th17 clones. **Methods:** Enriched IL-17 positive cells were cloned in a limited dilution approach. Phenotype and vβ T cell receptor repertoire were analyzed. Clones were exposed to the following conditions: high IL-2, high IL2 + IL-23, IL-23, low IL-2 and low IL-2 + IL-23, or TDC (CD11b-ligated moDC) vs control moDC. Differential cytokine secretion (IL-21, IL-22, GM-CSF, IL-10, IFNg, IL-17) and surface markers (CD161, CCR6) were assessed by intracellular and surface staining. **Results:** Th17 clones were obtained and monoclonality verified by vβ staining. With repeated expansions most cells increased co-secretion of IFNγ while maintaining IL-17 secretion. Expansions of established clones with exogeneous IL-23 and/or varying concentrations of IL-2 did not change the Th17 phenotype. Contrary to polyclonal CD4+ memory T cells, Th17 clones exposed to TDC vs control moDC did not significanly alter frequencies of IL-21, IL-22, IL-10, GM-CSF, IFNγ-secreting Th17 cells. **Conclusions:** Human CD4+ Th17 cells can be cloned and expanded in large numbers. IL-2 and IL-23 exposure during expansion does not alter their phenotype, and TDC do not modulate the secretion of Th17 effector cytokines from these terminally differentiated effector memory cells. However, TDC restrict Th17 expansion in polyclonal populations, suggesting that regulation of Th17 effector function depends on differential expansion/contraction of individual Th17 clones rather than plastic changes at the single cell level.

IW2-1

Patients with rheumatoid arthritis have multiple falls compared to healthy individuals – The TOMORROW Study-

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Conflict of interest: None

Background: Patients with rheumatoid arthritis (RA) who have muscle weakness and stiff or painful joints might be at increased risk of falling. The present study prospectively determines the incidence of falls 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 for a period of two years in 202 patients with RA (58 years) and 202 age- and sex-matched healthy volunteers (controls, 57 years). **Results:** There is no difference in incidence of falls between RA patients (30%) and controls (27%) during two years. RA patients had significantly more frequent number of falls (2.4 times) than that of controls (1.6 times) (p=0.03). After adjusting for risk factors of falls, multiple regression analysis identified that walking times (>30 m/day) were associated with incidence of falls in RA (odds 3.12, 95%CI: 1.23-7.75 p=0.014). In RA patients, use of prednisolone (PLS) appeared to be related to number of falls after adjusting for risk factors. (PLS: β=0.188, P=0.010). **Conclusions**: In conclusion, multiple fallers in RA patients were higher than in controls during two years. In RA patients, walking times and PLS appeared to be related to falls.

IW2-2

The diagnostic performance of anti-CCP antibody in undiagnosed rheumatoid factor positive population

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Conflict of interest: None

[Objectives] To evaluate the diagnostic performance of anti-CCP antibody (ACPA) in rheumatoid factor (RF) positive population without previous diagnosis of rheumatoid arthritis (RA). [Methods] Among 105778 patients who had been checked RF as screening test in health check, we retrospectively extracted all the 7876 patients who had shown elevated RF level more than upper limit of normal at least once. After excluding patients who had already have diagnosed of RA, a retrospective review of medical records was performed to evaluate the diagnostic utility of ACPA in RF positive population. [Results] ACPA was checked in 629 RF positive patients, and 74 patients showed ACPA positivity. The diagnosis of RA was made significantly frequent in ACPA positive group (35.1%) than in ACPA negative group (3.4%, p<0.001). The sensitivity and specificity of ACPA in this population were 57.8% and 90.2%, respectively. [Conclusion] ACPA showed high specificity for diagnosing RA in RF positive population. The combination of RF and ACPA screening in health check is useful for detecting undiagnosed RA.

IW2-3

Does anti-cyclic citrullinated peptide (CCP) antibody-negative rheumatoid arthritis (RA) become anti-CCP positive RA?

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Conflict of interest: None

[Objectives] The sensitivity of anti-CCP antibody (ACPA) in early RA has been reported to be as low as 50%, whereas that in

established RA is ~80%. The discrepancy of these figures is believed to be explained by the seroconversion from ACPA(-) RA to ACPA(+) RA, but we felt that the seroconversion of ACPA was much low in the real world. Therefore, we investigated the precise proportion of seroconversion retrospectively. [Methods] The ACPA(-) RA patients (defined by the patients taking anti-rheumatic drugs) who were measured ACPA more than once with the interval of 3 months or longer were investigated the percentage of seroconversion of ACPA. [Results] The 241 patients (17.1%) out of 1,412 RA cases were negative for ACPA. In the 120 cases of ACPA(-) RA whose ACPA were measured more than once, only 6 patients (5.0%) showed seroconversion of ACPA. All the 6 cases were RF positive and had bone erosions by X-ray. [Conclusion] The proportion of conversion from ACPA(-) to ACPA(+) RA was ~5%. This result is similar to the previous report in an early arthritis cohort in Europe. These results imply that the low percentage of ACPA in early RA patients is not mainly due to that ACPA has not developed yet but rather due to that ACPA(-) RA contains non-RA arthritides.

IW2-4

Automated Breast Volume Scanner (ABVS), a new automated ultrasonic device, is useful to examine joint injury in patients with rheumatoid arthritis

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Conflict of interest: None

[Objectives] ABVS is an ultrasonic device to be developed for the automated scanning for mammary glands. We have tried to explore the clinical application of ABVS toward the synovial lesion in RA patients. [Methods] 13 active RA patients of mean 53 y.o., whose mean disease duration 24 months and DAS28 6.02, were recruited. We have examined in total 130 MCP joints as well as 26 wrist joints at dorsal sites by both ABVS and conventional US. ABVS was scanned in a water tank. Presence of synovial hypertrophy (SH) and bone erosion (BE) by gray-scale were examined by both methods, and the association of both methods was calculated by kappa coefficient. [Results] The scanning time of ABVS was 2 min per patient. ABVS detected SH in 23 MCP joints and 20 wrist joints whereas conventional US detected SH in 18 MCP joints and 20 wrist joints. Kappa coefficient of SH was 0.80 in MCP joints and 1.00 in wrist joints, respectively. ABVS detected BE in 8 MCP joints and 12 wrist joints whereas conventional US detected BE in 5 MCP joints and 11 wrist joints. Kappa coefficient of bone erosion was 0.76 in MCP joints and 0.92 in wrist joints, respectively. [Conclusion] Present data have shown a substantial agreement of ABVS with conventional US to find SH and BE of wrist and finger joints in patients with RA.

IW2-5

Safety of tocilizumab and TNF inhibitors in patients with rheumatoid arthritis in clinical practice: analyses from the REAL database

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Background and Objective: Clinical trials, meta-analyses and cohort studies have shown similar therapeutic benefits of tocilizumab (TCZ) and tumor necrosis factor inhibitors (TNFI) for patients with rheumatoid arthritis (RA). To evaluate benefit-risk balance of these biologicals in clinical practice, we compared safety of TCZ and TNFI in a prospective cohort. **Methods:** Patients with RA starting TCZ [TCZ group, n=302, 238.5 patient-years (PY)] or TNFI [TNFI group, n=304, 241.4 PY] from 2008 to 2011 in the REAL database were included. We assessed types and incidence rates of serious adverse events (SAEs) and serious infections (SIs) during first year of the treatment. **Results:** In the TCZ group, patients had longer disease duration, higher frequency of renal diseases and concomitant corticosteroid use compared with the TNFI group. The incidence rates (/100PY) of SAEs and SIs in the TCZ group were higher than those in the TNFI group (SAEs, 20.1 vs. 14.1; SIs, 10.1 vs. 2.9). The incidence rate of non-respiratory infection, but not for respiratory infection, was conspicuously higher in the TCZ group compared with the TNFI group (7.1 vs. 1.7). However, after adjusting for confounding factors using the Cox proportional hazard analysis, treatment with TCZ was not associated with higher risk for SAEs [hazard ratio (HR) 1.2, 95% CI 0.7-2.1] or SIs (HR 2.2, 95% CI 0.9-5.4). **Conclusions:** TCZ was prescribed for RA patients with a higher risk for SAE, but the adjusted risks for SAEs and SIs were not significantly different between TCZ and TNFI treatment.

IW2-6

What is the Right Dose to Start Methotrexate (7.5 or 15mg) in Rheumatoid Arthritis?

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Background: Recent recommendations have suggested higher starting doses of methotrexate- 15 mg/week in rheumatoid arthritis. However, studies comparing conventional (7.5mg) and newer (15mg) starting dose limited. Methods: Randomized controlled trial included 100 rheumatoid arthritis patients (1987 ACR), having active disease (‘Disease activity score 28 joints 3 variables’ DAS28-3v≥ 5.1) and not on methotrexate ≥ 3 months. Patients randomized to two groups – starting methotrexate at 7.5mg or 15 mg/week. Similar folic acid dose (10 mg/week) given. Methotrexate escalated by 2.5 mg every 2 weeks; patients assessed 4 weekly by assessor (blinded) to assess disease activity (DAS28-3v), minor adverse effects (symptoms) and major adverse effects (cytopenias or transaminitis-). Analysis by intention to treat. Difference in disease activity. (Trial Reg# NCT01404429) Results: Patients in the two groups - 7.5 mg and 15 mg had similar age (44.5±10.3, 42.8±11.2 yrs, p=0.4), gender (F:M=36:11, 42:11, p=0.4), disease duration (4.8±4.8, 4.7±4.5 yrs, 0.9), disease activity (DAS28-3v=6.2±0.7, 6.2±0.8, p=0.9) and HAQ (1.3,1.3,p=0.9). In the 7.5 and 15 mg groups, 38 and 46 patients completed study, reaching final methotrexate dose of 19.3±1.8 mg and 24.3±2.0 mg per week respectively. Dropout rate was similar [9 (19.1%), 7 (13.2%), p=0.18]. There was a significant reduction in disease activity in

both groups at 12 weeks (p<0.001). There was no difference in DAS28-3v between the two groups at 4, 8 or 12 weeks, nor in HAQ at 12 weeks (1.1,0.9,p=0.4). No difference in 7.5 and 15mg groups in episodes of cytopenias (1,2, p=0.9) or transaminitis (6,7, p=0.8) or pneumonitis (0,0). However, minor adverse effects lower in 7.5mg compared to 15mg group (Relative Risk=0.58, 95%CI: 0.36-0.95). Common were nausea (more in 15mg), loss of appetite, fatigue and uneasiness. Conclusions: Starting treatment with either 7.5 mg or 15 mg per week of methotrexate followed by similar fast escalation (5mg/month) is equivalent in control of disease activity at 12 weeks. Although, no difference in transaminitis or cytopenia, higher minor adverse effects (symptoms), especially nausea in 15mg group.

IW2-7

Reduction of plasma IL-6 by methotrexate in patients with early rheumatoid arthritis: a potential biomarker for radiographic progression

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Conflict of interest: None

[Objective] To determine the effect of methotrexate (MTX) on plasma cytokines and to investigate their associations with radiographic responses in patients with early rheumatoid arthritis (RA) [Patients] RA patients in prospective cohort of newly diagnosed RA of our hospital and treated only with MTX. [Method] Plasma level of TNFα and IL-6 was measured before the treatment and 1 year later. Patients who used biological agents were excluded. [Result] Forty-two patients were included in this study. The median age was 56 years and 35 (83%) patients were female. The median disease duration was 3.5 months. Thirty-one (74%) patients were anti-CCP antibody-positive. DAS28-ESR and plasma IL-6 decreased significantly (p<0.01 and p<0.05, respectively) after MTX treatment, but plasma TNF-α did not. Radiographic progression was significantly correlated with DAS28-ESR and plasma IL-6 levels but not with TNF-α after MTX treatment. Patients with plasma IL-6 level above 4.03 pg/ml showed clinically relevant radiographic progression with a sensitivity of 89% and a specificity of 88%. [Discussion] In this early RA cohort, we demonstrated a significant reduction of plasma IL-6, but not TNF-α, during MTX treatment. The post-treatment IL-6 level was a strong indicator of radiographic progression.

IW2-8

The strategy after discontinuation of infliximab after attaining remission in patients with rheumatoid arthritis

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Conflict of interest: None

BACKGROUND: After achieving remission, discontinuation of Infliximab may become an important issue from Japanese study such as RRR in patients with established rheumatoid arthritis (RA). But, the therapeutic system is not established. OBJECTIVE: To analyse disease activity, joint destruction and another serological factors during the discontinuation and to built the therapeutic system after discontinuation of infliximab. METHOD: 100 patients with RA who had received IFX treatment, and whose Disease Activity Score, including a 28-joint count (DAS28) was <2.6 (remission) for at least 24 weeks, were studied. RESULTS: 69.3% attained bio-free remission and 30.7% do not attained at 1 year after discontinuing infliximab, and there were significant difference between delta mTSS and the rate of structural remission. RF and delta mTSS increased significantly at 2 year after discontinuing infliximab. Delta RF (2y-BL) correlated with delta RF (1y-BL) significantly. Delta RF (1y-BL) decreased significantly at bio-free remission group. BL-RF negative group or BL-RF positive group of lower delta RF attained lower disease activity and higher rate of remission. CONCLUSION: RF and mTSS are important factors after discontinuation of infliximab.

IW2-9

Presence of Peripheral Arthritis Prevents Radiographic Spinal Damage Progression in Ankylosing Spondylitis: Observation Study of Korean spondyloArthropathy Registry (OSKAR) Study over 5 years

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Objective: To determine whether presence of peripheral arthritis can affect the progression of structural damage in patients with ankylosing spondylitis (AS). **Methods:** A total of 915 patients with AS from the Observation Study of Korean spondyloArthropathy Registry (OSKAR) cohort were enrolled for this analysis. We used a two-step approach to explore the relationships between the peripheral arthritis and the progression of spinal structural damage in AS. First, all OSKAR data were analyzed in relation to the history of peripheral arthritis on cross-sectional survey. Second, we retrospectively analyzed the radiographic spinal progression for 5 years according to the presence or absence of peripheral arthritis. The modified Stoke AS Spinal Score (mSASSS) were examined by two experienced radiologists to validate the results. The collection of the clinical parameters was conducted to investigate the associations between clinical factors and the radiographic progression. **Results:** The agreement between the two readers regarding mSASSS was very good: ICC coefficient 0.75 (95% CI 0.61-0.82) and 0.71 (95% CI 0.58-0.82) at each time. On cross-sectional survey, in spite of adjusting for multiple comparisons by Bonferroni correction, the patients with history of peripheral arthritis had fewer mSASSS unit than those without history of peripheral arthritis (19.56±1.06 vs 22.67±0.81, p=0.005). In a retrospective analysis over 5 years, the mean progression of mSASSS in patients with peripheral arthritis was 3.26±0.58 units, while that of mSASSS in patients without peripheral arthritis was 4.97±0.44 units (p=0.024). **Conclusion**: The patients with the peripheral arthritis had slower radiographic spinal damage progression than those without peripheral arthritis.

IW2-10

Examination of the cytokine profile of the cerebrospinal fluid in Neuropsychiatric systemic lupus erythematosus

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Conflict of interest: None

[Background] Neuropsychiatric systemic lupus erythematosus (NPSLE) is serious complications as with lupus nephritis in systemic lupus erythematosus (SLE). [Objectives] We examined a cytokine profile in a cerebrospinal fluid (CSF) of NPSLE and the useful marker for the diagnosis. [Methods] We used the CSF of multiple sclerosis (MS) and the optic nerve myelitis (NMO) patient as a disease control group. We examined 27 kinds of cytokine, chemokines, growth factor with NPSLE group (N=27), MS group (N=10) and NMO group (N=10) patient using Bio-Plex Pro Assays. [Results] SELENA-SLEDAI score was 13.3±5.86. Anti ds-DNA antibody was 23.3±58.6 U/ml. The percentage of anti phospholipid antibody syndrome, anti ribosomal P antibody-positive and abnormality of brain MRI are 4/27 (14.8%), 5/27 (18.5%) and 9/27 (33.3%), respectively. The concentration of Basic FGF, IL-1ra, IL-5, IL-7, IL-9, IL-15 and IL -17 were significantly higher in comparison with other two groups in NPSLE group. According to multivariate analysis, the protein levels of IL-5 ($p<0.036$), IL-9 ($p<0.0005$), IL-15 (<p0.0065) and IL-17 ($p<0.0336$) were significantly correlated with IL-6. [Conclusion] The diagnosis of NPSLE would be enabled by examining various kinds of cytokine profiles and contribute for elucidation of its mechanism.

IW2-11

The Increased Risk of Acute Myocardial Infraction in Patients with Systemic Lupus Erythematosus: A Nationwide Cohort Study

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Background: The relationship between systemic lupus erythematosus (SLE) and risk of myocardial infarction (MI) was not completely understood. This study evaluates the risk of MI among patients with SLE in a longitudinal nationwide population-based cohort. **Methods:** We identified 1207 adults newly diagnosed with SLE in 2000-2003 from the Taiwan National Health Insurance Research Database. Comparison group consisted of 9656 adults without SLE randomly selected from the same dataset, frequency matched by age and sex with a case-control ratio=8. Events of MI from 2000-2008 were ascertained from medical claims (International Classification of Diseases, Ninth Revision, Clinical Modification, ICD-9-CM, codes 410). Multivariate adjusted hazard ratios (HRs) and 95% confidence intervals (CIs) were estimated for potential associated factors including SLE, age, sex, low-income status, urbanization, diabetes, hypertension, hyperlipidemia, renal dialysis, liver cirrhosis, mental disorders, and stroke. **Results:** During the follow-up period, there were 52 newly diagnosed MI cases. The incidences of MI for SLE cohort and non-SLE cohort were 0.49 and 2.10 per 1000 person-years, respectively. Compared with non-SLE cohort, SLE group were more likely to develop MI with an adjusted HR of 4.70 (95% CI 2.58-8.55). For males, the adjusted HR of MI associated with SLE was as high as 6.19 (95% CI 2.22-17.3). **Conclusion:** Patients with SLE were more likely to have higher risk of MI compared with non-SLE people and the risk seemed more significant in males.

IW2-12

Characterisation of the EULAR Scleroderma Trials and Research (EUSTAR) group database: an analysis of more than 9,000 scleroderma patients

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[Objectives] As systemic sclerosis (SSc) is a rare rheumatic disease, only multicenter collaboration is able to foster disease-related research. EUSTAR, founded in 2004, developed a Minimal Essential Data Set to collect data on SSc patients based on yearly follow-ups. [Methods] To reveal the profile of the EUSTAR cohort, baseline visit data from all SSc patients registered in the database were analysed using descriptive statistics. In 2008, the databank has been reorganized to include new items such as different treatment strategies. [Results] 9165 patients have been registered so far and 7655 fulfilled the preliminary ACR diagnostic criteria. The main disease characteristics like Raynaud's phenomenon (95.4%), antinuclear antibodies (92.9%, in 35.7% against centromeres, in 33.1% against topoisomerase I), and digital ulcers (32.2%) were frequent at baseline. The foremost immunosuppressant therapies included corticosteroids (45.3%), cyclophosphamide (15.9%), and methotrexate (13.7%) and were prescribed significantly more frequent in the diffuse subset. [Conclusion] Based on the collective work of 174 centres worldwide, the EUSTAR database sets a unique standard with respect to a rheumatic orphan disease and provides a great quantity of information on the clinical face of SSc.

IW2-13

Evaluation of Non-Invasive tests as an Early Diagnostic Screen for Pulmonary Arterial Hypertension in Systemic Sclerosis Patients

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Background: Pulmonary arterial hypertension (PAH) affects 5-15% of all systemic sclerosis (SSc) patients and is associated with up to 30% mortality at 3 years. Early diagnosis seems mandatory to improve the outcomes of this dreadful complication. We examined two cohorts: (1) The Pulmonary Hypertension Assessment and Recognition Outcomes in Scleroderma (PHAROS); a prospective cohort of SSc patients at risk for PAH or with incident PAH and (2) A subset of a European cohort; compiled from the Paris Cochin Rheumatology cohort evaluating SSc patients suspected of having PAH. **Objective**: To evaluate various routinely collected clinical parameters and determine their predictive value alone and in combination, as an early, non-invasive diagnostic screen for PAH (WHO Group I) in SSc patients. **Methods**: Non-invasive tests including, patient characteristics, systolic pulmonary arterial pressure (sPAP) on echocardiogram (TTE), FVC/DLCO ratio, and DLCO percent predicted were evaluated alone and in combination for their ability to diagnose PAH in SSc patients as compared to right heart catheterization (RHC), the gold standard for diagnosis. **Results:** In the PHAROS cohort (N=237), 59 had PAH. A sPAP threshold of 35-50mmHg missed 7-31% of patients with RHC diagnosed PAH. Of the missed patients, 50-70% (N=2-13) were captured by DLCO <60% or FVC/DLCO ≥ 1.6. In the Euro cohort (N=141), 10 had PAH. A sPAP threshold of 35-50mmHg missed 0-70% (N=0-7) patients with RHC diagnosed PAH. Of the patients missed 0-68% (N=0-6) were captured by DLCO <60% or FVC/DLCO ≥ 1.6. In a multivariant logistic regression model (PAH vs No-PH) of the combined data, sPAP>40mmHg (OR 8.1 [95%CI 2.9,25.1]) was the only significant determinant after adjusting for age, gender, disease duration, FVC/DLCO≥ 1.6, anti-centromere antibody and anti-SCL-70 antibody. **Conclusion**: Our results suggest that combining a TTE with PFT complement each other for

diagnosis of PAH.

IW2-14

Color Doppler Ultrasonography: An Alternative to CT/MR Angiography for Identifying Large Vessel Involvement in Giant Cell Arteritis?

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Introduction/Aim: Large vessel involvement has been reported to be present in 20-50% of patients with giant cell arteritis (GCA). Computed tomography (CT) and magnetic resonance (MR) angiography are used for assessment of large vessel involvement in patients with GCA. Our aim was to compare color Doppler ultrasonography (CDUS) to CT/ MR angiography for identifying large vessel involvement in patients with GCA at the time of initial evaluation. **Methods:** Consecutive GCA patients with large vessel involvement assessed by CDUS underwent CT/MR angiography between January 2010 and May 2012. The aorta and supraaortic vessels were assessed by CT/MR angiography, while the carotid and axillary arteries were assessed by CDUS. The patients were diagnosed by CDUS with large vessel vasculitis (LVV) when intima-media complex thickness was homogenous and more than 1.5 mm in the carotid artery and more than 1 mm in the axillary artery. **Results:** A total of 13 GCA patients (7 females, 6 males, mean age 70 years) were identified with LVV using CDUS. In these 13 patients aortic involvement was observed in 5 patients (38%) by CT/MR angiography. In all of these 5 patients, involvement of axillary arteries (4 patients) or carotid arteries (3 patients) were found by CDUS. In the other 8 patients axillary arteritis was visible on CDUS whereas only 2 these patients revealed large vessel vasculitis on CT/MR. Interestingly, inflammation in large vessels was retrospectively identified by CT/MR angiography in 6 of 13 patients and this after re-evaluating the images after the positive CDUS examination. **Conclusion:** CDUS seems to be a valuable tool for assessment of large vessel vasculitis. The data from our pilot study suggest that CDUS is comparable and even better than CT/MR angiography to detect large vessel involvement in GCA. In the future CDUS may become the gold standard for first line evaluation of large vessel involvement. However, further validation of the method is warranted.

IW2-15

The diagnostic utility of line immunoassay for patients with collagen disease

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Conflict of interest: None

[Objectives] To evaluate the diagnostic utility of the line immunoassay (LIA) in patients with collagen disease. [Methods] Thirty seven patients performed myositis- and SSc-LIA tests at Okayama University Hospital in 2012 were include in this study. The diagnostic performance of myositis-LIA was evaluated using Bohan's criteria as diagnostic golden standard. We also investigated the relationship between the initial clinical symptoms and each LIA results. [Results] Among 37 patients, 24 were women and the ages of onset were 60 (30-80) including 11 vasculitis, 7 PM/DM, 5 RA, 4 SLE, and 1 SSc patients. The sensitivity of anti-Jo-1 antibody was 43% in both ELISA and LIA, and the specificity was 100% for the diagnosis of PM/DM. The sensitivity of simultaneous use of anti-Jo-1, ARS, SRP, and Mi antibodies was 100%, and the specificity was 70%. Furthermore, the sensitivity of anti-PM75, PM100, and Ku antibodies in addition to the above antibodies was 100%, and the specificity was 47%. In all patients, we found that anti-PL-7 antibody is related to pulmonary hypertension, and anti-PM100, NOR90, and RP11 antibodies are related to interstitial pneumonia. [Conclusion] The combination of LIA for myositis-associated antibodies may be useful for the diagnosis of myositis.

IW2-16

Assessment of risks for pulmonary infection in patients receiving immunosuppressive treatment for rheumatic diseases: A report from a large-scale prospective cohort study (PREVENT study)

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Conflict of interest: Yes

[Objectives] To identify risk factors for pulmonary infection (PI) in patients receiving immunosuppressive treatment for rheumatic diseases. [Methods] We prospectively observed 765 inpatients who started immunosuppressive treatment for rheumatic diseases. We collected clinical data, usage of drugs and occurrence of PI for 12 months. [Results] During the observation period, 32 patients (4.2%) died and 66 (8.6%) patients were lost-to-follow up. Patients with PI (n=61, 8%) had a significantly worse accumulated survival rate than patients without. A COX hazard model using baseline data showed that age ≥65 years-old (HR: 3.9 [95%CI 2.2-6.9]), Brinkman index ≥400 (2.7 [1.4-5.3]), serum Cr (1.2 [1.0-1.4] per 1.0mg/dl increase), maximum prednisolone (PSL) dose during the first 2 weeks of treatment (3.2 [1.3-7.8] per 1.0 mg/kg/day increase) were significantly associated with PI. A nested case-control study with logistic regression analysis revealed that maximum PSL dose within 2 weeks before PI (OR: 4.9 [1.4-17.1] per 1.0mg/dl increase) was significantly associated with the events, while immunosuppressants and biologics were not. [Conclusion] Rheumatologists should assess these risk factors before and during immunosuppressive treatment and take appropriate measures to prevent PI.

Poster Session

P1-001

Excessive daytime sleepiness in patients with rheumatoid arthritis

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Conflict of interest: None

[Objectives] To investigate sleep disturbance in RA patients, we analyzed the excessive daytime sleepiness (EDS) that is one of the symptoms of sleep disturbance. [Methods] The subjects were participants of IORRA Study conducted in April 2010. We assessed EDS by using the Japanese version of the Epworth Sleepiness Scale (ESS) which classify EDS with score ≥11. The associated factors for presence of EDS were cross-sectionally analyzed in RA patient. [Results] In this study, 5097 RA patients (female 84.0%, age 58.9±13.0 years, disease duration 13.2±9.8 years, BMI 21.4±3.1kg/m^2, DAS28 3.12±1.11, ESS score 6.21±4.19) were included. EDS was observed in 14.3% of them. The age of patients with EDS was significantly younger (54.4±14.5 vs 59.6±12.7, $p<0.01$), disease duration was shorter(13.3±9.7 vs 12.7±10.2, $p<0.05$), health-related quality of life (HRQL) was lower (EQ-5D 0.73±0.18 vs 0.78±0.17, $p<0.01$), and physical disability was higher (J-HAQ score 0.78±0.79 vs 0.65±0.73, $p<0.01$) than those without EDS. The associated factors for presence of EDS were age, J-HAQ and EQ-5D. [Conclusion] The prevalence of EDS and association with decreased HRQL and physical disability to EDS in RA patients were shown by using IORRA cohort.

P1-002

The association between body mass index and disease activity in rheumatoid arthritis

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Conflict of interest: None

[Objectives] To investigate the influences of BMI on disease activity in patients with RA using data of NinJa (National Database of Rheumatic Diseases by iR-net in Japan) in 2011. [Methods] A total of 7,366 RA patients (5,920 women and 1,446 men) were included in this analyses. They were categorized by BMI as follows; Group A (underweight) : <18.5 kg/m2, Group B (normal) : 18.5-24.9 kg/m2, Group C (overweight) : 25.0-29.9 kg/m2, Group D (obese) : ≧30.0 kg/m2, and their composite disease activity indices (DAS28-ESR, DAS28-CRP, SDAI, CDAI), their components and other markers (TJC, SJC, PtGA, PtPain, PhGA, mHAQ, CRP, ESR) were compared. [Results] The mean composite disease activity indices were significantly highest in Group A in both women and men. Similarly, the mean their components except CRP were significantly highest in Group A. Chi-square-test revealed significantly higher odds of more than middle disease activity in BMI<18.5 group (Group A) than in BMI≧18.5 group (Group B,C,D). Multiple logistic regression revealed underweight was associated with high disease activity independently of disease duration. [Conclusion] Being underweight appears to be associated with high disease activity and resistance to treatment in rheumatoid arthritis.

P1-003

The causes of death in deceased patients with RA using NinJa 2011 cohort

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Conflict of interest: Yes

[Objectives] The purpose of the present stud y is to evaluate the age at death and the cause of death in patients with rheumatoid arthritis (RA) in 2011 [Methods] 91 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 73.3 years old.The major cause of death in deceased patients was infection in 28 patients involving in pneumonia in 17 patients. Next was malignancy in 14 patients, cardiovascular disease and intestinal pneumonia in 10 patients. [Conclusion] The major causes of death were still infection involving in pneumonia.

P1-004

Predictive factors of rheumatoid patients to undergo total knee arthroplasty

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Conflict of interest: None

We analyzed the data of NinJa (National Database of Rheumatic Diseases by iR-net in Japan) to clarify the predictive factors of RA patients to undergo total knee arthroplasty (TKA). The data of 2,996 RA patients who were enrolled in NinJa in fiscal year 2003 were subjected for analysis. The data from fiscal year 2003 to 2010 were collected. The data of 287 patients who underwent TKA (TKA(+)) during the observation period and 2,709 patiens who did not (TKA(-)) were compared. Duration of disease, mHAQ, DAS28, patient VAS, CDAI, SDAI, Steinbrocker stage, and Steinbrocker class were significantly higher in TKA(+) group than in TKA(-) group. On the other hand, no significant difference was observed in age, gender, and the history of joint replacement surgeries. There was no significant difference in the yearly change of DAS28 or pain VAS from 2003 to 2004, but estimated yearly progression of mHAQ was significantly higher in TKA(+) group. Number of patients who started using MTX and/or biologics during the observation period were significantly higher in TKA(+) group. Through stepwise elimination procedure using Cox's proportional-hazards regression model, mHAQ, DAS28, and the introduction of biologics during the observation period were extracted as predictive factors.

P1-005

Orthopedic surgery for RA in NinJa report 2011

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Conflict of interest: None

[Objectives] To analyze and report on surgical procedures on bones, joints, and tendons performed on patients with rheumatoid arthritis (RA surgery) in 2011 based on a rheumatoid arthritis database developed by iR-net (NinJa). [Methods] Data such as the type and frequency of surgery were investigated for a total of 10,368 patients registered in 2011 (8,375 women, 1,993 men), and changes since 2003 were also analyzed. [Results] In 2011, RA surgery was performed 390 times in 329 patients (3.8%/3.2% of 10,368 patients). The percentage of surgeries decreased from 8.5% in 2003. The types of RA surgery performed in 2011 were (times performed/total number of patients): joint replacement (2.04%), synovectomy (0.22%), joint arthroplasty (0.79%), arthrodesis (0.22%), and tendon reconstruction (0.13%). The frequency of surgery tended to decrease, particularly for joint replacement. Drug use tended to increase, with 60.6% of patients receiving methotrexate (MTX) and 22.6% receiving a biological agent. The proportion of patients undergoing surgery decreased to 4.7% from 15% in 2006 among patients primarily using a biological agent, and to 3.8% from 9.5% in 2003 among patients primarily using MTX. [Conclusion] Surgery is being performed less frequently as more drugs are developed.

P1-006

Analysis of parameters of the disease activity, functional measures, and patient-oriented evaluation of patients with rheumatoid arthritis undergoing surgery by using NinJa (National Database of Rheumatic Diseases by iR-net in Japan)

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Conflict of interest: None

We investigated the clinical data of patients undergoing surgery except joint arthroplasty from April 2011 through March 2012 by using NinJa (National Database of Rheumatic Diseases by iR-net in Japan) to examine the background of these patients and explore the effectiveness of these surgical procedures on the disease activity (DAS), functional measures (mHAQ), and patient-oriented evaluation (VAS). For this period, 177 patients underwent surgery, including ankle, foot, wrist, fingers, and spines. After surgery, the DAS score was 3.79 (3.87 before surgery), mHAQ was 0.92 (0.89), patient pain VAS was 3.73 (3.90), and patient global VAS was 3.89 (4.26). Moreover, in the analysis of each site of surgery, it was demonstrated that surgical treatment of foot could improve several functional measures of mHAQ. These findings suggested that it could be important to combine these parameters and joint-specific measures for evaluation after surgery.

P1-007

Do the Availability of Rheumatologists and the Cost Affect the Rate of Biologics and Methotrexate Use Among Rheumatoid Arthritis Patients?

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Conflict of interest: None

[Objectives] We assess whether use of methotrexate (MTX) and Biologics are correlated with patients' average income or number of rheumatologist. [Methods] The estimated number of RA patients in each prefecture was calculated based on population in November 2011. The data for number of patients using biologics and MTX were obtained. The number of rheumatologist in each prefecture, and the average income in each prefecture were also collected. The number of rheumatologist per population and the number of rheumatologists per square kilometer were used as a surrogate number for availability of rheumatologist. [Results] Methotrexate was prescribed between 22.2% and 48.8% of patients with RA in each prefecture. The biologics were given between 10.0% and 28.3%. The average income per year varies from 3245000yen-5997000yen in each prefecture. It shows no significant correlation between the rate of biologics use and of MTX use and the average income. However, it shows statistically significant weakly positive correlation between the rate of biologics use among RA patients and the number of rheumatologist per population ($R=0.330$, $P<0.05$). [Conclusion] The availability of rheumatologists is a more important factor for adequate use of biologics than the economic burden.

P1-008

The differences of patients' background and therapies among-hospitals (the Second analysis with data from NinJa 2011)

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Conflict of interest: None

[Objectives] We aim to analyze the variances of rheumatoid arthritis (RA) patients' background and clinical data among hospitals registered. [Methods] We divided hospitals by their scale using the number of RA patients registered to two groups, the large-scale (LSG) and the small-scale groups (SSG) and compared those two groups. Data from RA patients registered in the large cohort database (NinJa) in 2011 was analyzed. These data included age, sex, disease duration, disease activity, mHAQ and stage and so on. [Results] 10,368 patents' data were registered to NinJa 2011. LSG (the number more than 500 patients) showed higher age, longer disease duration, higher DAS28-ESR, lower SDAI and CDAI, higher mHAQ, more tender joint counts, less swollen joint counts, higher patient's assessment of pain by visual analog scale (painVAS), lower patient's (PtVAS) and physician's (PhVAS) global assessments of disease activity compared with SSG (less than 500). And also LSG showed a higher progression stage of joint damage. It is

considered that there are more patients with longer disease duration, more progressive joint damage and function. [Conclusion] Patients in LSG are considered to be associated with longer disease duration, more joint destruction and impairment.

P1-009

Studies on the production of cytokines from autoantibody-inducing CD4 T cell which is key for the cause of SLE

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Conflict of interest: None

[Objectives] We found that SLE was induced by repeatedly immunizing the mice with any antigen and have then proposed a novel 'self-organized criticality theory' that explains the cause of SLE. The autoreactive lymphocytes, which we name autoantibody-inducing CD4 T (*ai*CD4 T) cells are newly generated *via* T cell receptor (TCR) revision at periphery. They not only stimulated B cells to generate varieties of autoantibodies but also helped final differentiation of CD8 T cell into cytotoxic T lymphocyte (CTL) to induce lupus tissue injuries. Here we examine the production of cytokines from *ai*CD4 T cell. **[Methods]** BALB/c mice were repeatedly immunized with keyhole limpet hemocyanin (KLH) to induce autoantibodies. Splenic CD4 T cell was stimulated with anti-CD3 and anti-CD28 antibodies, and cytokines in the culture supernatant were detected by using ELISA. **[Results]** The production of IL-2 and IL-6 from CD4 T cell of the mice immunized 12x with KLH was significantly increased as compared to that of control mice immunized with PBS. IL-4 was also increased after 12x immunization with KLH, however, it was not statistically significant compared with controls. **[Conclusion]** The pattern of cytokines producing from *ai*CD4 T cell differs from normal CD4 T cell.

P1-010

CCR4^{+}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 here tried to assign the CD number on *ai*CD4 T cell. **[Methods]** BALB/c mice were repeatedly immunized with keyhole limpet hemocyanin (KLH), ovalbumin (OVA) or staphylococcal enterotoxin B (SEB). To assign CD number on the *ai*CD4 T cell, expression of effector/ memory markers on CD4 T cell were studied. These CD4 T cells were further isolated referring to CD45RB, CD27 and CD122, and were adoptively transferred into naïve recipients. Autoantibodies were measured in the recipients 2 weeks after transfer. Further, we performed microarray analysis to investigate gene expression of CD45RB^{lo}122^{lo} CD4 T cell in mice immunized 12x with OVA. **[Results]** We found that CD45RB^{lo}, CD27^{lo} and CD122^{hi} CD4 T cells were significantly expanded after repeated immunization with any antigens. We also noted that the transfer of CD45RB^{lo}122^{lo} CD4 T cells induced RF and anti-dsDNA antibodies in the recipient mice. Further, we found that gene and protein expressions of chemokine (C-C motif) receptor 4 (Ccr4) were increased in this subset. **[Conclusion]** The *ai*CD4 T cell that induces SLE belongs to CCR4^{+}CD45RB^{lo}122^{lo} CD4 T subpopulation.

P1-011

Overexpression of annexin A1 on CD4^{+}T cells in GPI induced arthritis

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Conflict of interest: None

[Objectives] In glucose-6-phosphate isomerase (GPI)-induced arthritis (GIA), Th1 and Th17 cells have a crucial role. The aims of this study were to explore highly expressed molecules on CD4^{+}T cells, and to characterize them in the generation of GIA. [Methods] 1) The mRNA expression profile of splenic CD4^{+}T cells was examined by DNA microarray in DBA/1 (arthritis susceptible) and C57BL/6 (arthritis resistant) after GPI immunization (day7). 2) Fluctuated expression of annexin A1 (ANX1) mRNA on splenic CD4^{+}T cells was analyzed in GIA. 3) The expression of ANX1 proteins in spleen was investigated by immunofluorescence. 4) Naïve CD4^{+}T cells were stimulated with anti-CD3/CD28 Ab in the absence or presence of recombinant ANX1 (rANX1), and the production of IFNγ and IL-17 was measured by ELISA. [Results] 1) Among the arrayed genes, the expression of ANX1 was the highest 2) The expression of ANX1 on splenic CD4^{+}T cells was significantly upregulated on day7. 3) ANX1 protein was mainly localized in CD4^{+}T cells in spleen. 4) The production of IFNγ and IL-17 was increased by rANX1 stimulation *in vitro*. [Conclusion] Overexpression of ANX1 was detected on CD4^{+}T cells, might be involved in the generation of Th1 and Th17 in GIA.

P1-012

The role of S1P3 receptor signaling in the bleomycin-induced pulmonary fibrodid model

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Conflict of interest: None

[Objectives] To clarify the role of S1P3 receptor signaling in the pathogenesis of pulmonary inflammation and fibrosis. [Methods] Mice were anesthetized with ether and recieved bleomycin intratracheally.Both lungs were excised on the 14th or 42nd day after administration.A paraffin section of lung,stained either with H&E or Masson&trichrome,was systematically scanned in a microscope. We observed the body weight of these mice. Bronchoalveolar lavage fluid (BALF) was collected and analyzed for total and differeftial leukocyte counts on 7th day.Activated MCP-1,TGF-b1,and CTGF concentrations in BALF were determined by ELISA. [Results] In acute phase,S1P3 KO mice exhibited attenuation of body weight loss and less inflammation histologically.In chronic phase,the pulmonary fibrosis in KO mice was also less than WT mice.S1P3 KO mice demonstrated 30% reduction of total cell count of BALF compared with WT mice,however differential cell counts showed a similar profile each other.The CTGF concentration in BALF was significantly decreased in S1P3 KO mice compared with WT mice.No significant differences were recognized for TGF-b1 and MCP-1 levels between WT and KO mice. [Conclusion] These results indicate that S1P3 receptor signaling plays an important role in the pulmonary inflammation and fibrosis.

P1-013

Activation of invariant NKT cells with glycolipid ligand α-galactosylceramide ameliorates glucose-6-phosphate isomerase peptide-induced arthritis

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Conflict of interest: None

[Objectives] We investigated whether α-GalCer, a potent ligand of invariant natural killer T (NKT) cells, has a protective effect on Glucose-6-phosphate isomerase (GPI) peptide-induced arthritis. [Methods] 1) DBA1 mice were intradermally immunized with GPI-peptide and co-immunized with DMSO or α-GalCer. 2) Immunized mice were killed on day 10 and NKT cells in draining lymph nodes (dLNs) were detected by flow cytometry. 3) Recall responses from dLN CD4+ T cells were assessed. 4) Recall responses from sorted dLN total CD4+ T cells and NKT-depleted CD4+ T cells were assessed. [Results] 1)α-GalCer significantly decreased the severity of arthritis. (scores:control 10.7±1.5 (mean±SD) α-GalCer 3.8±2.1;$p<0.05$). 2) α-GalCer induced expansion of NKT cells in dLNs. (%NKT cells / T cells: control 0.18±0.08 % α-GalCer 1.55±0.53 %;$p<0.05$). 3) α-GalCer suppressed antigen-specific IL-17 (control 1443±393 pg/ml α-GalCer 261±110 pg/ml;$p<0.05$) and IFNγ (control 7536±1936 pg/ml α-GalCer 132±82 pg/ml;$p<0.05$) production. 4) NKT depletion did not alter the suppressive effect of α-GalCer on recall responses. [Conclusion] α-GalCer ameliorates GPI-peptide induced arthritis through preventing naïve T cells from differentiating into antigen-specific T cells.

P1-014

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) have potential for joint repair in rheumatoid arthritis (RA) due to its immunoregulatory ability and pluripotency. In order to develop an effective delivery system of MSCs, we utilized a scaffold made of nano-diameter poly-lactic-co-glycolic acid fiber (nano-fiber). [Methods] Human MSCs were seeded on nano-fiber and implanted into ankles (IMP) of collagen-induced arthritis (CIA) rats or simply injected intra-articularly (IA) or intra-peritoneally (IP). [Results] Treatment with MSC through IMP significantly suppressed the severity of arthritis evaluated by arthritis score, hind paw thickness and body weight compared to CIA control and treatment via IA and IP. X-ray, micro-CT revealed less bone destruction in IMP than IA or IP. Histological analysis showed less infiltration of inflammatory cells and bone erosion in IMP, compared to other treatment groups. Furthermore, the draining lymph nodes and spleen revealed smaller in size and reduced pro-inflammatory cytokine expression. [Conclusion] Implantation of MSCs with nano-fiber scaffold efficiently suppressed arthritis and bone destruction and systemic inflammation, suggesting a novel MSCs delivery system for future RA treatment.

P1-015

Suppressive effect of Bortezomib against nephritis in NZB/W F1 mice

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Conflict of interest: None

[Objectives] NZB/W F1 mice spontaneously develop nephritis resembling human lupus nephritis. Although a combination therapy of steroid and immunosuppressant drugs has been established, the therapy is often not effective. Therefore, establishment of new alternative therapy is needed. Bortezomib is an inhibitor of proteasome and has already been used for a treatment of multiple myeloma. Some reports have shown that administration of Bortezomib ameliorated the nephritis in NZB/W F1 mice and Bortezomib is expected to become a new therapy for lupus nephritis. [Methods] Bortezomib was administrated subcutaneously into female NZB/W F1 mice during 22 to 40 week-old. Efficacy of suppressive effects for the development of nephritis was evaluated by measurement of serum anti-dsDNA antibody titer and proteinuria. [Results] Both levels of anti-dsDNA antibody titier and proteinuria were reduced by Bortezomib treatment. Although the titer of anti-dsDNA antibody immediately increased after interruption of Bortezomib administration, the suppressive effect of proteinuria was maintained long term period. [Conclusion] Bortezomib appeared to be new useful therapy for lupus nephritis. We are investigating more precise mechanisms of Bortezomib treatment for suppressive effects of lupus nephritis.

P1-016

Anti-IL-6 receptor antibody enhances the anti-inflammatory effect without increasing the side effects of steroids in arthritis

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Conflict of interest: None

[Objectives] We elucidated the combinational effect of steroid and IL-6 inhibitor in mouse arthritis model. **[Methods]** To prepare a collagen-induced arthritis (CIA) model, DBA/1J mice were immunized intradermally with bovine type II collagen twice on Day 0 and 21. The arthritis scores were evaluated by observation of joint swelling. Mice were intraperitoneally treated with the prednisolone (PSL) from Day 21 at doses of 1, 3, and 6 mg/kg five times a week and/or with 8 mg of anti-mouse IL-6R antibody (MR16-1) once on Day 21. For evaluating a side effect of PSL, bone mineral density (BMD) of lumbar spine was measured by DXA. **[Results]** PSL dose-dependently reduced the arthritis score in the CIA model on the peak of swelling (Day 33). MR16-1 in combination with low doses of PSL (1, 3 mg/kg) improved the arthritis score significantly more than PSL alone at the same doses on Day 33, although MR16-1 alone was ineffective for swelling when administered on Day 21. Furthermore, lumbar spine BMD in combination group of MR16-1 and PSL (3 mg/kg) was higher than that in PSL (3, 6 mg/kg) alone group. **[Conclusion]** We demonstrated that anti-IL-6R antibody enhanced the inhibitory effect against arthritis of PSL without decreasing BMD.

P1-017

Effects of oxygen nanobubble water on collagen-induced arthritis mice

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Conflict of interest: None

【Background】Recent studies have demonstrated intra-articular hypoxia is critical for the pathogenesis of RA. Here, we focused on the oxygen nanobubble (NB) which possess ability to increase dissolved oxygen concentration and to retain for months in the solution. We hypothesized that the administration of oxygen NB water may improve local tissue hypoxia and ameliorate arthritis.【Materials and Methods】CIA was induced in 6-week-old male DBA/1J mice. The control group(Ctl:n=6) received intra-peritoneal injection of distilled water and oxygen NB group(N:n=5) received oxygen NB water every 3days(200μl/mouse/day) from day0. Clinical and histological severity of arthritis, and relative mRNA expression of pro-inflammatory cytokines of joints were assessed.【Results】On day 28, all mice developed CIA. Clinical arthritis score, histological arthritis score, and relative mRNA expression of pro-inflammatory cytokines of joints demonstrated worsening of arthritis in the oxygen-nanobubble group compared to the control group.【Conclusion】The results suggest that systemic administration of oxygen NB water in CIA mice deteriorate the arthritis. Although the reasons are still under investigation, we speculate that the generated free radicals by oxygen NB may play a role in the results.

P1-018

The inhibitory effect of multi-targeted receptor tyrosine kinase inhibitor sunitinib on arthritis

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Conflict of interest: None

[Objectives] To investigate therapeutic effect of sunitinib, a receptor type tyrosine kinase inhibitor that targets vascular endothelial growth factor receptor (VEGFR) family and platelet-derived growth factor receptor (PDGFR) family, on murine experimental arthritis. [Methods] Sunitinib was administrated intraperitoneally once daily at 0, 30, 60mg/kg/day in type II collagen-induced arthritis (CIA) induced mice. Incidence rates, macroscopic severity and histopathological severity of arthritis were compared between each groups. Synovial microvascular density (MVD) and expression of IL-1beta, IL-6 and TNF-alpha in leg joint tissue were also compared. [Results] Sunitinib reduced incidence of arthritis and diminished macroscopic and microscopic arthritis severity in a dose dependent manner. IL-1beta and IL-6 expressions in joint tissue were also dose-dependently attenuated, and these two factors were correlated with macroscopic arthritis score. In the two treatment groups, MVDs in synovium were not only low compared with untreated CIA group but also similar to no arthritis group. [Conclusion] We demonstrated the anti-arthritic effect of sunitinib. We suggest that the anti-inflammatory effect includes anti-angiogenic pathway which is expected to the result of VEGFR selective blocking.

P1-019

Bone changes of the feet with the X-ray in the patient with rheumatoid arthritis -Compared with the change of the hand-

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Conflict of interest: None

【Objectives】Medical treatment for rheumatoid arthritis has progressed, the patients could be acquired good disease activity. As a results, Recently, Patients and Rheumatologists have focused to lesions of the feet.【Methods】72 patients has been more than 5 years follow-up period were investigated with rheumatoid arthritis. Average age was 63.0 years (21-83). Mean disease duration was 11.6 years (5-40). We evaluated the bone changes of the hands and feet with the X-ray at the time of the initial visit and the final. We investigated the blood laboratory data and Medication. We were using the DAS28 in clinical evaluation.【Results】43 patients (59.2%) cases there was in progress hand and feet. 11 patients (15.2%) there was a hand only changed cases. Only 3 cases were foot (4.2%). 15 cases of patients who did not change (20.8%). In sero-negative RA (5.6% 4 cases), joint changes were mild compared to patients with positive RF, and anti-CCP antibody-positive patients. ΔTSS was correlated with DAS28 at the first visit.【Conclusions】In patients with advanced changes of the hand, was in progress at the same time any change of feet. We do not forget that the existence of the feet changes in the patient with rheumatoid arthritis.

P1-020

The magnetic resonance imaging (MRI) findings of rheumatoid arthritis (RA) treated with biological therapy for at least 5 years and more

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Conflict of interest: None

[Objectives] The purpose of study is to investigate MRI findings of rheumatoid arthritis patients treated with biological therapy for at least 5 years and more. [Methods] Ten RA patients were enrolled in the study. Clinical disease activity was determined using the DAS28–ESR. MRI examinations were performed twice, once before biological therapy (at baseline) and the other after treated with biological therapy for at least 5 years and more. MRI findings were currently scored using the RA MRI scoring system (RAMRIS) as reported in the Outcome Measures in Rheumatology Clinical Trials. [Results] DAS28-ESR was improved from 5.69 at baseline to 3.19. The total RAMRIS MRI score was 65.00 at baseline and improved to 48.80. The synovitis score and bone edema score in RAMRIS MRI score was improved remarkably (5.70→1.90, 9.80→1.90). However, bone erosion score in RAMRIS MRI score has been not changed for 5 years (49.50→45.00). Some cases in DAS28-ESR low disease activity with biological therapy still remain synovitis and/or bone edema. [Conclusion] MRI assessment is useful to determine the therapeutic effect of RA patient with biological therapy for the medium-term.

P1-021

Evaluation of the effect of abatacept by low field compact magnetic resonance imaging in patients with rheumatoid arthritis

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Conflict of interest: Yes

Objective:The aim of this study was to evaluate the efficacy of abatacept (ABT) by using 0.3T low field compact MRI (cMRI) in patients with RA. Methods:Eleven RA patients treated with ABT were included. The clinical response was evaluated at baseline and at 24 week by DAS28-ESR. Two cMRI examinations were performed at the same time in 2 sequences; coronal T1WI and STIR image. Synovitis, bone marrow edema (BME) and bone erosion were scored by cMRI scoring system. Results:(1) There was a significant improvement in DAS28 after the ABT therapy (5.06±1.20 to 3.52±0.95, p=0.004). (2) Synovitis score was significantly decreased after the ABT treatment (14.64±9.58 to 8.00±6.15, p=0.004). There was a tendency of improvement in BME score (6.45±7.97 to 3.64±4.29, p=0.06) whereas no significant change was found in erosion score. (3) The baseline synovitis score of 6 patients who achieved low disease activity (DAS28 < 3.2) at week 24 was significantly lower than that of 5 patients who did not (8.17±4.60 vs. 22.4±8.11, P=0.018) whereas no significant change was found in erosion score and BME score. Conclusion: ABT improved synovitis observed by cMRI in RA. Low synovitis score at baseline might be the predictable factor of the achievement of low disease activity after the administration of ABT.

P1-022

Therapeutic efficacies of tocilizumab in patients with rheumatoid arthritis refractory to anti-tumour necrosis factor biologics: two year follow up by low-field extremity MRI

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Conflict of interest: Yes

[Objective] We reported that tocilizumab (TCZ) is effective for RA patients who were refractory to anti-TNF biologics for 12 month however inflammatory lesion was still remained. In this study, we follow up RA patients refectory to anti-TNF biologics treated TCZ for 24 month and compare the therapeutic efficacies of TCZ by DAS28-ESR and by MRI. [Methods] All patients who were treated by TCZ in university of Tsukuba Hospital because of refractory to anti-TNF biologics and were followed up by MRI, were enrolled in this study. Total 7 patients were included. DAS28-ESR and MRI images of both hands were examined at baseline, 6, 12, and 24 month. [Results] All patients had good or moderate response by DAS28-ESR and DAS28-ESR was decreased significantly at 20 weeks. MRI findings of synovitis and bone edema were not improved at 6 month. At 12 month, synovitis and bone edema score were decreased significantly. In this point, inflammatory lesion was still remained. DAS28-ESR remission was maintained for 24 month, However, synovitis and bone edema was not significantly changed. [Conclusions] MRI detected synovitis and bone edema was still remained at 24 month, even if clinical remission was maintained. We conclude that MRI evaluation is useful for the estimation of total disease activity of RA.

P1-023

Two cases of RA treated with biologics, in which a qualitative analysis of knee cartilage was conducted using MRI

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Conflict of interest: None

[Objective] To report on two cases of RA patients with arthritis in the knee, in which we conducted qualitative analysis of articular cartilage by MRI during the treatment with biologics. [Methods] MRIs were conducted by Philips 3.0 tesla, and the T1ρ, T2 relaxation times for the articular cartilage were calculated. [Results] Case 1. Male, 59 years old. Due to the exacerbation of swelling in the right knee joint, Abatacept (ABT) was commenced. The DAS 28 was improved from 4.3 to 3.2, 12 months afterward. Synovitis and degeneration of the cartilage were observed before initiation of ABT, while they had decreased by ABT. There was no change in the thinning of the cartilage. Case 2. Female, 57 years old. RA appeared in the left knee and three months after the onset, adalimumab (ADA) was commenced. The DAS 28 improved from 4.8 to 3.8 six months later, and remission was observed from the 12 month. In the MRI, there was a marked exacerbation of synovitis and degeneration of the cartilage at base line. The synovitis had abated 18 months later, but there was progression of degeneration of the articular cartilage. [Conclusion] In cartilage degeneration, mechanical factors are involved, so even if synovitis is controlled, the possibility of progression is present.

P1-024

Evaluation of availability of ultrasonography for undifferentiated arthritis

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Conflict of interest: None

[Objectives] Ultrasound imaging of joints (US) has high detection sensitivity of joint lesion.We analyzed the contribution of US to diagnosis in the case that patients with arthritis who were difficult to clinical diagnose and underwent ultrasound. [Methods] In this study,126 patients with undifferentiated arthritis (UA) who were underwent US and followed up at least 6 months were analyzed retrospective. The observations of US were compared between Rheumatoi Arthritis (RA) group, non-RA group, and UA group. Moreover, in RA group, we contrasted with 2010 ACR/EULAR criteria, and examined the contribution over RA diagnosis of US. [Results] Among 126 patients, 51 were diagnosed of RA, and 49 were diagnosed as PMR,etc, and 13 were still UA, and other 13 were almost normal. In RA group, 21 did not met the ACR/EULAR criteria, and 17 have not ACPA and RF.The observations more than PD2 were found in the wrist or fingers in 45 RA patients.Although having over PD2 observations at the same lesions, 18 patients diagnosed as non-RA (PMR,and so on), but they were diagnosed by the other clinical examinations. [Conclusion] These results indicated that US is useful for the differential diagnosis of UA, but we need to be careful when US imaging was considered as the basis of diagnosis.

P1-025

Sensitivity of the detection of power doppler signals of synovitis with two types of ultrasonography

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Conflict of interest: None

[Objective] Using two types of ultrasonography, we studied the most suitable color frequency and PRF(pulse repetition frequency), and compared the sensitivity of the detection of power Doppler signals of synovitis. [Methods] Examinations were performed on 12 MCP joints of 8 RA patients. We used 2 different models, TOSHIBA Aplio(TUS-A300) and Viamo(SSA-640A). The power doppler color frequency were changed as follows : 8.8MHz, 6.1MHz, 5.0MHz in Aplio, and 7.2MHz, 5.3MHz in Viamo. We changed PRF and selected the most suitable condition. [Results] Color doppler signals of 12 joints were evaluated from Grade I to III with Aprio(CF 8.8MHz), Grade I : 4 joints, Grade II : 5 joints, Grade III : 3 joints. In 4 joints of Grade I which were detected with Aplio(CF 8.8MHz), we couldn't detect the power doppler signal in 2 joints with Aplio(CF 5.0MHz), and in 1 joint with Viamo. 8 joints of Grade II and III with Aplio(CF 8.8MHz) were detected same level's power doppler signals with both Aplio and Viamo. [Conclusion] Color doppler signals of Grade I, the evaluation was different with Aplio and Viamo. But Grade II and III, no difference was observed in sensitivity of power doppler signals with two ultrasonography.

P1-026

The role of ultrasonography in the diagnosis of early rheumatoid arthritis

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Conflict of interest: None

[Objectives] We assessed the role of ultrasonography (US) in the diagnosis of early RA when the new 2010 criteria were applied clinically. [Methods] We studied 122 patients who first visited our department with arthralgia from 2009 to 2011. The patients were categorized into two groups: 50 patients received anti-rheumatic therapies within a year were placed in the RA group, and the remaining 72 constituted the non-RA group which involved 15 with osteoarthritis, 11 with undifferentiated arthritis. Clinical and US findings at entry were compared between the two groups. [Results] The patients of the RA group had more tender and swollen joints, especially in wrist joints, than those of the non-RA group and 70% of the RA group fulfilled the 2010 criteria. The proportion of patients with abnormal US findings was significantly higher in the RA group. In all 12 patients in the RA group who did not meet the 2010 criteria as well as the 1987 criteria at entry, active synovitis was proven by US. In contrast, one patient who had no proven synovitis on US despite high titer of anti-CCP antibody, did not develop clinical manifestations of RA during the observation period. [Conclusion] US can help us to select the patients who need to be treated by detecting synovitis precisely and sensitively.

P1-027

The programs of automatic acquisition of appropriate PD gain and automatic extraction of appropriate image in MSUS

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Conflict of interest: None

[Objectives] It is said that the issues of MSUS are poor objectivity and reliability in evaluating RA lesions. We assessed the efficacy and validity of two newly developed-programs; automatic acquisition of the most appropriate PD gain (Quick Scan) and automatic extraction of appropriate image. [Methods] Joints of RA patients (17 cases, 62 joints, 117 lesions) were evaluated with Aplio XG possessing the two programs by 2 experts in MSUS blindly each other. [Results] The gain values obtained by Quick Scan tended to be more similar between the examiners (Δ 1.33±0.92) than those adjusted manually (Δ2.60±4.47). One examiner conventionally evaluated PD signals in joints by capturing appropriate still image after manually adjusting PD gain, whereas the other examined the same joints by using Quick Scan and storing movies. PD scores evaluated from moving images and those of the automatically-extracted images from the movies were well matched (κ coefficient 0.85) as well as PD scores of conventionally-captured images and those of the extracted images were (κ coefficient 0.74). Moreover, the automatic extraction prevented the examiners from missing PD signals in some cases. [Conclusion] These new programs enable MSUS operators to evaluate arthritis objectively, efficiently, and accurately.

P1-028

Quantitative measurement for abnormal synovial hypertrophy of finger joints in rheumatoid arthritis

Jun Fukae, Akihiro Narita, Mihoko Henmi, Fumihiko Sakamoto, Akemi Kitano, Yuko Aoki, Hisanori Takamatsu, Masato Isobe, Masato Shimizu, Megumi Matsuhashi, Takeya Ito, Akio Mitsuzaki, Kazuhide Tanimura
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Conflict of interest: None

[Objectives] Joint ultrasonography is useful tool to obtain joint inflammatory information in clinical practice of rheumatoid arthritis (RA). Semi-quantitative score is developed for estimating abnormal synovial hypertrophy (SH) in RA. As the score is categorized into general 4 grades, clinical usefulness is not significant in previous reports. We designed quantitative measurement for SH and compared with semi-quantitative score. [Methods] MCP joints with abnormal SH were assessed by both semi-quantitative score and quantitative measurement. [Results] Our result revealed that grade 3 of semi-quantitative score showed extent range when estimated by quantitative measurement. [Conclusion] Although further study will be necessary for our method to be established, our result indicated problem of semi-quantitative score which might be necessary to be revised.

P1-029

Indocyanine green-fluorescence video vasculography detects abnormal synovial vascularity of finger joints in rheumatoid arthritis

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Conflict of interest: None

[Objectives] In rheumatoid arthritis (RA), there are strong relation between abnormal synovial vascularity (SV) and joint inflammation. Extent of abnormal SV reflects level of joint inflammation. Power Doppler sonography (PDS) is useful modality to detect SV, however having demerit in complicated scanning technique that affects output. Indocyanine green (ICG) is fluorescent agent which commonly used in ocular fundus examination. Simple video system can visualize small vascular flow by fluorescent image. We

used the method to visualize abnormal SV of finger joints in RA. In the report, we studied quantitative estimation of joint inflammation used by the method. [Methods] Finger joints of patients with RA were examined by both ICG vedeo vasculography and PDS. [Results] Fluorescent images were detected at same joints with positive SV. Characteristic intensity curves of fluorescent strength was obtained. [Conclusions] We will compare intensity curves of joints with positive SV and those of normal joints to establish useful parameters that reflects joint inflammation.

P1-030

Novel quantitative measurement for synovial vascularity in rheumatoid arthritis

Fumihiko Sakamoto, Mihoko Henmi, Akihiro Narita, Yuko Aoki, Akemi Kitano, Hisanori Takamatsu, Takeya Ito, Masato Isobe, Jun Fukae, Megumi Matsuhashi, Akio Mitsuzaki, Masato Shimizu, Kazuhide Tanimura
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Conflict of interest: None

[Objective] Semi-quantitative 4 graded scoring is used for estimation of synovial vascularity (SV), however its clinical significance has not been well established. We designed semi-automatic quantitative measurement for SV. While traditional quantitative method can output SV as counts of pixel dots which depended on machine performance, the novel method outputs as value of area. [Method] Ultrasonographic machines (Aplio300 TOSHIBA, LOGIQe GE, Avius HITACHI) were used. SV of finger joints in RA were examined. We studied reproducibility of free hand tracing, inter-examiner reliability of free hand tracing, comparison between free hand tracing and semi-automatic measurement, inter-machine reliability of semi-automatic measurement. [Results] All of the indices showed excellent outcomes. [Conclusion] Our significant result was that the novel method had excellent outcome in inter-machine reliability. This indicated that data from various models could be comparable. Although function of semi-automatic measurement is optional in each model, free hand tracing is common among all machines. Our result indicated that quantitative measurement for SV from semi-automatic or free hand tracing could be comparable. We planed to refine the method to be used for multicenter study.

P1-031

Basic study of metatarsophalangeal joint joint of healthy volunteers using ultrasonography

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Conflict of interest: None

There are many reports of usefulness of ultrasonographical EULAR criteria: ultrasound-combined classification with two different definitions of gray-scale synovitis for metacarpophalangeal joint involvement of reumatoid arthritis. But it is very difficult to evaluate synovitis of metatarsophalangeal joint because of the lack of the knowledge of normal ultrasonographical anatomy. So we study the metatarsophalangeal joint of healthy volunteers using ultrasonography. 100 healthy volunteers (27 male. 73 female, 41 years old on average) were examined with ultrasonographical machine of Ascendas (Hitachi-Aloka Tokyo). Length and thickness of articular capsle of Each 10 MTP were measured and the age, height, body weight were recorded. The length of the capsle were 1th>2th>3th>4th>5th,and there was significant difference. The thickness of the articular capsle were 2.6 mm and no significant difference of each MTP. We report the results in detail.

P1-032

Analysis for structure of joint synovitis by ultrasonography in rheumatoid arthritis

Akihiro Narita, Mihoko Henmi, Fumihiko Sakamoto, Yuko Aoki, Akemi Kitano, Hisanori Takamatsu, Takeya Ito, Masato Isobe, Jun Fukae, Megumi Matsuhashi, Akio Mitsuzaki, Masato Shimizu, Kazuhide Tanimura
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Conflict of interest: None

[Objective] Joint ultrasonography is currently reported as sensitive tool to obtain joint information. In our experience, there were several patterns of structure in synovitis. In the report, we analysed property of synovitis in finger joints by density histogram or elastography. [Methods] Ultrasonographic machine (HIVISION AVIUS HITACHI) was used. Finger joints with synovial hypertrophy (above grade 2 of semi-quantitative score) were examined. Structural pattern were grossly classified as homogeneous and heterogeneous hypertrophy types. Density histogram and elastography were used to show density pattern and output strain ratio which was index of tissue consistency. [Results] Homogeneous type showed relatively low density level in synovitis. Heterogeneous type showed mixed with low and high densities in synovitis. Elastography revealed that heterogeneous type had mixed with hard and soft tissue in synovitis. [Conclusion] Joint ultrasonography have potential to obtain detailed joint information such as structure. Heterogeneous hypertrophy might have mixed with acute and old inflammatory tissues that might be progressed arthritis. Further study will be necessary to observe change of the structural pattern by therapeutic response.

P1-033

Relationship between Powe Doppler activity evaluated by ultrasonography and disease activity in rheumatoid arthritis (RA)

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Conflict of interest: Yes

[Purpose] To investigate the relationship between Power Dopplar (PD) activity by ultrasonography (US) and the index of the disease activity of RA. [Method] Fourty-six patients with RA (12 men, woman 34, average age 66.9-year-old) underwent US study since January 2012 for four months, and differences of sex, age, duration of RA, tender joit counts, swollen joint counts, patient's VAS, DAS28, physian's global assessment and health assessment questionnaire (HAQ) between a PD-positive group and a PD-negative group were compared. [Result] Twenty-eight patients of 46 cases with PD-positive group had significantly higher patient VAS and DAS28, compared with the negative group. In addition, the ratio of patients with patient's VAS $\leq$10 was significantly higher in a PD-negative group. The mean HAQ score was modestly higher in a PD-positive group, but differences of other indicators did not reach statistical significant. [Conclusion] PD-positivity in US study was closely associated with disease activity indices of RA, and might be useful tool for evaluating the remission of RA.

P1-034

Pregnancy and parturition in patients with rheumatoid arthritis

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Conflict of interest: None

[Objectives] To know pregnancy and parturition in patients with rheumatoid arthritis (RA). [Methods] 281 women with RA (mean age at onset of RA 44.6y.o., mean age at last follow-up 57.4y.o.) were researched about their marriage, pregnancy and parturition. [Results] 254 patients (90%) were married. 227 patients (89%) experienced a total of 513 pregnancies. Outcome of their pregnancies were childbirth (408 before RA onset, 26 after RA onset), 64 miscarriages, 9 abortions, 3 ectopic pregnancies, 3 stillbirths. 73 (60%) of 121 patients, whose RA onset age were younger than 40 years, have children and 150 (94%) of 160, whose RA onset age were elder than 41 years, do. After their delivers, 19 patients became RA (18 childbirth, 1 miscarriage), 4 patients became aggravation of RA, 1 patient became remission of RA. 8 of 26 childbirths after RA onset, were in patients treated with etanercept. [Conclusion] The possibility of pregnancy and childbirth decreases in the patients with RA but the control of their desease activity by etanercept may improve the decreased possibillity.

P1-035

Clinical characteristic of elderly-onset rheumatoid arthritis (EORA) in NinJa2011 database

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Conflict of interest: None

[Objectives] To identify the clinical characteristics of elderly-onset rheumatoid arthritis patients (EORA) in NinJa 2011 registry in Japan. [Methods] Of 10368 patients registered in NinJa 2011, patients who recently diagnosed RA in two years or less, were selected for this study, to avoid the effect of the disease duration. EORA group (onset age was more than 65) was compared with adult onset RA (AORA) group (both onset and registration ages were less than 65). [Results] EORA group included 603 patients and its male/female ratio was 0.46, whereas AORA group did 733 patients and was 0.27. EORA group consisted of 52.2% of stage I, 37.1% of stage II, 8.9% of stage III, 1.9% of stage IV by Steinbrocker stage classification, and AORA group did 63.4%, 30.5%, 5.1%, 1.1%. The percentages of medication with prednisolone, methotrexate and biologics were 42.4%, 50.9%, and 12.0% in EORA group, and 33.2%, 67.5%, and 17.3% in AORA group, respectively. Disease activity estimated with DAS28 was 3.37 in EORA group, whereas 3.27 in AORA group. [Conclusion] In the early stage of EORA group, the ratio of Stage II and III were higher than AORA group, which suggested that radiological stages in EORA group could be more progressive than AORA group.

P1-036

A Study of The Influence of Oral Hygiene on The Pathogenesis of Rheumatoid Arthritis

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Conflict of interest: None

[Objectives] In the present study, we clarify how salivary secretion, as one of the indicators of oral hygiene, influences the pathogenesis of RA. [Methods] The study involved 61 patients with RA. Fourteen of these patients (23%) had concomitant Sjogren's syndrome. Their amounts of saliva secreted were measured by the filter paper method for saliva collection for diagnosing xerostomia, in order to examine the relationship between the presence of impaired salivary secretion and, radiographic findings, therapeutic drugs, disease activity, or MMP-3. [Results] There was no significant relationship between the presence of impaired salivary secretion and, impaired salivary function or radiographic changes. The use frequency of NSAIDs among other therapeutic drugs was significantly high in patients without impaired salivary secretion ($p<0.05$), whereas it had no significant relationship with the use of steroid, salazosulfapyridine, bucillamine, and MTX. However, the amount of MTX used was significantly large in patients without impaired salivary secretion ($p<0.05$). On the other hand, MMP-3, DAS28-CRP and bone destruction, showed no difference in the presence of impaired salivary secretion. [Conclusion] Oral hygiene seems less likely to influence the pathogenesis of RA.

P1-037

Algorithm using genome-wide SNP analysis for prediction of radiographic progression per year in RA patients from multiple medical cohorts

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Conflict of interest: None

[Objectives]We developed a SNP algorithm with the aim of enabling the prediction of yearly radiographic progression by means of genome-wide SNP analysis using multiple medical cohorts. **[Methods]**124 RA patients whose disease duration was within 5 years were enrolled. RA joint destruction was classified by Sharp score. Radiographic progression of joint destruction was estimated by Sharp score per year of disease duration. Twenty-three patients had a yearly Sharp score of >50 (rapid radiographic progression (R)), 76 had a yearly score of 50-10 (intermediate radiographic progression (I)) and 25 had a yearly score of <10 (slow radiographic progression (S)). We scored a relationship between each SNP and progress of joint destruction, the estimated total score of 10 SNPs (estimated scoring in each SNP was as follows: homo allele in the majority in R (or R+I) group: +1 point, hetero allele: 0 point, and homo allele in the majority of S (or I+S) group: -1 point). **[Results]**Accuracy of the algorithm for distinguishing the R from the I+S was 94%. Accuracy of the algorithm for distinguishing the R+I progression group from the S progression group ranged from 90%. **[Conclusion]**This SNP algorithm may be useful in initially distinguishing rapid radiographic progression.

P1-038

The evaluation of rheumatoid synovitis of atlantoaxial joint using FDG-PET/CT

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Conflict of interest: None

[Objectives] FDG-PET can detect subclinical arthritis in the cervical vertebrae of patients with rheumatoid arthritis (RA). In this study, we evaluated the grade of the synovitis in the atlantoaxial (AA) joint of RA patients using FDG-PET/CT, and measured the relation with FDG uptake of other joints, the disease activity of RA, and laboratory findings. [Methods] 23 RA patients (6 men, 17 women, age 62.0±10.4 years old, disease duration 15.0±11.3 year) were included. The FDG uptake into the AA joint, and the shoulders, elbows, wrists, hips, knees and ankle joints, were calculated using maximum standardized uptake value (SUVmax) for half-quantitative determination. The total of SUVmax of other joints except for AA joint was set to total SUV. The functional Xp of cervical spine were performed, and the existence and the grade of atlantoaxial subluxation (AAS) were checked. [Results] AA joint SUV; 2.26±1.04, total SUV; 26.3±9.9, DAS28; 5.11±1.23, SDAI; 23.1±15.4, and CDAI; 21.5±14.7. The AAS were detected in 3 RA patients, the ADI was 3 to 11 mm. AA joint SUV correlated with the age ($r=0.554$, $p=0.006$), total SUV ($r=0.791$, $p<0.001$), and AAS ($r=0.448$, $p=0.032$), respectively. [Conclusion] This study suggested that FDG-PET could objectively evaluate the synovial inflammation of the AA joints.

P1-039

Usefulness of the serum amyloid A in rheumatoid arthritis patients being treated with biologics

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Conflict of interest: None

【Objective】SAA level is one of the sensitive inflammatory marker. However, thus far, few reports have compared the SAA level, disease activity, other inflammatory markers and future outcomes following treatment with biologics in RA. The aim of this study was to assess the SAA level, the levels of other inflammatory markers and the disease activity in patients with RA who are receiving biologics.【Methods】The subjects included 32 RA patients who started to receive biologic treatment in or after July 2008 (17 patients received TNF inhibitors and 15 patients received TCZ). The swollen joint count, the tender joint count, the DAS28-ESR score and the levels of SAA, ESR, CRP and MMP-3 were assessed before treatment and at two, four and six months after treatment. 【Results】The DAS28-ESR scores obtained six months after treatment were significantly correlated with the SAA, ESR and CRP levels obtained two and four months after treatment in the TNF inhibitor group and with only the SAA levels obtained two and four months after treatment in the TCZ group.【Conclusions】These results suggest that it may be possible to use the SAA level as a predictive factor of the therapeutic effects for not only TNF inhibitor therapy, but also for TCZ therapy.

P1-040

Analysis of rheumatoid arthritis patients exaggerated or developed during tratment of diabetes mellitus with DPP4 inhibitors

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Conflict of interest: None

[Objectives] Recently, collaborators reported the development of polyarthritis including rheumatoid arthritis (RA) during treatment of diabetes mellitus with DPP4 inhibitors. We examined whether we could find RA patients exaggerated or developed during treatment with DPP4 inhibitors in new RA patients who attended a rheumatology clinic. [Methods] [Results] Numbers of new RA patients were eighty eight in one year from Sep., 2011. Of these patients, seven were also patients with diabetes mellitus treated in other hospitals or clinics. Five of these 7 patients were treated with DPP4. The arthritis in the 3 patients was exaggerated in one to three months after beginning of Sitagliptin. Another RA patient developed during treatment with Sitagliptin was observed in our medical records before Sep., 2011. Anti-CCP antibodies were high-positive in three of the 4 patients. [Conclusion] It may be necessary to examine further whether DPP-4 inhibitors participate in the exaggeration or development of RA in some patients.

P1-041

Increase of plasma lactoferrin(LTF) and myeloperoxidase (MPO) in patients with rheumatoid arthritis (RA) by leukocytapheresis(LCAP)

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Conflict of interest: None

We analyzed plasma LTF and MPO, which were stored in the granulocytes in patients with RA treated with LCAP. Mean plasma levels of LTF and MPO after the LCAP column (LTF 1713 ng/ml, MPO 1684 ng/ml) were significantly higher than those before the column (LTF 216 ng/ml, MPO 302 ng/ml). The final plasma levels of LTF and MPO after the treatment of LCAP were also significantly higher than those before. When the whole blood of patients with RA was incubated with unwoven polyester fiber for LCAP column, the levels of LTF and MPO increased. In addition, cytoplasmic vacuolation of granulocytes was observed by the electron microscope. These data suggested that LTF and MPO stored in the granulocytes are released during the LCAP, and they could be related with the improvement of RA after this therapy.

P1-042

Evaluation of sleep disturbance using Polysomnography of Rheumatoid Arthritis reflects probably on disiase activity

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Conflict of interest: None

Objective: We evaluate an association between sleep disturbance and disease activity of Rheumatoid Arthritis (RA) without sleep respiratory disorder, complicated with sleep disorder. To clarify sleep disorders of RA, we use Polysomnography (PSG) and subjective evaluations of the sleep quality Methods: From Apri, 2011 to August 2012, we performed PSG, and evaluation questionaries such as ISI,ESS,IRLS in 14 patients without sleep respiratory disorder. Results: For the sleep electroencephalogram, 4 Cases show α-δ Sleep Pattern. DAS28(CRP) was low level in these cases,

but was a high level in HAQ score. 3 cases show perodic limb movement disorder (PLMD) which PLM Index was 15 or more, and DAS28(CRP) were higher level than the other cases. However, IRLS was less than ten points in all cases, and there were no complication of the restless legs syndrome. Also, ESS was less than ten points in all cases. Three cases got 10 points or more in ISI, and showed α-δSleep pattern in two cases of those ones. Conclusions: Even if RA control looks well that DAS28(CRP) was low, sympathetic nervous activity is in high and having an insomnia in the cases of high HAQ score. When a disease control was poor, and inflammation was high

P1-043

Diagnosis and treatment of early rheumatoid and undifferentiated arthritis performed by orthopaedic surgeons

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Conflict of interest: None

[Objectives] Since the introduction of 2010 ACR/EULAR classification criteria for rheumatoid arthritis (RA), starting treatment earlier improved clinical outcomes. However, some study reported that new criteria may cause misclassified and overtreatment. The aim of this study was to analyze the effects of pharmacotherapy and orthopaedic treatment for early RA and undifferentiated arthritis (UA). [Methods] 93 patients with recent onset arthritis visited to our hospital between April 2009 and September 2012. Of these patients, 21 cases (18 female and 3 male) that was not defined as RA but likely to have RA or UA were included in this study. The defined diagnosis and clinical outcome were retrospectively reviewed. [Results] Eight cases were finally classified as RA; 9 cases were UA. Although non-biological agents were applied to 4 patients with UA, pharmacotherapy was not effective in all cases. On the other hand, injection of steroid was effective in 3 cases of UA. As for orthopaedic surgery, synovectomy was performed in 3 cases. Histological findings showed chronic inflammation with invention of lymphocytes, and postoperative recurrences were not seen in all cases. [Conclusion] Based on our results, orthopaedic treatment are recommended in the cases that pharmacotherapy are not effective.

P1-044

Four cases of rheumatoid arthritis patients which caused modification to the Distal interphalangeal (DIP) joint

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Conflict of interest: None

[Objective] In rheumatoid arthritis (RA), it is rare to cause modification to a Distal interphalangeal (DIP) joint. We report untypical RA of four cases which caused inflammation and joint space narrowing this time to the DIP joint. [Methods] Joint Space narrowing was caused to the DIP among RA patients under visitor medical treatment in our hospital, and four cases which resulted in the operation obstacle were examined. [Results] All case was a male. Case 1 is 59 years-old and case 2 80 years-old and case3 66 years-old and the case 4 were 69 years-old, the case 3 complicated Essential thrombocytosis, and case 4 complicated Lung cancer. Although CRP was positive in all the cases and RF was a weak positivity with the cases 1, 3, and 4, each anti-CCP antibody was negative. The merger of psoriasis and palmoplantar pustulosis was not seen, and any case observed swelling in at multiple MCP and wrist joint and met RA standard of classification of ACR/EULAR 2010 and advance of the DIP joint operation region obstacle advanced in several months. As for the change in X-ray, bone erosion is not seen but joint space it was at the core whether it is narrow. [Conclusions] RA which caused change to the DIP joint was experienced. Considered that are quick and early treatment is desirable.

P1-045

Relationship between 25-hydroxy-vitamin D and activity of rheumatoid arthritis

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Conflict of interest: None

[Objectives] To investigate the relationship between 25-hydroxy-vitamin D (25(OH) D) and activity of rheumatoid arthritis [Methods] Twenty six RA patients who fulfilled the 1987 ACR criteria, enter our hospital between May, 2011 and October 2012, accept to measure the 25(OH) D were enrolled in this study. Patients were consist of 2 males and 24 females. Average age was 71-year-old (56 to 84). A correlation between 25(OH) D and DAS28, tender joint count, swollen joint count, VAS, ESR, CRP and MMP-3 were investigated. Also 25(OH) D levels were compared in the stage between Steinbrocker's classifications. The gait ability by Fujibayashi classification was divided into two groups and also compared. [Results] 25(OH) D mean ± SD is 17.4 ± 4.8 ng/ml. About the correlations between 25(OH) D and parameters, VAS and DAS28(4)-CRP were found the significant negative correlation. Steinbrocker stage classification were devided into Stage 2, 3 and Stage 4 and compared, but no significant difference was observed. Fujibayashi classification was separate into two groups between class 3A and 3B and compared, found the significant change. [Conclusion] Negative correlation was found between 25(OH) D and VAS, DAS28(4)-CRP in RA patients. Along with the decline in walking ability, 25(OH) D decreased significantly.

P1-046

Measurement of muscle mass using bioelectrical impedance analysis(BIA) in patients with rheumatoid arthritis

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Conflict of interest: None

[Objectives] There are few reports about measurement of muscle mass in rheumatoid arthritis (RA) patients. We measured muscle mass in RA patients using BIA, and discussed about the relationship of the patients' backgrounds or RA activity and their muscle mass. [Methods] 101 RA patients who could stand still were measured their muscle mass using MC180 Body Composition Analyzer from November to December 2010 at our hospital. Muscle mass between RA patients and 82 healthy women who were matched for age were compared. [Results] Average age of RA

patients was 62.6 years old. Average duration of RA disease was 17.2 years. Proportions of low, middle, high disease activity groups of DAS28(ESR) were respectively 57.4%, 37.6%, 5.0%. RA patients had significantly less muscle mass than the healthy women, but a higher body fat percentage. Muscle mass in RA patients showed significant negative correlation with their ages, RA disease duration, number of artificial joints, pain VAS, patients global VAS, physical function evaluations (mHAQ), CRPs, erythrocyte sedimentation rates. Muscle mass were significantly less in RA patients with higher disease activity on stage, class, DAS28(ESR). [Conclusion] Muscle mass was less in RA patients with higher disease activity.

P1-047

Study on the expression level of *CDK6* transcripts controlled by *SPACIA1*, which associated with synoviocyte proliferation

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Conflict of interest: None

[Objectives] *SPACIA1* is a novel gene associated with abnormal synovial proliferation. We have already shown that *SPACIA1* is involved in the progression of synovitis *in vivo*. We previously reported that *SPACIA1* siRNA inhibited the proliferation of RA synovial fibroblasts (RASFs) and delayed the cell cycle at G1 phase. However, the mechanisms behind this process are still unclear. [Methods] We examined the effect of *SPACIA1* knockdown on mRNA levels in RASFs cyclopaedically and confirmed it using real-time PCR. Reporter gene used to assay for the activity of *CDK6* promoter. To measure *CDK6* mRNA half-life, transcription was blocked by adding actinomycin D. [Results] *CDK6* mRNA was reduced by half with *SPACIA1* siRNA in transcriptome analysis. It was confirmed by using real-time PCR. *CDK6* promoter activity was not affected by *SPACIA1* knockdown. While remaining *CDK6* mRNA (%) with *SPACIA1* siRNA after actinomycin D treatment (30min) was 60%. In contrast, that with mock siRNA didn't significantly change. [Conclusion] We identified *CDK6*, one of functional genes at G1 phase, which is regulated by *SPACIA1*. *SPACIA1* should be related to *CDK6* mRNA turnover.

P1-048

The Remission Subsets: Complete Remission and Incomplete Remission -A Repot from NinJa Cohort-

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Conflict of interest: None

[Objectives] Two subsets of "Remission" were found in the clinical practice. One is cases with DMARDs only (Complete remission i.e.CR), the other is remission cases that need NSAIDs or Corticosteroid (Incomplete remission i.e. IR). [Methods] The remission cases classified by the EULAR Criteria of Disease Activity were extracted from NinJa cohort. The ratios of IR and its serial change were examined and evaluated regarding background factors, drugs, and the effect of disease duration. [Results] The remission cases classified by the EULAR Criteria of Disease Activity were extracted from NinJa cohort. The ratios of IR and its serial change were examined and evaluated regarding background factors, drugs, and the effect of disease duration. [Conclusion] The remission cases classified by the EULAR Criteria of Disease Activity were extracted from NinJa cohort. The ratios of IR and its serial change were examined and evaluated regarding background factors, drugs, and the effect of disease duration.

P1-049

Clinical factors that correlate with progression of functional impairment in patients with rheumatoid arthritis who continued to achieve the Boolean's new ACR/EULAR remission criteria –A data from prospective observational IORRA cohort study-

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Conflict of interest: None

[Objectives] To evaluate clinical factors that correlate with progression of functional impairment in patients with rheumatoid arthritis (RA), who continued to achieve the Boolean's new ACR/EULAR remission criteria. [Methods] Among those patients who achieved DAS28 remission criteria on April 2008 and who also kept attending to the next following 5 IORRA survey, 248 RA patients who achieved the Boolean's new ACR/EULAR remission criteria for more than 5 times were entered to this study. Their progression of functional impairment was assessed based on Japanese version of health assessment questionnaire (J-HAQ) score. [Results] The baseline demographics of 248 patients at their entry survey were female: 76%, mean age: 60 years old, mean disease duration: 10 years, mean DAS28: 1.9, mean J-HAQ: 0.09. The J-HAQ score proceeded in 25 patients at their last survey, compared to their entry survey. Longer disease duration and higher J-HAQ score significantly correlated with progression of J-HAQ score, both in univariate and multivariate logistic regression analyses. [Conclusion] It may be important to keep achieving Boolean's new ACR/EULAR remission criteria from the early stage of RA before the functional impairment occur, in order to prevent progression of functional impairment.

P1-050

Differences of evaluation in rheumatoid arthritis by patient's VAS and physician's VAS

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Conflict of interest: None

[Objectives] Patient's VAS (p-VAS) is generally reported as the highest hurdle to achieve the clinical remission in rheumatoid arthritis (RA). We have studied various influential factors on p-VAS in comparison with physician's VAS (d-VAS). [Methods] We have examined statistically correlations of p-VAS and d-VAS with various factors (age, duration of disease, DAS28-ESR, CDAI, RAPID3, HAQ-DI, patient's pain-VAS, TJC (28), SJC (28), CRP, ESR and MMP3 in 692 patients with RA. [Results] The mean age of the patients was 63 years old, and the mean of duration of disease was 7.6 years. P-VAS was most correlated with RAPID3 (r = 0.86), and then with in the order of patient's pain-VAS (r = 0.78), CDAI (r = 0.75), DAS28-ESR (0.66), HAQ-DI (r = 0.66), d-VAS (r = 0.65) and TJC(28) (r = 0.51). SJC(28), MMP3, ESR and CRP were not

correlated. D-VAS was most correlated with CDAI (r = 0.89), and then with in the order of DAS28-ESR (r=0.75), RAPID3 (r=0.67), TJC(28) (r=0.67), p-VAS (r = 0.65), SJC(28) (r = 0.59), HAQ-DI (r=0.58) and patient's pain-VAS(0.57). MMP3, ESR and CRP were not correlated. [Conclusion] P-VAS was most correlated with RAPID3 (p-VAS+patient's pain VAS+ HAQ) consisting of subjective evaluations by patients. Improvement of the pain and HAQ is expected to improve the P-VAS.

P1-051

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 rheumatoid arthritis (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 January 2009 to December 2010 were included in this study. 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 studied remission rate at one year. [Results] Among 56 patients who were originally included, 51 could be followed at one year. Baseline characteristics of patients include mean age 54.3 years, female 65%, disease duration 27.8 weeks, mean DAS28-ESR 4.80 and radiographic erosion 14%. The rates of remission (<2.6), low disease activity (<3.2) defined by DAS28-ESR at one year were 47% and 61% respectively. When compared baseline characteristics of remission group with those of non-remission group, we could not find any significant factor for achievement of remission. [Conclusion] In routine practice, about half of the active RA patients whose disease duration less than 2 years have achieved remission defined by DAS28-ESR at one year.

P1-052

Analysis of general patient VAS in RA clinical assessment

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Conflict of interest: None

[Objectives] General patients VAS (VAS) utilizes all disease activity scales; DAS28, CDAI, SDAL and Boolean remission. However, whether the patient feels their condition is 'good' or 'bad', sometimes there are differences between self-evaluation and that of health care providers. We therefore modified the VAS in order to standardize it. [Methods] 105 RA patients treated with biologics or DMARDs participated in this study. We took original VAS (mVAS) after taking VAS of all patients. 'mVAS'makes average for 4 VAS of healthcare, pain, tender joint and swollen joint after we asked RA patients to describe to us the symptoms during their worst disease phase. [Results] 43% of RA patients were treated with biologics. VAS and mVAS are correlated statistically and both VAS are also correlated with doctor's VAS. We separated the patients who had attained HAQ-remission (HAQ-R) and Non-HAQ-R and analyzed the groups. VAS are lower correlated with doctor's VAS in both Non HAQ-R and HAQ-R groups, but the same correlation was observed in mVAS. [Conclusions] We realized that VAS is often dissociated from doctor VAS because VAS, especially of low-ADL patients, are often not objective. mVAS is more appropriate as an evaluation tool.

P1-053

The factors affecting Patient Global Assessment (PtGA) and Physician Global Assessment (PhGA)

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Conflict of interest: None

[Objectives] The major clinical score for evaluating the disease activity of RA is DAS. A new ACR/EULAR remission criteria recommends using SDAI in clinical trial and CDAI in clinical practice. PtGA is included in DAS, PhGA is in DAS, SDAI and CDAI. However, it is not clear whether PtGA and PhGA reflect RA inflammatory activity. We examined the factors affecting PtGA and PhGA. [Methods] The subjects are 119 patients with RA. The avg age was 63.1 yrs (30-84), 30 males and 89 females. The avg disease duration was 10.4 yrs (0.5-46). The relation between PtGA, PhGA and, disease duration, TJC, SJC, DAS28-CRP, pain VAS, CRP, MMP-3, HAQ were calcurated using Pearson correlation coefficient for a statistical analysis. [Results] The factors correlating closely with PtGA are pain VAS, PhGA, DAS, TJC, CRP, HAQ. r= 0.81,0.64,0.62,0.46,0.31,0.31. Pains VAS, PhGA and DAS have high correlation with PtGA. And the factors correlating closely with PhGA are DAS, SJC, PtGA, pain VAS, TJC, CRP. r=0.84,0.70,0.64,0.55,0.49. DAS, SJC and PtGA have high correlation with PhGA. [Conclusion] PtGA has high correlation with pain VAS. RA patients have residual pain causing by joint destruction or other reasons. It is possible that PtGA does not indicate RA inflammatory activity exactly.

P1-054

Is PGA necessary for judgment of remission in ACR/EULAR remission criteria ?

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Conflict of interest: None

Objectives ACR/EULAR remission criteria (Boolean) is well known as most stringent index for rheumatoid arthritis (RA) disease activity. However, PGA is not well evaluated. We have tried to evaluate if it is necessary. Methods We have been measured simplified disease activity index (SDAI) and Boolean 4479 times from 384 RA patients. In these, Boolean remission, and remission except of PGA were picked up. Measurement was classified into 10 groups for PGA with 10mm in scale. Relationship between PGA and SDAI was evaluated statistically. Boolean remission group and other were compared statistically. Then, PGA was divided into 20 groups for 5mm in scale, sensitivity and specificity of SDAI remission was calculated for each group. Results PGA and SDAI demonstrated significant close relationship with correlation coefficients (>0.8). Boolean remission group demonstrated significantly small average SDAI than any of other groups (<0.01). Sensitivity showed more than 80% in any PGA level, however, specificity demonstrated linear increase as PGA increases until 30mm.

Up to 20mm, specificity demonstrated approximately 80%. Conclusion Therefore, we have concluded that PGA is essential for Boolean, however, 10mm is too stringent to evaluate. 20mm is appropriate level to evaluate remission.

P1-055

Combined pulmonary fibrosis and emphysema is very high risk complication in the treatment of rheumatoid arthritis - Treatment of rheumatoid arthritis complicated with interstitial lung disease -

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Conflict of interest: None

[Objectives] We have to be careful for treatment of RA with interstitial lung disease (ILD) has a risk factor of lung infection. Combined pulmonary fibrosis and emphysema (CPFE) is closed up as a recently defined syndrome, manifested as upper-lobe emphysema and lower-lobe fibrosis. This syndrome shows normal %VC and reduced DLco at spirometry, frequently occurs pulmonary hypertension. [Methods] We analyzed clinical features and prognosis of RA treatment in 33 RA-ILD patients. RA-ILD was classified to 23 NSIP, 10 UIP/IPF. We excluded ILD without determination by X-ray. Sixteen patients could not use MTX because of ILD. [Results] We achieved in low disease activity of RA in 7 of 8 tacrolimus cases, 2 of 2 etanercept cases, 1 of 1 tocilizumab case, 1 of 3 abatacept cases after 24 weeks or later. Exacerbation of ILD was observed in 8 cases. Infectious complications had developed in 10 cases. Four smoking men were diagnosed in CPFE. Among 2 CPFE patients, one died due to respiratory failure caused by pneumothorax with infection. [Conclusion] Although decreased %VC is the contraindication of MTX administration, decreased DLco is even more important. Immunosuppressive therapy in RA with CPFE is very high risk to develope lethal infection, because of poor preliminary pulmonary function.

P1-056

Respiratory manifestation detected by screening test using chest CT scan in patient with RA

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Conflict of interest: None

We investigated respiratory manifestation detected by chest CT scan which was assessed for the purpose of screening before introducing biologics in patients with RA. 190 patients who admitted to our hospital to start biologics during the period Jan to Dec 2011 and were biologics-naïve and had not had abnormal chest findings in the history were enrolled. The detection rate and patterns of abnormal findings in respiratory organs were investigated using 32 or 64 slice CT scanner without contrast media. Background characteristics were as followings; mean age was 59.4, disease duration 6.3y, concomitant MTX 86.9% (12.1mg/w), concomitant PSL 20.9% (4.75mg/d), SDAI 30.3, DAS28(ESR) 5.61. 132 cases (69.5%) showed abnormal findings: UIP patterns 10, NSIP patterns 20, OP patterns 2, bronchiolitis 6, bronchiectasis 2, old tuberculosis 10, non-tuberculous mycobacteria suspected 5, lung cancer suspected 2, old inflammatory change 61. The respiratory manifestation was related to longer disease duration (8.1y), but not disease activity and concomitant medication. Thus, abnormal chest CT findings were detected in 69.5% of RA patients before introducing biologics and it is hence useful to perform screening chest CT scan to detect RA-related interstitial lung diseases, infections and neoplasms.

P1-057

Three cases of rheumatoid arthritis with a high titer of IL-6 in pleural or ascitic fluid

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Conflict of interest: None

79 year-old-year woman, 76 year-old man and 80year-old man who had been treated for rheumatoid arthritis for long term were admitted to our hospital because of dyspnea or abdominal bloating. The laboratory examination was elevated CRP and anti CCP antibody. While, ANA and MPO-ANCA was negative. Radiograpy and CT showed massive amount of pleural effusion or ascitic fluid. The result of paracentesis was exudative fluid on one, other were exudative fluid, and were differed from typical rheumatoid pleurisy such as glucose concentration, pH and LDH levels. Although we have carefully worked up for the possibility of various causes, there was no evidence of cardiac failure, liver cirrhosis, malignant tumor, nephrotic syndrome and infections. The three patients received a diagnosis of pleural or ascitic fluid related to RA. Several cytokines were measured. Above all, IL-6 levels were remarkably high titers as compared to serum. It is known that the serum TNF-α and IL-6 is proportional to the RA activity. The potential mechanisms of the cytokines in fluid have not been elucidated. This report has important implication in that elevated IL-6 level in pleural or ascitic fluid may be involved in the pathological mechanisms.

P1-058

A case of simultaneous onset of organizing pneumonia(OP) and rheumatoid arthritis(RA)

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Conflict of interest: None

A 43 years old non-smoking woman admitted to our hospital because of high fever and polyarthritis. One month before admission, she consulted nearby clinic for fever and arthralgia. She was treated with antibiotics and NSAIDs, but her condition was getting worse. At the time of her administration, she had polyarthralgia, such as bilateral wrist, knee and MTP joints. A chest radiography and CT revealed consolidation in right lower lobe. High titer of CRP, RF and CCP-Ab were also revealed in her laboratory data. We examined BAL, showing significant increase of lymphocyte. We diagnosed with a simultaneous onset of OP and RA. She was treated with PSL 40mg daily, and promptly responded. OP is well known as a major complication of RA, however, simultaneous onset of OP and RA is rare. We demonstrated and considered this case with some literature.

P1-059

Membranous nephropathy in the rheumatic patients - Comparison of two cases of membranous nephropathy that had different courses after treatment of rheumatoid arthritis

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Conflict of interest: None

Case 1. Patient is a 79-year-old woman. She was diagnosed as having rheumatoid arthritis (RA) in 1960. She has had only prednisolone (PSL) from 1994 because of allergy to other drugs. Proteinuria developed in September, 2008 and she was underwent renal biopsy. It revealed membranous nephropathy (MN). She had arthralgia and started Infliximab. Proteinuria was improved according to decrease the activity of RA. Case 2. She is a 54-year-old woman. She was diagnosed as having RA in 2009. She had a complete remission by using Salazosulfapyridine (SASP). She had exacerbation of the arthritis in August, 2010, and started MTX. But MTX was not effective and she started Etanercept in February, 2011. She had proteinuria and had a diagnosis of membranous nephropathy by renal biopsy. She obtained remission of RA by using Etanercept, but proteinuria did not improve. So she changed Etanercept to Tocilizumab in November. Proteinuria lasted subsequently. She started PSL 30mg in January, 2012 and proteinuria improved. Bucillamine-induced MN is well known in RA patients, and MN improve by bucillamine cancellation. But it is not clear the treatment of non bucillamine-induced MN in RA patients. We report the difference of therapeutic response for non bucillamine-induced MN in RA patients.

P1-060

Prevalence and incidence of chronic kidney disease in the patients with rheumatoid arthritis

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Conflict of interest: None

[Objectives] To determine the prevalence and the incidence of chronic kidney disease (CKD) in the patients with rheumatoid arthritis (RA). [Methods] We reviewed the prevalence and incidence of CKD among 167 patients with RA (RA group) followed during two years. As negative control, we used the data of 1174 individuals who visited our hospital for medical checkup (control group). We also investigate the relationship between the disease activity of RA and the decrement of estimated glomerular filtration rate (eGFR). [Results] After one year, decrement of eGFR was significantly greater than control group(3.84 % vs. 0.48 %, $p = 0.000$). The incidence CKD more than stage 3 were higher in RA group after 1 and 2 years (10.7 % vs 1.2 %, $p = 0.000$ and 19.6 % vs 1.6 %, $p = 0.000$, respectively). Multiple regression analysis revealed significantly greater decrement of eGFR in RA group compared with control group ($p = 0.004$). Among RA group, DAS28 at baseline significantly correlated with the decrement of eGFR after 1 year ($R = -0.213$, $p = 0.032$ and $R = -0.255$, $p = 0.010$, respectively). [Conclusion] The patients with RA had greater decrement of eGFR and higher prevalence and incidence of CKD than those in general population. Disease activity of RA might be related to decrement of eGFR.

P1-061

A case of AA amyloidosis and cytomegalovirus enteritis with rheumatoid arthritis

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Conflict of interest: None

A 78-year-old woman treated rheumatoid arthritis with prednisolone for 5 years suffered from proximal muscle weakness. She admitted to our hospital due to progressive muscle weakness. On admission, she had a fever and dehydration. Her general condition improved by infusion therapy and antimicrobial treatment, but high fever and elevated CRP levels continued. Subsequently, she developed diarrhea and also had a pain in her left foot. Contrast-enhanced CT scan revealed occlusion of a left popliteal artery and we performed catheter intervention to remove clots and started administration of antiplatelets and vasodilators. At the same period, we found inflammation with the bleeding on the colonic mucosa by colonoscopy. As arterial occlusion and nonspecific inflammation of the colon suggested collagen-vascular disease-related vasculitis, so administration of prednisolone at 1mg/kg/day was started. Four weeks later, CMV antigenemia test turned positive and we administered ganciclovir. However, she developed severe watery diarrhea, resulting in death. Autopsy revealed AA amyloidosis and cytomegalovirus enteritis.

P1-062

The atlantoaxial subluxation in the patients with rheumatoid arthritis

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Conflict of interest: None

[Objectives] To evaluate the ratio of atlantoaxial lesions in the patients with rheumatoid arthiritis (RA). [Methods] We studied 421 patients with RA who could be able to evaluate disease activity in total 650 patients with RA in our Division at the end of January 2012. [Results] The patiets were consisted with 83 males and 338 females. The average age was 64.4±13.5 (17.2-91.9) years old, and they were followed in 8.4±5.5 years in our hospital. The stage was I 64, II 170, III 81, and IV 94, respecitively. The class was I 68, II 265, III 84, and IV 4, respecitively. We could evaluate atlantoaxial lesions in 397 patients, and found no lesion in 297 patients, horizontal subluxation in 99 patients (24.9%) who included 10 already operated patients and 10 severe subluxation, and vertical subluxation in 4 patients. [Conclusion] As the clinical results of cervical lesions in RA are very severe and serious, these are very important complications of RA. Although many of our RA patietns were in the state of clinical remission or low disease activity, some patients showed severe atlantaxial lesions in this study. Also, as the ratio of atlantaxial lesions are not low, we consider that we should commonly evaluate these complications.

P1-063

A case of Felty's syndrome treated with tacrolimus

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Conflict of interest: None

A 67-year-old male visited a community hospital for general fatigue in 2002. The patient was diagnosed rheumatoid arthritis (RA), because of bilateral joints swelling and tenderness with rheumatoid factor positive. Then he transferred to our hospital and we found he presented leukocytopenia (WBC:1600/μl) with splenomegaly seen on abdominal computed tomography. We diagnosed Felty's syndrome and started to treat with gold sodium thiomalate (GST) and prednisolone (PSL) at 5 mg/day. The therapy was effective, thus we could discontinue GST and taper PSL in December 2006. However, he had relapsed leukocytopenia (WBC:640/μl) in August 2008 and we added oral PSL at 30 mg/day. After leukocytepenia improved by the treatment, he had recurrent leukocytopenia (WBC:2800/μl) with right knee joints pain in December 2008. We added oral PSL and started to treat with tacrolimus for the purpose of tapering PSL and preventing the relapse of leukocytopenia and arthritis. After we added tacrolimus, we could taper oral PSL with no recurrence of the symptoms. Although methotrexate is well known treatment for Felty's syndrome, we chose tacrolimus for avoiding drug induced leukocytopenia. Here, we report a rare case of Felty's syndrome successfully treated with tacrolimus.

P1-064

A case of multiple joint pain and rash, suspected erythema elevatum diutinum

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Conflict of interest: None

A 25-year-old woman was aware of bilateral elbow and knee join pain one month ago. Rash were appeared on her bilateral elbow and around Achilles' tendon at same time. She presented to our hospital because pain and rash got worse. She had 17 tenderness joints, 5 swelling joints, and tenderness on Achilles' tendon. CRP, rheumatoid factor and anti-CCP antibody were negative. X-ray image showed no marked bony change. Biopsy was done for skin lesions by Dermatolosist. Pathological findings were inflammatory cell infiltration(neutrophil and lymphocyte) and nuclear dust. We suspected the lesions as erythema elevatum diutinum (EED). Joint pain and skin lesions were self-healing after that. EED is characterized by infiltrated and elevated erythema which occur on back of the limbs joints. EED is accompanied by joint pain, like rheumatoid arthritis (RA), 25%. On the other hand, RA is complicated by EED. EED often repeats recovery and recurrence. This case has possibility of EED recurrence and RA diagnosis.

P1-065

Case of methotrexate-associated lymphoproliferative disorder (MTX-LPD)

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Conflict of interest: None

[Objectives] Methotrexate-associated lymphoproliferative disorder (MTX-LPD) is important complication by methotrexate (MTX). We experienced MTX-LPD in the patient used MTX so we report this case and bibliographical consideration. [Case] 60year-old woman treated with MTX (total dose 1950 mg) had a fever for 19 days. We searched source of fever by CT. CT shown many masses. We thought those were abscess so stoped MTX and gave Sulbactam/Ampicillin and Vancomycin. Her fever went down, however CT finding was no change. Considering malignant lymphoma, we did a biopsy on the swelled lymph nodes. This biopsy revealed MTX-LPD. In addition, she presented drug eruption so we did steroid therapy and stoped antibiotics. After 1 week, many masses found first CT was reduced or vanished. Because MTX-LPD was treated, she was discharged from hospital. [Conclusion] We think steroid therapy is effective against MTX-LPD because many masses was vanished after steroid therapy.

P1-066

The significance of combination therapy for rheumatoid arthritis

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Conflict of interest: None

[Objectives] Early aggressive therapy is recommended for better clinical outcomes in patients with rheumatoid arthritis (RA); however, not all the patients can achieve disease remission. We aimed to evaluate the significance of combination therapy by using our database. [Methods] Patients with RA (n = 826) were stratified to five groups according to a number of therapeutic drugs and the use of biologics (F: drug free, D1: one low molecular anti-rheumatic drug without biologics, D2: two drugs without biologics, D3: three drugs without biologics, B: biologics). The study protocol was approved by the ethical committee of our university. [Results] RA patients were stratified as groups of F: 12.8 %, D1: 26.6 %, D2: 25.4 %, D3: 9.6 %, B: 25.5 %. Mean age (years) was F: 57.9, D1: 60.4, D2: 63.9, D3: 67.9, B: 56.8. Each clinical outcome was worse in the group of D2 or D3 compared with F or D1. (Mean HAQ-DI was F: 0.29, D1: 0.36, D2: 0.55, D3: 0.78, B: 0.53; Mean DAS28ESR was F: 2.84, D1: 2.93, D2: 3.17, D3: 3.28, B: 2.81; Mean SDAI was F: 8.47, D1: 8.45, D2: 10.03, D3: 10.21, B: 7.43; Mean CDAI was F: 7.48, D1: 7.90, D2: 8.98, D3: 8.59, B:6.90) [Conclusions] Current options of therapeutic drugs were not sufficient for disease remission.

P1-067

Two cases of Intraductal papillary mucinous neoplasm with rheumatoid arthritis

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Conflict of interest: None

As for the rheumatoid arthritis (RA) patients, various complications including malignant tumor may develop in their long clinical course. Intraductal papillary mucinous neoplasm (IPMN) is a relatively new disease concept, which is recognized by the development of image analyses. Here, we report two cases of IPMN

which complicated with RA. [Case 1] The patient is a 60-year-old woman who was diagnosed RA in June 2005. We found almost 3cm of IPMN on a pancreas body to tailpiece in May 2009. She can maintain low disease activity, currently with PSL 2 mg +MTX 12mg/wk + salazosulfapyridine (SASP) 1000 mg. [Case 2] The patient is a 74-year-old male who was diagnosed RA in April 2009. He was inducted infliximab therapy in February, 2010 and terminated 7 month later, because he reached remission status. However, the disease activity increased, we started 40mg of adalimumab (ADA) biweekly in August 2011. We found almost 3cm of IPMN on a pancreas body in March 2012. We decreased ADA and then discontinued. He can maintain low disease activity only with MTX 10 mg/wk. Both of two cases keep stable of IPMN. It has been reported long term follow up of IPMN could occur conventional pancreatic cancer, its management during immunosuppressive therapy including biological agents is very important.

P1-068

Effectiveness study of new oral triple therapy in rheumatoid arthritis (analysis of in vitro and prospective clinical study)

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Conflict of interest: None

[Objectives] To confirm the feasibility of new oral triple therapy in rheumatoid arthritis by means of in vitro and prospective clinical analysis. **[Methods]** Triple therapy with combination of methotrexate (MTX), mizoribine (MZB) and tacrolimus (TAC) were employed on in vitro study with osteoclasts and prospective clinical study in order to show those efficacies for refractory rheumatoid arthritis (RA). In particular, low dose TAC or MZB were added to treat ten patients with RA that was resistant to MTX+MZB or MTX+TAC dual therapy. **[Results]** Triple therapy showed statistically significant difference to reduce differentiation induction and activity of osteoclasts comparing with mono and dual therapy. Triple therapy also showed statistically significant difference to improve disease activity score28-ESR/CRP (DAS28-ESR/CRP), simplified disease activity index (SDAI) and clinical disease activity index (CDAI) around eight month. In addition, serum MMP-3 level was significantly decreased. There were no dropout patients due to adverse effects. **[Conclusion]** Based on in vitro and prospective clinical studies, oral triple therapy might be effective against refractory RA patients. Furthermore, this therapy showed possibility to be safe and valid for economy of health care.

P1-069

Is it possible to predict the effectiveness of increased dose of MTX more than 10mg/w?

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Conflict of interest: None

[Objectives] To investigate retrospectively whether the effectiveness of increased dose of MTX over 10mg/w (MTX up>10mg) for RA patients can be predicted by their former data about the effectiveness of increased dose of MTX under 8mg/w (MTX up<8mg). [Methods] Twenty patients who took MTX up>10mg were evaluated. DAS28-CRP was examined before and after MTX up<8mg, and MTX up>10mg. More than 15% decrease of DAS28-CRP was considered as effective, and less than 15% decrease as non-effective. [Results] No apparent tendency was observed about the effectiveness of MTX up<10mg when evaluated by that of single-stage escalation of MTX<8mg. Two-stage escalation was performed and the data was taken at the dose less than 10mg in 8 patients. Some tendency was confirmed about the effectiveness of MTX>10mg when estimated using the both data of 2-stage escalation. [Conclusion] These results indicate the possibility that the effectiveness of MTX up<8mg predict that of MTX up>10mg.

P1-070

Radiographic progression of hands in patients with early rheumatoid arthritis receiving conventional DMARDs over 15 years of follow-up

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Conflict of interest: None

[Objectives] For early RA, we performed early DMARDs treatment and analyzed hand radiographic progression and reviewed it in retrospective about progress of the joint destruction. [Methods] We intended for twenty RA patients which we performed early treatment by conventional DMARDs for onset less than 1 year and were able to follow up more than 15 years. All cases were female, RA onset time average age was 45.3±13.3 years old, the onset for average was 6.2±4.0 months from the period to a DMARD start. Number of the tenderness joints ; 6.4±4.6, number of the swelling joints ; 3.3±3.4, CRP ; 3.1 ±3.6mg/dl, number of DMARDs ; 3.8±2.0 which they used were agents. We used modified Sharp method (van der Heidje method) with both hands simple radiographs and evaluated the joint destruction at initiation, 3, 5, 10 and 15 years. [Results] Radiographs at the time of the initiation already showed a bone erosions in six cases, and, as for the TSS, 3.5±5.1 at the time of the initiation changed into each 22.1±19.3, 44.5±34.9, 76.0±42.6 and 92.3±48.5 at time in 3, 5, 10 and 15 years. [Conclusion] Joint destruction progresses for the case to present a bone erosion early, and a control of RA is insufficient, and the case that there is much number of DMARDs to use is at risk factor of joint destruction progresses.

P1-071

The efficacy of combination therapy of tacrolimus and methotrexate to RA patients for midterm results

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Conflict of interest: None

[Objectives] To evaluate the combination therapy of tacrolimus (TAC) and methotrexate (MTX) in RA patients intolerant to MTX. [Methods] From November 2006, thirty cases treated with TAC and MTX were evaluated by recording DAS28(4/CRP). The average amount of MTX was 5.6mg, the average dose of TAC was 1.1mg. [Results] After follow up five years, escape cases was nine cases. The patients continuing combination therapy were seventeen cases. DAS28 was 4.55 and decreased to 2.19 at five years, CRP was also reduced from 2.25 to 0.58. According to EULAR response criteria, good response was sixteen cases, moderate re-

sponse was one cases. [Conclusion] The combination therapy of TAC and MTX was effective for midterm results.

P1-072

Adding therapy of non-biological DMARDs for rheumatoid arthritis patients who did not improve their disease activity by methotorexate

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Conflict of interest: None

[Objectives] Biologics have evolved dramatically in rheumatoid arthritis (RA) therapy. Nevertheless all patients are not prescribed biologics because of complications or economic reasons. The aim of the present study was to evaluate adding therapy of non-biological DMARDs for RA patients who did not improve their disease activity with methotorexate (MTX). [Methods] Twenty five RA patients (5 males and 20 females) who did not improve their disease activity by MTX were involved. Five patients were given Salazosulfapyridine (SASP) by 1000mg/day, 10 patients Mizoribine (MZR) by 300mg/week or 150mg/day and 10 patients Taclorimus (TAC) by 1.0~2.0mg/day. After addition we evaluated disease activity by CRP and DAS28CRP, radiographic changes, functional disability by HAQDI and safety. [Results] Nine patients discontinued because of inadequate effectiveness. Fifteen patients (one patients SASP, 6 patients MZR, 8 patients TAC) achieved moderate response by EULAR criteria. Mean delta total sharp score/year was 0.87. Mean HAQ score was 0.74. Serious side-effects did not occur. [Conclusion] Overall, adding MZR and TAC therapy was effective for RA patients who did not improve their disease activity with MTX therapy. This therapy is useful for these RA patients.

P1-073

Efficacy of MTX toward elderly RA patients who is older than 75 years old

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Conflict of interest: None

[Objectives] Although MTX is an anchor-drug in RA, It is sometimes difficult to introduce in elderly patients with RA. We have tried to investigate the efficacy of sDMARDs, especially MTX, toward elderly RA patients who is older than 75 years old (y.o.) at introducing sDMARDs. [Methods] This is a retrospective study of 81 RA patients who is older than 75 y.o. at entry. RA patients older than 75 y.o., sDMARDs, newly introduced between April 2009 and March 2011, were investigated about the efficacy, continuation rate and side effects regarding to MTX and non-MTX groups. [Results] Average of age and disease duration at entry were 80.3 y.o. and 2.3 years, respectively. MTX group contained 46 patients and non-MTX group contained 35 patients, respectively. As compared with non-MTX group, the decrement of DAS28-ESR at each time point was remarkable in MTX-group. The rate of achieving low disease activity as well as remission showed a similar fashion. Side effects of MTX were tolerable and the continuation rate at 1 year of MTX was high as 91%. [Conclusion] Our data suggest a superiority of MTX than non-MTX DMARDs in elderly patients with RA if MTX is successfully introduced in these patients.

P1-074

Effects of MTX dose escalation on treatment of RA

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Conflict of interest: None

We studied the effects of MTX on outpatients with RA in our hospital. In February 2011 (2011 group), the patients treated with MTX were 65.1 % of total RA patients (n=370), while those treated with MTX increased to 66.8% of total RA patients (n=446) in August, 2012 (2012 group). MTX monotherapy was carried out in 40.6% of all RA patients and MTX combination therapy with other DMARDs or biologics was 28.0%. As for latter, the combination therapy with biologics was 50.3%, and salazosulfapyridine which was most frequently used among DMARDs was 25.6%. Patients treated with more than 8mg/week dose of MTX were 24.5 % in 2011 group, those increased to 50.3% in 2012 group. We assessed the disease activity of RA patients treated with MTX using DAS28-ESR. DAS28-ESR was 3.17±1.08, and the patients who achieved DAS28-ESR remission (score<2.6) and/or low disease activity state (score<3.2) were 54.5% in 2011 group. On the other hand, DAS28-ESR was 3.10±1.30, and remission and/or low disease activity were 59.7% in 2012 group, suggesting the beneficial effect of MTX dose escalation on treatment of RA.

P1-075

Increase in methotrexate dose in patients with rheumatoid arthritis who have an insufficient response to biologics

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Conflict of interest: None

PURPOSES: To evaluate effect of increase in methotrexate (MTX) dose in patients with rheumatoid arthritis (RA) who have an insufficient response to biologics. METHODS: Nineteen patients whose dose of MTX was increased due to insufficient response was included. The observation was available for 24 weeks or more. The number of swollen joints, tender joints, VAS score, mHAQ, CRP, ESR, DAS28-CRP/ESR, adverse effects by 24 weeks, and the effect by the EULAR response criteria at 24 weeks were examined. RESULTS: The average MTX dose was increased from 8.6±1.4 mg to 11.2±1.8 mg in 24 weeks. In 24 weeks, average DAS28-CRP and DAS28-ESR improved significantly from 2.93±0.88 to 2.07±0.86 and 3.79±0.93 to 3.04±0.91 respectively ($p<0.01$, each). The number of patients of more than moderate disease activity decreased from seven to four. Seven patients were considered as more than moderate response (MR) at 24 weeks, whose average MMP-3 value at 0 week was significantly lower than no response group. CONCLUSIONS: It was suggested that increase of MTX dose was effective in RA patient who have an insufficient response to biologics, and MMP-3 value may be useful

in the estimation of its effectiveness.

P1-076

Change of serum MMP-3 levels by renal function in patients with rheumatoid arthritis

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Conflict of interest: None

[Objectives] Serum MMP-3 is excreted from the kidney, it has been reported for serum MMP-3 concentration to increase due to a renal dysfunction. We examined the influence which renal function has on change of serum MMP-3 in RA patients with biologic therapy. [Methods] We analyzed 110 patients in continuation with Adalimumub therapy at 12 weeks in TBC registry. They were divided into 3 groups by the estimate glomerular filtration rate (eGFR) at baseline: low value group (L group, average:63ml/min./1.73m^2), medium value group (M group, 87ml/min./1.73m^2), and high value group (H group, 116ml/min./1.73m^2). We evaluated the improvement rate of serum MMP-3 at 4 weeks. [Results] DAS28-CRP at baseline were the L group 4.6, the M group 4.9, and the H group 4.9. MMP-3 at baseline were the L group 266(ng/mL), the M group 315(ng/mL), and the H group 415(ng/mL). DAS28-CRP at 12 weeks were the L group 2.9, the M group 3.4, and the H group 3.2. MMP-3 at 12 weeks were the L group 120(ng/mL), the M group 224(ng/mL), and the H group 240(ng/mL). The improvement rate of serum MMP-3 at 12 weeks did not have a significant difference among 3 groups by 39% in L group, 30% in M group, and 38% in H group. [Conclusion] In biologic therapy, a slight renal dysfunction does not influence change of serum MMP-3.

P1-077

Long-term Efficacy of Golimumab on Rheumatoid Arthritis Patients

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Conflict of interest: None

[Objectives] I reported long-term efficacy of GLM on RA patients. [Methods] From 46 RA patients using GLM at the clinic, 18 patients who were administrated GLM more than 52 weeks were evaluated the disease activity, the remission rate and the dosage of MTX at starting time of GLM and 52 weeks respectively. It was 8 of biologics naïve patients, 10 of switching from other biologics. 17 patients were administrated 50mg dose of GLM (all with MTX), and one patient was 100mg without MTX. [Results] DAS28-CRP at before GLM initiation and after 52 weeks of GLM administration were 4.58 and 1.71 respectively. Also, SDAI were 27.61 and 3.14 respectively. The clinical improvement was observed at both evaluations. The remission rate (DAS<2.3) at 52 weeks was 88.9%. It was 100% in case of naïve, and 80% in switching. The mean dosages of MTX at before GLM initiation and after 52 weeks of GLM administration were 6.2mg and 8.0mg/week respectively. All of 12 patients who were increased MTX during GLM administration achieved DAS28-CRP remission. [Conclusion] GLM is an efficient biologics in long-term using not only for the biologics naïve patients, but also the switching patients from other biologics. And, it was expected to increase efficacy of GLM by increasing dose of MTX.

P1-078

New-onset demyelination induced by infliximab therapy for rheumatoid arthritis patients

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Conflict of interest: None

A 66-year-old male RA patient was treated with infliximab (300mg over 8week), tacrolimus (3mg/d), prednisolone (5mg/d), and salazosulfapyridine (1000mg/d) for 2 years. These treatments were effective and induced clinical remission status. However, numbness of lips, left cheek and auricle was appeared on Feb. 20, 2011. Treatment of acyclovir for a presumed virus infection was not effective, and symptons were continued. MRI of brain showed multiple progression of the ring-like white matter signal intensity in the cerebral cortex on T2-WI. CSF analysis revealed elevated IgG index, and mildly elevated protein level and the number of cells. We diagnosed new-onset demyelination induced by infliximab, then it was discontinued. Infections, tumors, blood vessel disorders and autoimmune diseases were excluded. Methylprednisolone (1000mg/d) pulse therapy was started on Apr. 13. It was effective and abnormality lesions of MRI were decreased on May 23. Since anti-TNF agents came in wide use for treatment of autoimmune diseases, including Crohn's disease and RA, reports of neurological complications by anti-TNF agents have been accumulating. Demyelination diseases should be considered if neurological symptons appeared during treatment of anti-TNF agents.

P1-079

Development of sarcoidosis during etanercept therapy

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Conflict of interest: None

A 65-year-old woman developed granulomatous lesions consistent with sarcoidosis during etanercept therapy for rheumatoid arthritis. Hilar and mediastinal lymphadenopathy and nodules in left lung field developed 8 months after administration of etanercept. Angiotensin converting enzyme (ACE) was increased (59.4IU/L). Transbronchial lung biopsies showed noncaseating epithelioid cell granulomas consistent with sarcoidosis. Two weeks after being diagnosed with lung sarcoidosis, she was suffered from acute cardiac failure. The Ga scintigraphy image showed the uptake by heart and hilar lymph nodes. Transesophageal echocardiography revealed severe cardiac dysfunction (EF 26%). So she was diagnosed as cardiac sarcoidosis, either. She was recovered by administration of 30mg prednisolone. We should keep in mind that granulomatous disease such as sarcoidosis, can develop during treatment with a tumor necrosis factor-alpha blocking agent, such as etanercept.

P1-080

A case of SLE that developed in the course of RA treatment with Etanercept

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Conflict of interest: None

[Case] 35 years old,female. [Chief complaint] Fever [Clinical history] She was diagnosed as having RA in 2004. Joint pain exacerbated in July 2011 in spite of the administration of salazosulfapyridine (SASP) from August 2011. Etanercept (ETN) was started in March 2012, and joint pain was gradually improved. From June 26, the administration of ETN was discontinued because she had fever, rash, cough, and was complicated with pancytopenia, and she was admitted on July 19. According to clinical and laboratory criteria (ANA-positive, anti-ds-DNA antibody-positive, proteinuria, arthritis, facial rash, painless oral ulceration, blood disorders; 7 of 11), SLE was diagnosed. In addition, a 3-day pulse of methylprednisolone (750mg/day), and then the administration of high dose prednisolone (PSL) (1mg/kg/day) were started. Renal biopsy was performed and the renal specimen was diagnosed as type IV-S(A) + V of lupus nephritis. Combined administration of Tacrolimus (TAC) was added in August. Currently she sustained the clinical remission in SLE and RA. [Discussion] Appearance of serum antinuclear antibodies is known with the treatment of ETN in RA, but there are few cases about the development of SLE. We report that the appearance of autoimmune antibody in SLE with anti-TNF agent treatment.

P1-081

The Incidence of Exacerbation of Pre-existing Interstitial Lung Disease (ILD) is Higher in TNF blockers than in Non-TNF blockers in RA

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Conflict of interest: None

Purpose: According to the post-marketing surveillance report of TNF blockers, the development/exacerbation rate of ILD was 0.5 %, however we have shown that in patients with pre-existing ILD, the rate is nearly 30%. Here we compared the incidence of exacerbation of pre-existing ILD in patients administrated with TNF blockers and non-TNF blockers. Method: Subjects were 58 patients with RA, with the mean age of 66. As a part of workup before administration of biologics, chest CT scan was done. After administration of biologics, chest X-ray film (CXR) was taken at least every 3 months. When newly developed shadows were found on CXR or when patients complained of respiratory symptoms for more than 2 weeks, chest CT scan was done again. The duration of observation was 12 months. Results: The ILD exacerbated in 14 subjects (24.1 %). The biologics used at the exacerbation of ILD were IFX in 5, ETN in 8, ADA in 1, TCZ in 0 and ABT in 0, respectively. The incidence of ILD exacerbation with TNF blockers and non-TNF blockers were 30.4 % (14/46) and 0 % (0/12), respectively, a significant difference between them ($p = 0.024$). Conclusions: The exacerbation rate was high in patients with pre-existing ILD when TNF blockers were administrated.

P1-082

A prospective study of the influence of biologic agents on the standardized incidence ratio (SIR) of tuberculosis (TB) in patients with RA by *NinJa* for 9 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 9 years. [Results] Among 53,952 RA patients registered from 2003 to 2011, 46 patients developed TB. 5 patients (10.9%) were treated with biologic agents. The SIR of TB in RA patients treated with biologic agents was 4.11, and the SIR of TB in patients treated without biologic agents was 3.76. [Conclusion] The incidence of TB in RA patients treated with biologic agents was higher than that in RA patients treated without biologic agents.

P1-083

Examination of the treatment for patients with rheumatoid arthritis (RA) after improvement of organizing pneumonia (OP) during treatment with TNF inhibitor (TNFi)

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Conflict of interest: None

Purpose: To investigate the treatment of patients with RA after improvement of OP during treatment with TNFi. Method: We retrospectively reviewed four patients with RA, who diagnosed as OP during treatment with TNFi. Result: Two men and two women were included. The mean age at diagnosis as OP was 65 years old. They were treated with infliximab or etanercept (ETN). TNFi and DMARD were stopped and treatment of PSL (15-30mg/day) improved the development of OP. But, the activity of RA got worse during tapering of PSL (1~8 months after onset of OP). Case 1: Disease activity was improved by tacrolimus (TAC). (SDAI:10.65 →1.01) Case 2: Disease activity was reduced by resumption of MTX and ETN. (SDAI:10.65→6.1) Case 3: TAC, resumption of MTX and ETN, and switching to adalimumab did not improve disease activity but abatacept (ABT) was improved disease activity. (SDAI: 7.83→3.96) Case 4: TAC did not improve disease activity, but ABT was lead to clinical remission. (SDAI: 7.01→2.96) Moreover, the recurrence of OP and pulmonary complication do not have any case under treatment of PSL Conclusion: It is suggested that the recurrence of RA activity after onset of OP is controlled to treat with DMARD and biologics under use of corticosteroid. But it should be fully taken the adaptation.

P1-084

Prospective study on side effects of biologics. Comparison with side effects of MTX-treated RA patients

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Conflict of interest: None

[Objectives] Prospective study was done to evaluate side effects of biologics and to see how to avoid major ones. [Methods] Four hundreds of RA patients were incorporated in this study. For purpose of accuracy, each patient was asked for a year to describe questionnaire on daily symptoms and signs which were assessed on every visit to the clinic. If patients experienced one of those, they were encouraged to call to the clinic. Two hundred and seventy patients were treated only with MTX. One hundreds and tweleve received biologics with MTX. Eighteen were only with biologics. [Results] Pneumonia developed in a patient on hemodialysis receiving a biologic. Cellulitis occurred in a MTX-treated patient. Many patients treated with biologics experienced minor side effects which were either respiratory symptoms or fatigue. However, those numbers were not significantly high compared to patients with MTX. [Conclusion] Monitoring of symptoms and signs was proved effective in patients treated with biologics, if appropriate intervention were carried out to avoid major side effects.

P1-085

A case of peripheral T-cell lymphoma with RA patient who had been treated with infliximab plus methotrexate

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Conflict of interest: None

76 years-old man, who had been treated with IFX plus MTX for six years complained systemic lymphadenopathy with skin-rush and high fever. Administration of antibiotics had no effect and he developed a liver dysfunction with severe jaundice. He was guessed to have an aggressive type of malignant lymphoma (ML) and admitted December 2 in 2011. Because of his severe systemic symptoms, he was immediately treated with steroid-pulse therapy (from December 8 to 10). As quantification test of EBV-DNA was remarkably increased, re-activation of EBV might have some influences on his clinical status. Histological examination from his inguinal lymphnode revealed peripheral T-cell lymphoma (TCRβ1 positive, Ig (H) JH positive, EBER positive). But Ga scintigraphy showed no abnormal uptake lesion. After steroid-pulse treatment, every clinical symptoms and laboratory examinations had apparently improved. On December 19, chemotherapy for ML had added only once. All of his clinical problems diminished gradually. Peripheral T-cell lymphoma is rare disease with poor prognosis. In RA patients, some reports mentioned MTX and anti-TNF therapy might be associated independently with an increased risk of lymphoma and EBV re-activation is thought to be one cause of MTX related lymphoproliferative disease in RA.

P1-086

Tuberculosis in RA patients receiving anti-TNF agents despite keeping guidelines for screening and management of LTBI : Comparison between TST only versus TST plus QTF-GIT for screening LTBI

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Conflict of interest: None

[Objectives] To compare the outcomes of two strategies for LTBI screening; TST only vs. TST plus QFT-GIT in RA patients using TNF inhibitors (TNFI) [Methods] Data was extracted from RESEARCh (retrospective cohort for TNFI users). Among the 409 RA patients who underwent TST, 355 patients who strictly followed screening guideline for LTBI before starting TNFI were included in this study. Patients were divided into two groups according to the strategy for screening LTBI. We calculated the SIR (standardized incidence ratio) of TB in TNFI users and compared the TB incidence between two groups. [Results] In patients with TNFI who strictly followed screening for LTBI guidelines, the overall crude incidence of new-onset TB was 305.9/100,000 person-years (PY). Compared with the general population, the overall age-sex SI in above patients was 4.4. In the patients with TST only strategy (n=222, 545.3 PY), 2 patients developed TB during TNFI treatment, while no patient developed TB in patients with TST plus QFT-GIT strategy (n=133, 108.5 PY). [Conclusion] Despite of following screening guideline for LTBI, TB incidence for RA patients receiving TNFI is higher than general population. Combining QFT-GIT with TST as a screening for LTBI might be reduce the incidence of TB in TNFI users.

P1-087

A patient with RA who manifested HCV hepatitis after the treatment with etanercept

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Conflict of interest: None

[Objectives] Compared to HBV hepatitis, aggravation of HCV hepatitis after administration of biological drugs for RA has not been widely recognized. [Methods] A 70-year-old woman, who had been negative with 3rd-HCVAb, was treated with etanercept (25 mg)/1 - 2w and MTx 6 mg/w. After the 5-year treatment, liver damages (AST 81, ALT 75) were detected by regular blood examination. HBcAb was positive but HBV revitalization was negative, because of undetected HBV-DNA. Suspecting of drug-induced liver damage, administration of MTx, etanercept and NSAID were once stopped and treatments with glycyrrhizic acid and Ursodeoxycholic acid commenced. Since liver damages have been further progressed (AST 313, ALT 254), HCVAb was re-examined and HCV-RNA (+)-genotype 2A was found to be positive. She had no past history of blood transfusion. [Results] Since her RA has been inactive, treatment for HCV hepatitis was immediately started by using peginterferon alfa-2a (90μg/w). [Conclusion] Thus, it is important to regularly examine liver function and HCVAb at some points, even for the undetected cases of HCVAb before administration of etanercept.

P1-088

A case of subcutaneous abscess caused by Salmonella during etanercept therapy

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Conflict of interest: None

The case was a 25-year-old woman.She was diagnosed with idiopathic thrombocytopenic purpura at the age of 3, juvenile myelomonocytic leukemia at the age of 4, and had splenectomy at the age of 14. She develop rheumatoid arthritis at the age of 23, systemic lupus erythematosus at the age of 22.During administration of ETN (50mg/week)+prednisolone (8mg/day)+methotrexate (MTX) (6mg/week), she noticed a left abdomen ache. A mass developed and gradually increased. We touched a large hard tumor 5cm under the skin on the left hypochondrium, and showed tenderness. Tumor was punctured, we collected a small amount of purulent component. Since infection was suspected, we discontinued MTX and ETN and started ceftriaxone. We also suspected mycobacterial infection, but negative. *Salmonella* O4 group was detected by incubated aspirate (Blood cultures were negative). Changed to levofloxacin, she continued to oral 4 weeks. Both pain and tumor has disappeared. The same bacteria were cultured from the stool. Because of no gastrointestinal symptoms before the onset, we think that bacteria were seeded to the skin hematogenously after infected the intestinal tract asymptomatically. We report a case of valuable experience, because report of Salmonella infection during use of TNF inhibitors is extremely rare in Japan.

P1-089

The incidence of infusion reactions in rheumatoid arthritis patients who received infliximab with shorter infusion times

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Conflict of interest: None

[Objectives] To examine whether the shortening infusion times of infliximab (IFX) increase the incidence of infusion reactions (IRs) in patients with rheumatoid arthritis (RA). [Methods] All RA patients who received IFX at our institution between 2004 and September 2012 were reviewed. The incidence of IRs in patients with shorter IFX infusions (short group) were analyzed by comparing to those in non-short group in our cohort and those in the results of postmarketing surveillance (PMS) study. [Results] 404 shorter IFX infusions in 42 patients were observed in a total of 1,626 IFX infusions in 127 patients. The infusion times were reduced to 1.5 hours in 16 patients, and to 1 hour in 26 patients. In the non-short group, IRs appeared in 8/85 (9.4%), and 2 of 8 received prophylactic corticosteroids. IFX was discontinued by the IRs in 6 patients. In the short group, IRs appeared in 2 (4.8%). None developed serious IRs. The incidence of IRs in the short group was similar to those in the non-short group, as well as those in the results from PMS study. [Conclusion] In RA patients who have been successfully treated with two-hour IFX infusion, the shortening infusion times of IFX does not increase the incidence of IRs.

P1-090

Clinical features of rheumatoid arthritis patients with severe infection after using biologics

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Conflict of interest: None

Objective: The purpose of this study is to analyze clinical features of rheumatoid arthritis (RA) patients with severe infection after using biological agents. Methods: A total of 211 patients treated with biological agents, etanercept (ETN) 88cases, infliximab (IFX) 55cases, tocilizumab (TCZ) 47cases, abatacept (ABT)20cases and golimumab 1case, were included in this study. Medical records were analyzed retrospectively. Results: 9 severe infections were occurred in 9 patients (mean age 69.8 year-old). The sites and the pathogens of these severe infections were pneumocystis pneumonia 1case, military tuberculosis 1case, pyelonephritis 1case, bacterial pneumonia 2cases, uterine abscess 1case and subcutaneous abscess 3cases. Non-respiratory infections were 66.7%. The biological therapies were included 1 IFX, 3 TCZ and 5 ETN. MTX were given average 8.7mg/week (6-12mg/week) and prednisolone were given 5.7mg/day (2-10mg/day). All patients were treated with antibiotics and improved. Conclusions: Biological agents should be needed assessment with both respiratory and non-respiratory infections.

P1-091

Development of autoantibodies during biological therapies in rheumatoid arthritis (RA)

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Conflict of interest: None

Objectives:Development of anti-nucleosome antibodies (ANA) and anti-dsDNA antibodies, and drugs-induced SLE during biological therapies have been reported.The aim of our study was to detect the positivity of autoantibodies in RA patients during biological therapies which have been continued for more than one year until the present time. Methods:We detected autoantibodies (ANA, anti-dsDNA, Sm, RNP, CL, SS-A/B antibodies) under infliximab (IFX) 24 cases, etanercept (ETN) 43 cases, adalimumab (ADA) 5 cases, tocilizumab (TCZ) 23 cases, abatacept (ABT) 13 cases at baseline, in 2011, and in 2012. Results: IFX (average observation periods 4.8 years)-at baseline ANA 6/24(25.0%), in 2012 ANA, anti-dsDNA antibodies 8/24(33.3%), 0/24(0%) ETN (3.7 years)-at baseline 16/43(37.2%), in 2012 9/44(20.5%), 2/44(4.5%). ADA (3.7 years)-at baseline 1/5(20.0%), in 2012 0/5(0%), 0/5(0%). TCZ (3.1 years)-at baseline 4/23(17.4%), in 2012 1/23(4.3%), 0/23(0%). ABT (1.3 years)-at baseline 2/13(15.4%), in 2012 0/13(0%), 0/13(0%). By the present time, two patients developed drug-induced SLE, one with ETN and one with ADA. Conclution: ANA induction was only observed under IFX therapy. Drug-induced SLE was developed under ETN and ADA therapy. We must pay attention to symptoms of SLE during anti-TNFα therapies in RA.

P1-092

Severe listeria meningoencephalitis in an infliximab-treated patient with rheumatoid arthritis

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Conflict of interest: None

A 58-year-old woman with rheumatoid arthritis (RA), was diagnosed 30 years earlier and was treated with prednisolone and methotrexate. Infliximab therapy (5 mg/kg infusion every 8 weeks) started 5 years earlier because of an active RA. In June 2012, she admitted with high fever, vomiting, confusion and right hemiplegia. Lumbar puncture yielded cloudy CSF, revealing considerable increases in a white blood count of 780/3 ul and proteins and decreased glucose level. An MRI revealed signs of meningoencephalitis and abscess formation. Blood bacterial cultures 5 days after admission demonstrated the growth of *Listeria monocytogenes*. In-

travenous ampicillin (2 g every 6 hours) and gentamicin (1.7 mg/kg every 8 hours) treatment was started. Within 48 hours after the antibiotic therapy, her fever and neurologic complications greatly improved. Follow-up studies of CSF and MRI improved as well, and the antibiotic therapy was continued for the 11 weeks. Infliximab neutralize the biologic action of TNF-α, but it has an important bearing on the host resistant against intracellular microorganisms such as *Mycobacterium* and *L. monocytogenes*. Our case report stresses the need to consider a possible infection with *L. monocytogenes* when meningitis symptoms occur in anti TNF-α treated patients.

P1-093

A case of psoriasiform eruption induced by abatacept after TNF inhibitor treatment in a patient with rheumatoid arthritis

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Conflict of interest: None

A 72-year-old woman with a 41-year history of RA, had been treated with etanercept (ETN) weekly for 38 months. Due to loss of efficacy, the agent was changed to adalimumab (ADA) every 2 weeks. Ten days later she felt uncomfortable with mild facial erythema. After 6 infusion of ADA, ETN weekly was restarted, and the erythema was disappeared. Six months after discontinuation of ADA, abatacept (ABT) monthly was started. Six weeks after switching to ABT, severe psoriasiform eruption was appeared on scalp, face and upper extremities. A skin biopsy was performed, psoriasiform findings with microabscess, acanthosis and inflammatory cell infiltration were shown. But eosinophils were also detected in the dermis which suggests drug-induced. The agent was switched to tacrolimus, and it took 8 months to be recovered. Then golimumab monthly was started, and used 4 times, however, she does not have any eruption and the arthralgia was improved. A paradoxical reaction of that psoriasis is induced or deteriorated by TNF inhibitor, which is developed as a treatment for psoriasis, has been reported. ABT does not inhibit TNF directly, but regulates cytokines indirectly by brocking the constimulation of T cells. Cytokine regulation by ABT may have triggered of the reaction as well as by TNF inhibitor.

P1-094

A case of causing neutropenia by adalimumab

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Conflict of interest: None

[Objectives] Treatment of rheumatoid arthritis (RA) was advanced significantly with the use of biological drugs. Its side effects are widely known, there are few reports of neutropenia. We reported a case of causing neutropenia by adalimumab (ADA). [Methods] A 76-year-old woman with a 34-year history of RA was treated with bucillamine. Then she was treated with prednisolone (PSL) and salazosulfapyridine (SASP). Without improvement, she was referred to our hospital for the purpose of control RA and knee surgery in 2011. Her Disease Activity Score was 5.04. Though She was treated with tacrolimus, she had diarrhea in 2-3 days. And, Gastrointestinal ulceration occured after changing to treat with methotrexate and PSL. ADA was started for the purpose of decreasing PSL. After 2 and 3 weeks after the first injection, the neutrophils was 476/mm^3 and 202/mm^3 respectively. After 4 weeks, neutrophils count rapidly rises to 6258/mm^3. There was no infection without antibiotics and G-CSF preparation. 70 days later, the complete blood count was almost normalized. [Results] We reported a case of neutropenia after the use of ADA. [Conclusion] If there is a previous history of neutropenia after use of biologic response modifiers, we should take care and monitor the complete blood count.

P1-095

A case of Lung tuberculosis and tuberculosis peritonitis after treatment of of Rheumatoid arthritis with golimumab

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Conflict of interest: None

[case raport] Tuberculosis is serious complication associated with treatment of rheumatoid arthritis (RA). We report the case of a 57-year-old Japanese woman with RA who had the lung and peritoneal tuberculosis. She had been diagnosed with RA in 1975. Oral methotrexate (MTX) and methylprednisolone had been administered since 2001. In 2011, MTX dose had to be increased form 10mg/week to12mg/week to control her disease activity. But her symptom was no change and DAS28-CRP score was increased(DAS28-CRP:3.12). so golimumab(100mg) was brought into use for treatment. After 5 times of use of glimumab, fever spikes of 38.9 °C, abdominal pain was had. CT scan results showed that there ware ascites, edema of the gastrointestinal tract, preural effusion and nodular density. PCR test of tuberculosis from stomach fluid was positive. Quontiferon TB-2G test was positive change. So she had diagnosed with lung tuberculosis and tuberculosis peritonitis. Then she was proceeded to treatment use of INH, REF, EB and PZA. [Conclusion] We have to pay attention to the probability that the tubercular infections develop in other than lung too.

P1-096

Sarcoidosis during infliximab therapy for rheumatoid arthritis. A case report

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Conflict of interest: None

We report a rheumatoid arthritis patient who developed sarcoidosis during infliximab therapy, and review the most recent literature. A 34-year-old male was diagnosed with seronegative rheumatoid arthritis by a rheumatologist in 2004, and referred to our hospital in 2010. He was initially treated with bucillamine, corticosteroids and methotrexate that were withdrawn due to lack of efficacy. In 2009, tocilizumab was added due to ongoing disease activity. In 2010 tocilizumab was switched to infliximab because of suboptimal response. There was complete resolution of swollen and tender joint after infliximab therapy. In 2011 he developed fever and malaise, and inflammatory markers elevated. CT scan findings of chest and abdomen was normal except for symmetrical hilar lymphadenopathy. A biopsy of hilar lymph node performed and histopathological examination showed non-caseating epitheloid granulomas with lymphadenitis, suggestive of sarcoidosis. Infliximab was discontinued and he was administered high-dose corticosteroid therapy (30mg/day) with sudden clinical improvement. A

number of case reports have emerged demonstrating the development of sarcoidosis in patients on TNF-alpha antagonists therapy. It is important to be aware of this potential and uncommon complication of this therapy.

P1-097

Septic arthritis after golimumab treatment

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Conflict of interest: None

We describe A-76-years-old woman who developed septic arthritis despite in stable condition after receiving Total Knee Arthroplasty (TKA). This woman was admitted to our hospital, complaining of acute pain and swelling of her bipedal knees. She had had a TKA procedure 10 years earlier and received golimumab 50mg/month since March 2012. Her physical examination revealed high fever, swelling, pain, redness and warmth in her both knees. Laboratory data revealed white blood cell count 10200 /mm^3, elevated erythrocyte sedimentation rate (82 mm/h), C-reactive protein (19.60 mg/dl), elevated procalcitonin level (0.79 pg/ml). Artherocentesis was performed and cloudy and dark yellow synovial fluid (SF) was aspirated and analysis of SF revealed elevated levels of leukocyte (153,000 /μl). Though, culture of the drainage and a blood culture were negative. Consequently, prosthetic joint infection was diagnosed and the patient underwent an emergency open debridement and removal of the polyethylene insert, followed by admisteration of antibiotics for four weeks. It is controversial that biological agents have an increased susceptibility to infection. To the best of our knowledge, this is the first report that developed septic arthritis receiving golomumab after receiving TKA procedure.

P1-098

ARDS observed in the patient with Rheumatoid Arthritis treating with the anti-TNF-α drug

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Conflict of interest: None

The patient is the 56-years-old woman in seropositive rheumatoid arthritis with a history for 10 years (stage 3, class 3). She was ill with renal dysfunction and nasal sinusitis. Cy-A, PSL, were administered to the patient for treating RA and LCAP was performed before admittance to our outpatient. FK and MTX were sterted on year of 2008. ETN was selected to treat the patient that were uncontrollable with preceding DMARDs alone. Because of the infusion reaction those of arthralgia and low grade fever, ETN was changed to IFX. Two days after 6th drip intravenous of IFX, left hemiplegia and speech disturbance was observed. Discontinuation of IFX and introduce of anti-platelet therapy, the symptoms were almost resolved. After 8 month treating with non-biologic therapy, we started ETN because of high disease activity of RA. Less infusion reaction and improvement of arthritis was observed. The patient developed rapidly progressive dyspnea and cough after starting ETN for a year. A chest radiograph showed bilateral multifocal GGO and pneumothorax with bulla. Despite the intubation and high dose therapy of PSL for the patient under the antibacterial therapy, deterioration of lung progressed.

P1-099

Safety and efficiency of golimumab therapy in patiet with rheumatoid arthritis

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Conflict of interest: None

[Objec tives]:To assess efficacy and safety of golimumab (GLM) in patients with active rheumatoid arthritis (RA). [Methods]: The GLM was given in 15 RA patients (one male, 14 female) treating with concomitant methotrexate (MTX) or without MTX. Five patients were bio-naive and 10 were bio- switching (5 from infliximab, 5 from tocilizumab).The efficacy of GLM was evaluated byDAS 28 -CRP and serum values of MMP-3 measured every 4 weeks. In several patients reached low disease activity (LDA), ultrasonic findings of joints were asessed. [Results]: Adverse effects occurred within 8 weeks of GML therapy.Mild pyoderma cured by antibioticswas presented in one switching patient. General fatigue appeared in a naive patient. In these patients GML was withdrawn. Two other patients were droped out at 12 weeks because of unresponsiveness for GLM. Eleven patients (78%) including 4 naive and 7 switchers receiving GML achieved LDA at 16 weeks and subsequently sustained LDA. In patients defined as LDA after 24 weeks of GLM therapy, ultrasonic findings demonstrated improvement of synovial lesions. [Conclusion]: Serious side effect was not found during treatment with GML except for mild pyoderma or general fatigue. GML is useful agent for treating bio-naive and bio-switch patients with active RA.

P1-100

Investigation of 2 RA Patients Who Have Been Receiving Infliximab Therapy for 8 Years

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Conflict of interest: None

[Objective] To investigate the safety and efficacy of 2 RA patients with 8 years of Infliximab therapy. [Methods] I examined the safety and efficacy of the long-term continuous administration of Infliximab through continuous investigation on backgrounds and disease activity progress of the 2 RA patients. [Case1] 48-year-old woman, hypertension, RA diagnosis in 2001, stageIII, classII, introduced with MTX8mg/w. July, 2004, 3 years from RA diagnosis, TJC7, SJC1, ESR101mm/hr, CRP0.19, first introduced with IFX-3mg/kg with RF14, MMP-3 75.4, and PSL12.5mg. Afterwards increased to IFX6mg/kg and continuing. [Case2] 64-year-old woman, hypertension, gallstones, have received artificial joint replacement, RA diagnosis in 1992, stageIV, classII, introduced with MTX6mg/w. July, 2004, 12 years from RA diagnosis, TJC7, SJC4, ESR35mm/hr, CRP0.98, first introduced with IFX3mg/kg with RF30, MMP-3 80.8, and PSL35mg. Afterwards increased to IFX6mg/kg and continuing. [Conclusion] I continued administering IFX for 8 years when there were 6 biological choices. 2 patients are continued to be treated with an increased dose of IFX-6mg/kg. Looking back on 8 years of joint destruction progress control and on HAQ, I confirmed the efficacy and the tolerability of long-term continuation of Infliximab.

P1-101

Malti-focal septic arthritis with rheumatoid arthritis after switching biologics: 2case reports

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Conflict of interest: None

[Case 1] They are a 58 years-old male and a rheumatoid arthritis patient. Symptoms parts were a right leg MTP joint (fistula penetrated to a plantar part), a right knee joint, and the left articulatio cubiti in golimumab from infliximab in after-switch six months.. The reason bacillus was MSSA. MTX and golimumab were stopped, incision discharge of pus was performed to the urgent operation, and self-sustaining washing was performed. [Case 2] They are a 55 years-old woman and a rheumatoid arthritis patient. From infliximab, nine months after switching to golimumab, the symptoms of pyelonephritis are shown and it once carries out light. a both-sides iliopsoas abscess, pyogenic spondylitis, and the left septic knee were seen and stopped in 11 months. The reason bacillus was MSSA. MTX and golimumab were stopped, incision discharge of pus was performed to the urgent operation, and self-sustaining washing was performed. Meningitis was also concurred with and ICU management was also performed. [Conclusion] Multi-focal arthritis was experienced after the biologicals switch. Although it is infection with both critical cases, development-of-symptoms progress is gradual and cautions are required for the development-of-symptoms form under biologicals medication.

P1-102

A case of rheumatoid srthritis complicating with polymyositis after the usage of etanercept

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Conflict of interest: None

Clinical importance: Anti-TNF therapy has been associated with adverse immunologic events including Systemic lupus erytematosus. However, the development of polymyositis (PM) is extremely rare. **Case**: 56 years-female. **Current history**: She developed RA since 2001 and treated with methotrexate and tacrolimus. Since her disease activity was not controlled with these DMARDs, she was administered eranercept since January 2012. In July 2012,after the initiation etanercept, she felt difficulties of raising her upper arm, and her laboratory date revealed increased serum creatine kinase (1113 IU/L), aldolase (18.6 IU/L), cardiac enzyme levels, and anti Jo-1 antibody positive, Interstitial pneumonia was also occurred in her lung. She was hospitalized in our hospital in August 2012 and diagnosed as polymyositis by the results of examinations including needle electrode examination, muscle MRI scan and muscle biopsy from her left dertoid muscle, although she did not have obvious muscle weakness. She was discontinued with etanercept and treated with oral predomizolone (40 mg/day) and tacrolimus. These medications were effective for her polymyositis. We report this case with some discussions in terms of anti-TNF therapy induced myositis.

P1-103

Incidences of cancers in rheumatoid arthritis patients treated with biologic agent

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Conflict of interest: None

[Objectives] Incidences of cancers in rheumatoid arthritis patients treated with biologic agent have been evaluated. [Methods] A total of 248 patients registered in our hospital from the SECURE database between December 2008 and August 2012 were included. [Results] We observed 7 cancers (2 unknown primary cancers, lung cancer, gastric cancer, colon cancer, skin cancer, chronic lymphocytic leukemia).The number of rheumatoid arthritis patients ever treated with tocilizumab was 18, etanerept 75, infliximab 119, abatacept 28 and adalimumab 8.The number of cancer patients ever treated with tocilizumab was 3 (16.7%), etanerept 2 (2.7%), infliximab 2 (1.7%), abatacept 0 and adalimumab 0. [Conclusion] Observational studies and recent meta-analyses reported that no increase in the overall cancer risk was observed among rheumatoid arthritis patients treated with TNFα inhibitor compared to non-treated patients.Our results suggested that rheumatoid arthritis patients treated with tocilizumab tended to increase in cancer incidence.

P1-104

A case of the patient who was infected with HSV1, HSV2 in view of administering Golimumab

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Conflict of interest: None

Past history: gastric cancer in2003.Complication: interstitial pneumonia (IP), diabetes. [Clinical course] We diagnosed him as RA(class II, stage II) in April 2011.We started treatment for him with MTX. Because his disease activity has been still high (DAS-28CRP scores were > 6.5), Golimumab (GLM)50mg/4weeks was added in November 2011.The dosage of GLM was increased up to 100mg in March 2012 due to poor control. His disease activity has been significantly improved ever since. But In July 2012, he went to near otorhinologist with complaints of pharyngeal discomfort and hoarseness. At this time, a furred glottis was found. we examined it by cultivation, cytodiagnosis test which resulted in negative for MRSA, fungus, TB smears, no findings of malignancy. Blood sample showed HSV, VZV past infection pattern. Immunostaining test proved positive for both HSV-1 and HSV-2.We diagnosed him as HSV infection on pharynx. Afterward, his furred glottis was improved by the otorhinologist. I restarted treatment of RA with MTX10mg/week and GLM50mg/4weeks respectively in August, which resulted in favorable condition. [Discussion] In Japan, we can use GLM100mg /4weeks. But as the other biologics, it is necessary to be careful of patients who have risk factors such as aging, diabetes, cancer or lung disease.

P1-105

Developing of ANCA-associated glomerulonephritis during the treatment of rheumatoid arthritis with etanercept

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Conflict of interest: None

Developing of ANCA-associated glomerulonephritis during the treatment of rheumatoid arthritis with etanercept We report a 60-year-old woman with rheumatoid arthritis who developed ANCA-associated glomerulonephritis during treatment with etanercept. Her arithritis activity was in good control after using etanercept,so she could stop using steroid.Although the relationship between etanercept and ANCA-associated glomerulonephritis is unknown.Some patients with autoimmune disease also have another autoimmune disease,and stopping steroid may also the risk. But there are some case report which develop vasculitis after using

etanercept..It may better to check urine,serum creatinine.and ANCA titer during using etanercept..

P1-106

A case of myeloperoxidase-antineutrophil cytoplasmic antibody-associated glomerulonephritis during etanercept therapy for rheumatoid arthritis

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Conflict of interest: None

A 71-year-old woman had been diagnosed with rheumatoid arthritis (RA), suffering from polyarthritis, including bilateral fingers and toes, 16 months previously. She was treated with prednisone (PSL) 10mg/day and methotrexate (MTX). Etanercept (ETN) 25mg/w was administered 7 months before admission. Thereafter, RA activity improved and PSL was decreased to 5mg/day. As arthralgia worsened, the dose of ETN had been increased to 50mg/w 3 months previously. As a result of edema on the legs and worsening renal function, she was admitted. Serum creatinine was 1.7mg/dl, urine protein was 1.22g/day and myeloperoxidase-antineutrophil cytoplasmic antibody (MPO-ANCA) was positive at 187EU. Renal biopsy revealed necrotizing crescentic glomerulonephritis. ETN and MTX were discontinued immediately, and PSL 60mg/day was administered. Thereafter, her kidney function gradually improved and MPO-ANCA decreased. Some cases of the development of vasculitis with anti-TNF treatment have been reported, but ANCA-associated vasculitis is rare. We therefore report this rare case.

P1-107

Complications and the side effects of lung by administration of biological DMARDS

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Conflict of interest: None

[Objectives] The treatment of the rheumatoid arthritis improves by an appearance of the biological DMARDS drastically. However,there are some cases that Biological DMARDS are discontinued and are changes to another biological DMARDS by the side effects and complications. [Methods] Among the cases administrated the biological DMARDS in our hospital, we examined the side effects and complications of lung and its treatment about the cases that a side effect and complications appeared. [Results] There were five cases that the side effects and complications of lung appeared in administration of biological DMARDS in our hospital since 2008.The side effects and complications were pneumonia, bronchitis, suspect of nontuberculous mycobacteriosis, suspect of sarcoidosis, et al. About these cases, we examine its treatment and its subsequent course.

P1-108

A Case of Vasculitis in Rheumatoid Arthritis associated with two different Tumor Necrosis Factor α Inhibitors

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Conflict of interest: None

A 67-year-old woman suffered from RA for 30 years was treated with adalimumab (ADA) monotherapy for over a year, as MTX was stopped due to her schizophrenia. The treatment was discontinued for three weeks because of severe pneumonia, and then she was referred to our department with aggravation of RA (DAS 6.58). After resuming ADA monotherapy, she got purpura, skin ulcer and edema on her both legs. Biopsy of the skin revealed necrotizing angitis. After discontinuation of ADA, Her symptom was markedly improved. Four weeks later, golimumab (GOL) was started as a monotherapy. Few weeks after the treatment, she got purpura on her both legs again. The second biopsy was performed and the milder vasculitis as compare to last specimen was found. Although several vasculitis cases caused by biological drugs were reported, the precise mechanisms were still unclear. Two possibilities were speculated in this case; i.e. 1) the antigenicity of the biologics was involved, or/and 2) Type1 IFN induced by TNF-α inhibition caused the induction/progression of the vasculitis. As detailed investigation of this case will help to reveal the mechanisms of vasculitis associated with biologics, we are negotiating with the pharmaceutical companies for detecting the two kinds of anti-biologics antibodies.

P1-109

Anti-TNF biologics treatment in HTLV-1 positive patients with rheumatoid arthritis(RA)

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Conflict of interest: None

[Objectives] It is still not conclusive whether anti-tumor necrosis factor (anti-TNF) biologics promotes the development of malignancies such as lymphoma. Human T-lymphotropic virus type 1 (HTLV-1), which is a causative agent of adult T-cell lymphoma (ATL), is prevalent in Japan. Many HTLV-1 positive patients with RA are assumed to exist; however, there has been no report on the effect of anti-TNF biologics on HTLV-1 positive patients thus far. [Methods] We analyzed the response to anti-TNF biologics and time-sequential change of HTLV-1 markers in two cases of HTLV-1 positive RA. [Results] These cases showed no response based on the EULAR response criteria 60-96 weeks after administration of anti-TNF (infliximab and etanercept). One of two cases showed good response after switching to tocilizumab. HTLV-1 markers, such as proviral load and clonality of HTLV-1 infected cells, did not show any significant change and no sign of development to ATL was observed. [Conclusion] Treatment with anti-TNF biologics on HTLV-1 positive patients with RA seemed not to increase the risk of ATL, but to be less effective to RA in this study. Further long-term study with greater number of patients is necessary to clarify the safety and efficacy of anti-TNF biologics in HTLV-1 positive patients with RA.

P1-110

Golimumab in patients of rheumatoid arthritis with renal insufficiency

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Conflict of interest: None

[Objectives] Altough many studies have reported the efficacy and sefety of Golimumab (GLM) in patients of rheumatoid arthritis (RA), there are few reports on them of GLM for the patients with renal insuffiency. The aim of this study is to elucidate the safety and efficacy of GLM in patients of RA. [Methods] We evaluated the renal function of patients with RA treated with GLM in our hospital from December 2011 to May 2012. A total of 21 patients with RA (4 male and 17 female, mean age of 64.4±11.6 years old, and mean disease duration of 12.6±15.7 years) were enrolled in this study. We devided patients into two groups, with (n=7, including 2 dialysis patients) or without (n=14) renal insufficiency (estimated glomerular filtration ratio (eGFR) <60 ml/min./1.73m^2), and compared the safety and efficacy between the two groups, 24 weeks after administration of GLM. [Results] There were no differences of age, gender, pre-biologics treatment, and prednisone use between the two groups.The persistency rate and number of dropout patients during treatment were also not different between the two groups. The exacerbation of renal function was not observed during the treatment. [Conclusion] Our results suggest that GLM is a safe and effective treatment for the patients of RA with renal insufficiency.

P1-111

Experience of Golimumab Treatment for 1 year on Rheumatoid Arthritis Patients -Results from 53 patients treated with Golimumab-

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Conflict of interest: None

[Objectives] We investigated the efficacy and safety of Golimumab (GLM) on 53 rheumatoid arthritis (RA) patients in my clinic. [Methods] 53 RA patients who were started GLM (50mg) treatment from January 2012 included 39 biologics-naïve patients and one patient increased GLM dosage (100mg), were evaluated on DAS28-CRP, DAS28-ESR, HAQ and continuation rate of GLM treatment. [Results] 18 RA patients completed with GLM treatment during 20 weeks were improved to 2.0 on mean DAS28-CRP (4.4 at baseline), 2.5 on mean DAS28-ESR (5.2 at baseline), 4.7 on mean SDAI (22.4 at baseline) and 0.5 on mean HAQ (1.4 at baseline). These efficacy by GLM treatment were not affected by MTX combination or prior biologics exposure. The continuation rate of GLM treatment was 89%. The reasons for withdrawn patients were not adverse effects or insufficient efficacy. [Conclusion] These data suggested that the efficacy of GLM was excellent as well as other biologics and high continuation rate at least only 20 weeks treatment. Finally, GLM has easy treatment with once a month may be one of effective biologics for RA treatment.

P1-112

Methods for assessment of HBV reactivation in rheumatoid arthritis with hepatitis B virus carrier

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Conflict of interest: None

[Objectives] We evaluated methods for determining HBV reactivation in patients with RA receiving biological agents. [Methods] Four HBV female carrier patients with RA were included in this study (mean age, 59 years); the mean observation period was 41 months. All patients received MTX, and 3 patients received PSL. 3 patients received infliximab, and 1 received tocilizumab. AST, ALT, and HBsAg levels were recorded. In 2 patients, HBV-DNA levels were tested by real-time PCR, and 2 were subjected to a DNA polymerase assay to evaluate HBV reactivation. HBV-DNA levels were tested every 1- 2 months. We determined the presence of HBV reactivation in RA patients receiving biological agents. [Results] In 2 patients, HBV-DNA reactivation occurred. HBV-DNA was not detected by the DNA polymerase assay. In 1 patient, HBV reactivation was suspected because liver enzyme level increased and HBV-DNA was detected by real-time PCR. In 1 patient, HBV-DNA was detected by real-time PCR, although liver enzyme level was normal. HBV-DNA level decreased after treatment with entecavir. This may be due to the low sensitivity of the DNA polymerase assay compared with real-time PCR. [Conclusion] Our data suggest that for HBV carrier patients with RA HBV-DNA levels must be carefully monitored using real-time PCR.

P1-113

Biologics administration to oldest old rheumatoid arthritis patients

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Conflict of interest: None

[Objectives] In late years, the oldest old rheumatoid arthritis (RA) patients increase with aging society. Among those patients, several patients had high disease activity, but due to dementia and/or the decrease of the body function, we always hesitates aggressive treatment. We treated biologics to the oldest old RA patients whose disease activity was high and examined it. [Methods] We treated the biologics to seven non-biological DMARDs-resistant RA patients aged 85 years or older. We evaluated the effectiveness, safety and problems. [Results] Average age was 88.0 years old (85-92). We used infliximab for four cases, etanercept, tocilizumab, adalimumab each for one. They were effective and the improvement of body function was provided for all cases. Two patients were discontinued biologics because of bone fracture maxillary sinusitis, but the other patients are continuously administeraated. In two patients, oral medicine was stopped by a self-judgment, and in one case, stopped hospital visit was recognized. [Conclusion] The high effectiveness was accepted in the oldest old RA patients by biologics treatment, and improvement of the ADL was provided. There were the problems such as cognitive functions, and enough attention was necessary on the occasion of the biologics treatment.

P1-114

Experience in the use of golimumab in our hospital

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Conflict of interest: None

[Objectives] When combined with MTX, Golimumab is used in 50mg/4W. And, it is possible to increase 100mg/4W. When not combined with MTX, Golimumab is used in 100mg/4W. We investigated the difference in the effectiveness of the combination of MTX and of the not combination MTX. [Methods] Subjects were 15 patients (13 women) with rheumatoid arthritis treated with golimumab in our hospital. We have compared DAS28-CRP, DAS28-ESR, SDAI, CDAI, HAQ-DI, for MMP-3 for each of eight patients without MTX combined seven patients with a combination of MTX. [Results] In In the example used in combination MTX example good response4, cases of moderate response1, in the non-MTX combination cases were cases of moderate response4 cases good response2. In combination with MTX cases 5 cases, patients went into remission by DAS28-CRP is a combination of two cases in the example non-MTX, were many of the combination group toward MTX. [Conclusion] Effect can be obtained early in the non-combination MTX, remission rate has been shown to be higher in the combination group MTX.

P1-115

Improvement of arterial stiffness for use of golimumab in patients with rheumatoid arthritis

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Conflict of interest: None

[Objectives] Rheumatoid arthritis (RA) is commordity with cardio-vascular event. We investigate the efficacy of golimumab on arterial stiffness as a one of surrogate marker of cardio vascular event in RA. [Methods] We evaluate concequence 13 RA cases at baseline, and weeks 12 after induction of golimumab. We compare the cardio-ankle vascular index (CAVI) from baseline to weeks 12. [Results] CAVI was significantly improved from baseline(10.22±0.22) to weeks 12(9.22±0.68). [Conclusions] Golimumab improves arterial stiffness like as other TNF blockers. Interestingly there is no correlatoin between improvement of arterial stiffness and disease activity.

P1-116

Study of the Efficacy and Safety of 60-Minute Shortened Infliximab Administration for Cases of Rheumatoid Arthritis

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Conflict of interest: None

[Objective] The approval of an increased dosage of infliximab (IFX) in 2009 contributed to an improved therapeutic effect. In 2012, the time-shortened administration of IFX was also approved. In this Clinic, we examined the efficacy and the rate of occurrence of adverse effects in patients undergoing treatment with 60-minutes shortened administration of IFX. **[Methods]** In addition to those patients who had failed to show reactions despite IFX administration performed according to the protocol practiced at this hospital, IFX 60- minute, 240-ml/h shortened administration were also performed in patients who had failed to show reactions three times at the time of administration. **[Results]** Of the 31 cases that had undergone IFX administration at the time of September 2012, two cases were unable to undergo time-shortened administration due to side effect, although 29 cases were able to undergo 60-minute shortened administration. All the cases that were able to receive 60-minute shortened administration of IFX were free from adverse effects. The mean dosage of IFX in patients was 5.21 mg/kg, 300mg, and mean DAS28 was 1.92, showing that the control was successful. **[Conclusions]** The 60-minute shortened administration of IFX can be performed without causing problems involving safety and efficacy.

P1-117

A case of rheumatoid arthritis who had been untreated for 25 years to progress to stageIV, classIV was administered Golimumab and achieved good response

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Conflict of interest: None

A 58 year old woman have not been diagnosed as rheumatoid arthritis for 25 years. She had several swollen joints for the first time at 33. She gradually had several joint contractures and was forced to ride a wheel chair at 36. At the first visit of our hospital, she suffered from joint pain and swollen joints. She apparently had progressive joint destruction on radiography. She could not do anything without other`s help in her daily life. She had high level rheumatoid factor and anti-CCP antibody. We diagnosed her as rheumatoid arthritis. Golimumab administered to her in 2 months after we started to treat her. After10months since we treated to her, we achieved good response. For example, DAS28(CRP) 6.04→2.67, CRP5.45mg/dl→0.19mg/dl, MMP-3 1047.9ng/dl→32.8ng/dl, mHAQ2.5→1.9. She said, “I could walk myself for the first time in 20 years.” “I could clean up my anal with my hand.” etc. Generally speaking, administering biologics to progressed rheumatoid arthritis is not necessarily more effective than we expected. But in our case, she was happy to decrease her joint pain and to improve her daily activity.

P1-118

Examination about a Tocilizumab independent treatment

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Conflict of interest: None

[Objectives] We examined effect and safety about the Tocilizumab independent treatment. [Methods] 16 rheumatoid arthritis patients who are using the as Tocilizumab of October, 2012 by our hospital, and 11 persons of them were Tocilizumab independent treatments. Comparison examination was carried out about effect, safety, etc. about the independent treatment group and the oral medicine combined use group. [Results] By the Tocilizumab independent treatment group, inflammatory reactions, such as CRP, fell promptly from the Tocilizumab start, and it has stopped the oral medicine in an average of 3.2 months. Moreover, it was possible to have been able to introduce into remission by the patient of all after that, and to have maintained this. By the oral medicine combined use group, although it passed satisfactorily about the curative effect and there were not a Tocilizumab independent treatment group and a significant difference, since it was using prednisolone (PSL) together in all the examples and the slight pain of a joint and a morning stiffened, it was difficult to stop PSL. What has both clear groups was not accepted about the adverse event. [Conclusion] The Tocilizumab was able to recognize the effect also in the independent treatment.

P1-119

Elevated activation of T cells in anti-cyclic citrullinated peptide antibodies (ACPA)-positive patients but not in ACPA-negative patients

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Conflict of interest: Yes

[Objective] Anti-cyclic citrullinated peptide antibodies (ACPA) has been reported to be highly specific for rheumatoid arthritis (RA) and a useful diagnostic marker. It has been suggested that ACPA production depends on autoimmune reactions through CD4+ helper T cell activation. This study aims to compare the T cell activation, T cell subsets and cytokine profiles between ACPA (+) and (-) RA patients. **[Methods]**PBMCs were isolated from 45 patients enrolled in ABROAD study at baseline. The proportion of CD25 in CD4+ T cells, Treg, Th1, Th2 and Th17 were analyzed with FACS. The ACPA and cytokines were measured with EliA CCP kit and BD CBA Assay kit, respectively. **[Results]** Thirty-eight patients (84.4%) were ACPA positive. There were no significant differences in CRP, DAS28-CRP, MMP-3 between the ACPA (+) and (-) groups. The CD25 proportions in CD4+ T cells were significantly higher in the ACPA (+) than in the (-) group (11.1±5.8 vs. 5.9±2.9%) though CD4+ T cells were not different. Treg, Th1, Th2, Th17 proportions and cytokine levels were not significantly different between the groups. IL-6 increased in the both groups compared to healthy donors. **[Conclusion]** CD4+ T cells are more activated in the ACPA (+) patients than the (-) patients. IL-6 increase is not related to ACPA existence.

P1-120

Efficacy of total elbow arthroplasty in patients with rheumatoid arthritis treated with biologics : improved longitudinal effects on disease activity and on health-related quality of life

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Conflict of interest: None

[ObjectivesThis study examines the postoperative disease activity of TEA conducted on RA patients treated with biologics and the operation's impact on HAQ and Mayo Elbow Performance Score (MEPS). [Methods] The study examines 16 joints belonging to RA patients on biologics, for which TEA was conducted at our department between 2006 and 2011. For clinical appraisal, DAS 28 ESR and CDAI before and after the operations were used. Functional disorders were examined with HAQ and MEPS before and after the operations. [Results] The average age was 62.3, and the disease duration was 25.9 years. The disease activity was significantly improved from 4.3 (DAS 28 ESR) and 11.9 (CDAI) before the operation to 3.3 (DAS 28) and 6.2 (CDAI) respectively., HAQ value changed from 2.2 to 0.4, and MEPS from 50.6 to 96.3, both indicating significant improvement. [Conclusion] It was found that after conducting TEA, the functional disability and disease activity of RA patients were improved. For the established RA treated with biologics, it was indicated that the provision of added treatment with upper limb operation effectively contributes to the improved physical function of RA patients and that the provision of combined treatment consisting of tight control by drug therapy and operative therapy is important.

P1-121

The influence of the previous biologic treatment in clinical efficacy of biologics for RA patients

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Conflict of interest: None

[Objectives] To detect the influence on the clinical efficacy of biologic therapy for RA patients by previous biologic treatment. [Methods] DAS28 of the patients with previous biologic use 'abbreviated to (+)' were compared with that of the patients without previous biologics 'abbreviated to (-)' before and 1 year after treatment in 23 ADA patients, 44 ETN patients, 53 and 29 ABA patients. Previous treatment rates were 56.5%, 18.2%, 65.5%. [Results] DAS28 after one year, the achievement rate of DAS28<3.2, DAS28 improvement, the achievement rate of DAS28 improvement>0.6 were 3.26±0.98, 50.0%, 2.34±0.97, 100% in ADA(-) group, 4.97±3.26, 7.1%, 0.57±1.23, 38.5% in ADA(+) group, 4.06±1.05, 19.4%, 2.69±1.24, 91.7% in ETN(-) group, 4.81±1.68, 12.5%, 1.57±1.05, 87.5% in ETN(+) group, 3.81±1.18, 30.0%, 1.76±0.98, 90.0% in ABA(-) group, 4.35±1.62, 21.1%, 0.53±1.66, 42.1% in ABA(+) group. [Conclusion] Clinical response of biologics was deteriorated in previously treated patients with biologis. In the patients without previous biologics, clinical response of was similar by ADA, ETN and ABA, and ADA could be superior to achieve the therapeutic goal. In the patients with previous biologic use, ETN could be superior to obtain clinical response, ADA, ETN and ABA were similar to reach the therapeutic goal.

P1-122

Study of the altered cytokine network in the example switch to other drugs due to insufficient effect of TNFα inhibitor therapy in patients with rheumatoid arthritis

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Conflict of interest: None

[Objectives] From inhibitors TNF, such as changes to the selection criteria of the other cytokine inhibitors, it is not yet clear. We report discussed retorospective, the adequacy, timeliness of case that we measure in patients treated with TNFα inhibitors now, the serum concentration of various cytokines. [Materials] 18 patients with RA of more than one year after the start of observation (13 men, 5 women; mean age 45.4 years); inhibitors TNF {IFX / ETN infliximab and etanercept}. Three cases {tocilizumab from IFX / ETN; 1 case to TCZ, TCZ from one case to IFX, adalimumab from IFX; 1 case to ADM} has been changed and selected. [Methods] In 27 serum samples with 18 RA, at the same time many kinds of cytokine concentration; IL-6, IL-10, etc., was measured by multiplex Beads-array method, Inc. Bio-Rad. [Results]

From inhibitors TNFα, Il-15 and IL-1β has been controlled almost all cases. In the case of insufficient switch, an increase in IL-6 and Il-10 was seen in common. Changes to TCZ example, there was an ultra high IL-6. [Conclusion] Evaluation of anti-inflammatory cytokine cascade is useful in continuation or discontinuation of inhibitors of TNF. Cases increased IL-6 is present in no small measure, the switch to an anti-IL-6R antibody was appropriate.

P1-123

The effect of biologics on inhibition of large joint-destruction in patients with rheumatoid arthritis

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Conflict of interest: None

[Objectives] The goal of the treatment for rheumatoid arthritis (RA) is to inhibit joint destruction. Clinical trials have revealed that all biologics inhibited small joint-destruction, however, there have been few reports focusing on large joint-destruction. [Methods] Forty-four patients, who received the latest biologics over a year, were included in this study. We evaluated the X-ray for the shoulder (11 joints), elbow (15 joints), hip (11 joints), knee (50 joints) and ankle (41 joints). [Results] DAS28/ESR was improved from 4.53 to 2.41 after biologics treatment, and the response to the treatment was good (32 patients), moderate (7 patients), and poor (5 patients) according to the EULAR improvement criteria. A total of 20 joints, which included one shoulder (9.1%), 3 elbows (20%), 6 knees (12%), 10 ankles (24%) and no hip, showed progression of joint-destruction. [Conclusion] These results suggest that joint-destruction may proceed in 10-20% of large joints even if the disease activity is well controlled. Since large joint destruction, rather than small joints causes marked decrease in ADL, patients sometimes need joint replacement surgery. To achieve the structural remission, regular check and evaluation for not only small but also large joints is necessary.

P1-124

A study on efficacy of biologics in methotrexate-intolerable Bio-naive patients with rheumatoid arthritis

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Conflict of interest: None

[***Objective***] The efficacy of biologics (Bio) were assessed comparatively in Bio-naive rheumatoid arthritis (RA) patients showing poor tolerance to methotrexate (MTX) therapy. [***Subjects and Methods***] The biologics studied were etanercept (ETN; 16 patients), tocilizumab (TCZ; 12 patients) and abatacept (ABT; 8 patients). Therapeutic responses were assessed by CRP, DAS28ESR and SDAI measurements. [***Results***] The mean CRP decreased from 1.87, 1.82 and 2.03 mg/dL at baseline (week 0) to 0.3, 0.31 and 0.66 mg/dL at week 24 in the ETN, TCZ and ABT groups, respectively. The mean DAS28ESR score decreased from 4.89 and 4.95 at baseline to 2.92 and 3.0 at week 24 in the ETN and TCZ groups, respectively; in the ABT group, the decrease from 5.16 at baseline was limited to 3.66 at week 24, although the score remained as low as in the ETN and TCZ groups from week 28 onward. The mean SDAI showed similar changes. The percentages of patients in the ETN, TCZ and ABT groups showing low disease activity on the DAS scale were 50%, 60% and 10% at week 12, and 50%, 60% and 30% at week 24, respectively. [***Discussion***] Thus, treatment with ETN, TCZ or ABT yielded clinical remission in Bio-naïve RA patients not tolerating MTX therapy, although the rate of DAS change was affected by the age and illness duration.

P1-125

The effects of abatacept therapy for the change of urinary level of collagen crosslinks in patients with rheumattoid arthritis-from the data of multicenter study in Shizuoka-

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Conflict of interest: None

[Objectives] We investigated the effects of abatacept therapy for the change of urinary level of collagen crosslinks in patients with rheumattoid arthritis (RA). [Methods] Fifty-three patients wiyh RA were enrolled in the multicenter study of Aatacept therapy in Shizuoka from 2010 to 2012. The mean age was 61.3 y.o., and mean disease duration was 9y. we measured urinary pyridinoline (PYD) and deoxypyridinoline (DPD) with HPLC at baseline, and 3,6,12 months. We evaluated the inflammatory of RA and the disease activity by the data of CRP, MMP-3, and DAS-CRP. We compared the effects of disease activity for PYD and DPD at 12months between two groups defined as High (high and moderate DAS-CRP score) and Low (low and remission DAS-CRP score). [Results] The both index of inflammatory and disease activty were decreased significantly at 3 months from the baseline. The level of PYD was devreased significantly at 6 months from the baseline. DPD showed no difference in this study period. High group showed no improvement of PYD and DPD in this study. On the other hands, Low group showed the significant miprovement of DPD at 12 months from baseline. [Conclusion] The urinary PYD and DPD showed the late improvement in RA with abatacept therapy and may reflect the efficacy of abatacept.

P1-126

Efficacy and tolerance of abatacept over 48 weeks in patients with rheumatoid arthritis

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Conflict of interest: None

[Objectives] To evaluate efficacy and tolerance of abatacept (ABT) over 48 weeks in patients with rheumatoid arthritis (RA). [Methods] Twenty-five RA patients were treated with ABT for over 48 weeks in our department. Mean age was 56.6 years old. Mean disease duration was 7.8 years. Eighteen patients were treated with methotrexate (MTX). Seven patients had no history of biological agents (Bio) use. Efficacy was evaluated based on DAS28-CRP, SDAI, and Boolean remission criteria. We also examined whether the patient background factors (age, duration of disease, combination of MTX, anti-citrullinated protein antibody (ACPA),

and history of Bio use) affect the efficacy of ABT. [Results] Mean DAS28-CRP was 4.46/3.23/3.16 (baseline/24weeks/48weeks), SDAI was 27.1/15.3/14.0. Remission rate at 48 weeks was 24/16/16% (DAS28-CRP/SDAI/Boolean criteria). Patient background factors did not affect the efficacy of ABT statistically. Persistence rate was 96/84% (24weeks/48weeks), and there was no case that ABT was discontinued due to adverse events. [Conclusion] The efficacy of ABT emerges by 24 weeks, and the efficacy is maintained until 48 weeks. ABT is efficacious regardless of the background factors. This study indicates that ABT is a very efficient and tolerant biological agent.

P1-127

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 156 RA patients. The retention rate at 52 weeks period was 77.4% in combined group, 74.6% in not combined group. Average of DAS28 improved 4.46±1.24 to 3.17±1.28 in combined group, 4.48±1.38 to 3.47±1.28 in not combined group after 52 weeks later. Average of SDAI improved 22.4±12.7 to 12.1±9.2 in combined group, 24.9±12.8 to 14.1±9.7 in not combined group. In each analysis, there was no difference in effectiveness of concomitant MTX. Adverse events occurred in 36 cases in combined group, 19 cases in not combined group. In analysis of MTX combined group, patients were divided into 3 groups which dosage of MTX are ≧10mg, 8mg, ≦6mg /week at starting ABT, there were no difference in effectiveness between 3 groups.

P1-128

Clinical Evaluation and Structural Analysis at Week 52 in a Multicenter Clinical Study of Abatacept (ABT) for Rheumatoid Arthritis (RA)

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Conflict of interest: None

Objective: Evaluation of results of 52-week multicenter clinical study of ABT for RA Methods: Ninety-five RA patients who received ABT in a facility participating in the Academy of Clinical Rheumatoid Arthritis Gunma Institute (ACAGI) for at least 52 weeks were included in the efficacy analysis that was based on the SDAI scores stratified by MTX treatment and prior treatment with biologics using the LOCF method. Structural analysis was performed at Week 52 in 44 patients who underwent joint radiography and the annual progression rate was assessed using modified Total Sharp Score (mTSS). Results: Mean SDAI scores decreased from 22.4 at Week 0 to 6.7 at Week 52 in biologics-naive patients (n = 28). The mean SDAI scores decreased from 24.6 at Week 0 to 11.5 at Week 52 in patients who switched treatments (n = 67).The mean SDAI scores decreased from 26.7 at Week 0 to 11.3 at Week 52 in patients who received ABT only (n = 37). The annual progression rate at Week 52 was 0.1, showing a significant suppression of joint destruction compared to the estimated annual progression rate at baseline of 9.2. Conclusion: Based on the clinical evaluation and structural analysis at Week 52, greater effects and retention can be expected in ABT. ABT could be an effective option in RA treatment.

P1-129

Clinical Effects of Abatacept for Rheumatoid Arthritis - Results at Week 52: A Multicenter Observational Study by Fukuoka RA Biologics Registry

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Conflict of interest: Yes

[Objectives] The results from the Fukuoka RA Biologics Registry are reported to evaluate the efficacy and safety of abatacept [Methods] Ninety-one patients who received treatment with abatacept for at least 52 weeks as of September 2012 were included in the study. The dose regimen used is approved in Japan. The clinical effects were measured by DAS28 and SDAI. [Results] Fifty patients were switched from biologics (S group) and 41 patients were biologics-naive (N group). 50 patients received a combination of abatacept and MTX. The mean DAS28 was 4.97 at baseline and improved to 3.74 at Weeks 48. The mean SDAI was 23.65 at baseline and improved to 16.97, 14.18, and 12.83 at Weeks 4, 24, and 48, respectively. The SDAI remission rate at Week 52 was significantly higher in the N group than in the S group, 44% and 8%, respectively (p=0.0001). No significant difference was found in the SDAI remission rate at Week 52 with or without MTX; 30% (15/50 patients) in the abatacept plus MTX group and 17% (7/41 patients) in the abatacept alone group (p=0.15). A total of 22 patients discontinued treatment due to lack of response. The treatment retention rate at Week 52 showed good results; 75.8% in all the patients. [Conclusion] Abatacept is a usuful in the real world.

P1-130

The clinical effect of abatacept for rheumatoid arthritis (RA) with high ESR/CRP

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Conflict of interest: None

[Objectives] A substantial number of patients with rheumatoid arthritis (RA) have a high ESR/CRP ratio. There is a possibility that factors other than TNF related to the pathogenesis in these patients, and the T-cell function control may be useful. We evaluate the efficacy of abatacept in patients of RA with high ESR/CRP. [Methods] Average ESR/CRP in 103 RA patients was 29.8±20.5. We divided RA patients to 2 groups, high ESR/CRP (ESR/CRP>50.3) and low ESR/CRP group (the other cases). 7 patients

with high group and 4 patients with low group were assigned to receive abatacept. DAS28 (4ESR), C-DAI were assessed. [Results] 4 weeks after, DAS28 was significantly lower in high group (3.28±0.24) compared with low group (4.06±0.53). There was no significant difference after 12 weeks in both groups. 24 weeks after, C-DAI was significantly lower in high group (4.22±1.40) compared with low group (7.55±2.57). [Conclusion] Our data suggests that abatacept was more effective in high group in response to early effect and remission rate, and useful for treatment of RA patients with high ESR/CRP.

P1-131

Experience with the use of ABT

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Conflict of interest: None

Objective: Efficacy assessments of various biologics provide important information during selection of these drugs for RA. We summarized our experience with the use of ABT at our department. **Subjects:** Participants comprised 27 RA patients for whom ABT was initiated before the end of February 2012. **Methods:** We investigated the continuation rate and efficacy both overall and by classifying patients based on concomitant use of MTX and history of treatment with biologics. **Results:** The 1-year continuation rate for ABT was 56.7%. DAS28-CRP decreased from 4.16 to 2.99. No difference in continuation rate was seen based on MTX use. Comparison based on use of MTX, improvements in activity were observed in both groups, but activity was more favorable in the non-MTX use group. Comparison based on history of treatment with biologics showed a tendency toward a higher continuation rate in the naïve group. While improvements in activity were observed in both groups, activity was more favorable in the naïve group. **Discussion and conclusion:** ABT was highly effective for patients naïve to biologics, and can be expected to be at least as effective in patients not receiving concomitant MTX as in those receiving concomitant MTX. ABT appears useful in RA treatment.

P1-132

Clinical evaluation of abatacept in our hospital 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] Diagnosis of RA was by ACR classification criteria (1987). Twenty-two RA (6 males), age 62.9±11.9 years old, and disease duration 10.3±8.6 years. Corticosteroids were administered to 21 patients (6.6 mg/day) and MTX was used in 13 patients (8.3±2.1mg/wk). Fifteen patients were switched from other biologics. Overlapping diseases: SLE: 4, SSc: 1, SS: 1, MCTD: 1, MRA: 1, PM: 1. [Methods] Efficacy of ABT was evaluated by CDAI and DAS28CRP at 0, 12 and 24 week after injection of ABT. [Results] At 24 w, overall, the proportion of either clinical remission or low disease activity by CDAI and DAS28CRP increased by 36% and 21%, respectively. With MTX, the rate increased to 43% and 26%, however, without MTX 27% and 14%. In bio-naive cases, the rate were 41% and 36%. In bio-switch cases, the rate were 36% and 14%. Two of 9 cases with high disease activity and 8 of 13 with moderate disease activity achieved low disease activity. Discontinuation: 2 cases (no response; 1, infection and pneumothorax; 1). [Conclusion] ABT seems more effective in RA patients with moderate disease activity at background or using concomitant MTX or biologics-naive.

P1-133

Analysis of the clinical effect during the first year after initiation of abatacept administration

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Conflict of interest: None

[Objectives] To assess the effect in patients with rheumatoid arthritis (RA) who received abatacept (ABT) for one year or more in the first year after induction. [Methods] The 29 patients were 5 males and 24 females. The average age was 63.8 years (45–72) and average disease duration 10.1 years (1–30); 8 patients were bio naïve and 21 patients switching, and 17 patients were treated concomitantly with MTX and 12 patients without MTX. The efficacy and safety were assessed by the LOCF method. [Results] The one-year persistence rate of ABT was 82.8% (24/29). All 5 discontinued patients had secondary failure. DAS28-CRP(4) (mean) improved from 5.4 (at ABT induction [Week 0]) to 3.2 (Week 4) ($p<0.01$) and improved further from 2.8 (after 6 months) to 2.3 (after 1 year) ($p<0.01$). TJC, SJC, PtVAS, and CRP, excluding ESR, significantly improved at Week 4, verifying the efficacy from an early period after the start of ABT administration. All components including ESR improved further from 6 months to 1 year after induction. [Conclusion] ABT showed an immediate effect 4 weeks after the start of administration and a sustained improvement from 6 months to 1 year after the start. ABT was considered suitable biologics for the continued treatment of RA also in terms of efficacy and safety.

P1-134

Treatment with abatacept in biologics naïve and switched patients with rheumatoid arthritis

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Conflict of interest: None

[Objectives] To determine responses to abatacept among patients with rheumatoid arthritis (RA) who switched to biologics and those who are biologics naïve. [Methods] This retrospective study investigated 24 patients with RA who were treated with abatacept. At baseline, 11 of them had already been treated with biologics (8 patients after one biologic (switched group) and 3 patients after 3 or 4 biologics (more switched group)), and 13 were biologics naïve (naïve group). Treatment responses to abatacept at week 24 and LOCF were compared between the switched and naïve groups using DAS28-ESR. [Results] Thirteen (100%), 7 (87.5%) and 2 (66.7%) patients in the naïve, switched and more switched groups, respectively, completed 24 weeks of abatacept treatment. The mean DAS28 values at weeks 24 compared to baseline decreased significantly for the naïve and switched groups, but

not more switched group. Among the therapeutic outcomes of abatacept using the EULAR response criteria, the ratios (%) of good responses at week 24 were 61.5%, 25.0% and 0% in the naïve group, switched group and more switched group, respectively. [Conclusion] Abatacept was clinically effective for patients with inadequate responses to biologics and for those who were biologics naïve.

P1-135

Therapeutic results for abatacept in our hospital

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Conflict of interest: None

【Objective】To evaluate the efficacy and safety of abatacept in rheumatoid arthritis (RA) patients in our hospital.【Methods】Included in the present study were 42 patients followed up for at least 24 weeks of treatment with abatacept from October 2010 in this unit, including 37 women (mean age: 61.0 years; mean duration of illness: 7.1 years).【Results】All patients had previously used at least one DMARD (biologics in 13 patients). PSL was used by 7 patient at 5.3 mg. MTX (8-14 mg/week) was concurrently used by 35 patients. Tree patients received monotherapy. At the baseline, Week 12 and Week 24, DAS28 (ESR) was 5.4±1.4, 3.4±1.2 and 2.6±0.9 respectively, while SDAI was 26.4±16.1, 7.3±7.9 and 2.7±2.8. The remission rate (DAS28 (ESR<2.6) and SDAI<3.3)) at 24 was 50% and 71%, respectively. Treatment was continued in 95.2 % of patients. It was discontinued in one patient due to inefficacy and in another due to hepatic dysfunction. In the evaluation of safety, pneumonia, herpes zoster, hepatic dysfunction and hyperlipidemia were reported from two, one, tree and five patients, respectively.【Conclusion】To date, a high efficacy rate and continuation rate have been obtained as with RCT, suggesting that abatacept offers great therapeutic benefits in routine medical practice as well.

P1-136

Safety and efficacy of abatacept in the elderly patients with rheumatoid arthritis after inadequate response to the other biologics

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Conflict of interest: None

[Objectives] To analyze the efficacy and safety of abatacept (ABT) in patients with rheumatoid arthritis (RA). [Methods] A retrospective chart review was conducted of 18 patients with RA treated with ABT in 2011 and 2012 (2 males and 16 females; mean age, 67.6±12.4 years). [Results] At 24 weeks after ABT treatment, seven patients achieved a moderate response (DAS28-CRP, 3.29±0.98; CDAI, 13.7±9.4; SDAI,14.3±9.3). Six patients (33.3%) could continue ABT treatment over 24 weeks. Eight patients exhibited advers enevents (respiratory infection in 4 patients, interstitial pneumonia, adenoiditis, lymphopenia, and postoperative infection in each patient). The patients who discontinued ABT treatment by the advers enevents had significantly higher anti-CCP antibody. Seven patients discontinued ABT treatment due to inadequate response. They were older age, received pre-treatment with the other biologics, and had higher CRP value. The six of seven patients have achieved remission after switching the other biologics. [Conclusion] Elderly patients using ABT exhibited high frequencies of advers enevents. There may be discontinuation due to lack of effectiveness in patients switching from the other biologics. Resistance to the other biologics following the ABT treatment is rare.

P1-137

Factors affecting continuance of abatacept treatment (ABT) on rheumatoid arthritis (RA); analysis of data from a single center

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Conflict of interest: None

[Objectives] To identify factors affecting continuance of ABT therapy on RA [Methods] We analysis medical records of 25 patients who received ABT for RA in our clinic, retrospectively. [Results] Among patients, 56% was bio-naïve, and 82% was MTX-treated. Mean DAS28-CRP (DAS) was 5.56 before starting ABT. Continuance rate was 86% at 6Mo and 56% at 12mo after starting ABT. Causes for discontinuance were inefficiency in 6 cases and exacerbation of Sjogren syndrome in one. Two factors affecting continuance of ABT was identified; bio-naïve and short disease duration. In bio-naïve patients, continuance rate was 90% at 6Mo and 12mo, while in switching group, the rate was 80% at 6Mo and only 20% at 12Mo. Moreover, 69% of bio-naïve patients achieved DAS<2.7, while none of switching group did. In patients who received ABT within 2 years after the onset of RA, continuance rate was 100% at 6 and 12 Mo. In contrast, the rates at 12 Mo were 55% and 0% in patients whose disease duration was 2-10 years and >10 years. In patients with disease duration <2 year, 55% of them achieved DAS<2.7. Whereas only 33% and 20% of patients with disease duration 2-10 years and >10 years achieved DAS<2.7. [Conclusion] Bio-naïve and short disease duration are beneficent factors for continuance and efficacy of ABT therapy for RA.

P1-138

Efficacy of half dose abatacept treatment

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Conflict of interest: None

[Objectives] Standard dosage of abatacept is more than 500mg based on several international clinical trial studies. However domestic clinical trial study showed satisfactory efficacy of low dosage as much as 100mg in Japanese rheumatoid arthritis patients. We examined efficacy of half dose abatacept to determine capability of regulation of dosage. [Methods] Each patient was given either standard dosage or half dosage through free choice. Administration interval was accordance with the standard regimen. [Results] Standard dosage of 12 patients and half dosege of 6 patients were entried. The reasons for selection of half dosage were low body weight, past adverse event during other biologics treatment, and economic status. Disease activity of baseline indicated with DAS28-ESR showed no difference in standard dosage and half dosage patients, however comparatively lower global health VAS assesment showed in half dosage than standard dosage. Faverable clinical responcses were achieved in both standard and half dosage. [Conclusion] Since half dose abatacept treatment showed a favarable clinical response, it broadened treatment options of RA economically.

P1-139

Comparison of effectiveness and safety of biological treatment options after switching from tumour necrosis factor inhibitor to Tocilizumab or Abataseptin in rheumatoid arthritis patients

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Conflict of interest: None

[Objectives] The objective of this analysis was to compare the relative effectiveness and safety of Tocilizumab (TCZ) vs Abatacept (ABT) that was switched from TNF inhibitor. [Methods] We analized the clinical outcomes and safety of TCZ (32 cases) or ABT (19 cases) patients switched by TNF failure. Each clinical composite measure (DAS28-ESR·DAS28-CRP·SDAI·CDAI) was assessed at 24 weeks change from baseline. Safety was also assessed. [Results] The mean age was 58.0±15.0, 61.7±14.9 year old and the mean duration of RA was 12.9±10.2, 11.4±7.9 years (TCZ, ABT respectively). Both TCZ and ABT patients, at baseline DAS28-ESR, DAS28-CRP, SDAI, CDAI were not significant different. Only DAS28-ESR of TCZ at 8 and 16 week was significantly less than ABT, but the difference was lost at 24w (3.3±1.4, 4.1±1.2). DAS28-CRP (3.1±1.2·3.3±1.2), SDAI (15.0±12.5, 13.0±9.8) and CDAI (15.0±12.5, 12.4±9.8) were not significant different at 24w. The incidence of adverse events was 40.6%, 63.2% and infection was 15.6%, 15.8%. Serious adverse events were only one case of patients treated with TCZ. [Conclusion] In switching from TNF failure, there was no significant difference in the efficacy of both TCZ and ABT at 24 weeks. There was also no difference in the incidence of adverse events, including infections.

P1-140

Efficacy of low-dose abatacept in Japanese patients with active rheumatoid arthritis

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Conflict of interest: None

[Objective] 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 (250 mg) with active RA and inadequate response to other DMARDs. [Methods] This trial was 24-week single center prospective study. The registered consecutive 26 Japanese patients were active RA despite various other DMARDs therapy. Disease activity, health assessment questionnaire (HAQ) score and safety were evaluated at 24 weeks after administration of 250mg ABT. Disease activity of RA was assessed using clinical disease activity index (CDAI). [Results] 26 patients (81% was female) were included. Median age was 52.2 years, and median disease duration was 80.5 months. All patients had anti-CCP antibodies. Low-dose ABT therapy lead to significant improvement in CDAI (from 25.2 ± 11.2 to 14.9 ± 9.9) and HAQ score (from 1.00 ± 0.82 to 0.79 ± 0.83) at 24-week. There were no serious adverse events observed during the study. [Conclusion] Low-dose ABT therapy might be sufficient for the treatment of active RA in Japanese patients. It is necessary to clarify how low dose ABT is appropriate in the future study.

P1-141

Efficacy of abatacept during 1 year in the patients with inadequate response to TNF-a inhibitors, registered in Tsurumai Biologics Communication Registry (TBCR)

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Conflict of interest: Yes

[Objectives] To investigate the efficacy of abatacept (ABT) for the patients with inadequate response (IR) to TNF-a inhibitors, comparing the efficacy and timing of achievement of treatment response by previous biologics. [Methods] 280 cases treated with ABT were registered in TBCR. In these cases, we analyzed the patients with 52 weeks and more of observation period from initiation of ABT. The efficacy of ABT by each previous anti-TNF therapy (IFX, ADA, ETN) was compared. [Results] In 50 cases, the reason for switch of previous anti-TNF therapies was IR. IFX or ADA was used in 24 cases and ETN in 26 cases. 71 % of the patients treated with IFX, ADA achieved improving of one and more categorical disease activity based on DAS28-ESR at 12 w after switching while 46 % of the patients treated with ETN. At 52w, the patients treated with IFX, ADA had more effectiveness based on improving DAS28-ESR-categorical disease activity (one step: 26%, two and more step: 35 %) than those treated with ETN (one step: 32%, two and more step: 12 %). [Conclusion] One of reasons for IR of anti-TNF a antibodies is inadequate dosage against disease activity. ABT could replace the inadequate dosage of anti-TNF-a antibodies. These facts should be consider at planning of switching from TNF inhibitor to ABT.

P1-142

Index for predicting the joint destruction inhibiting effect of Abatacept at an early stage

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Conflict of interest: None

[Objectives] Indices for determining the efficacy of Abatacept (ABT) at an early stage were retrospectively examined from the results of ABT treatment for 52 weeks. [Methods] Fourteen patients prescribed ABT for 52 weeks were divided into a structural remission group (≤0.5) and an advanced joint destruction group (>0.5) by ΔmTSS (vdH), and a comparison of the changes in the DAS28-ESR, SDAI, MMP-3, and max-PDUS scores was conducted. [Results] There were seven patients in the structural remission group (average age: 61.7 years; 3 males/4 females; average disease duration: 8.4 years). Seven patients had advanced joint destruction (average age: 61.6 years; 2 males/5 females; average disease duration: 7.4 years). Changes from baseline measured at 12 weeks and 52 weeks for each index in the structural remission and advanced joint destruction groups were as follows. DAS: 4.16/4.37→3.37/3.15→3.10/3.54; SDAI: 20.63/18.37→7.53/10.83→7.51/11.81; MMP-3 (change from baseline): 0/0 → −69.06/37.79 → −74.23/31.01; max-PDUS scores: 1.57/1.86 → 0.86/1.86 → 0.57/1.71. [Conclusion] It is possible that the MMP-3 and max-PDUS scores could serve as effective indices for determining efficacy at 12 weeks rather than DAS and SDAI.

P1-143

SNP algorithms for prediction of efficacy and adverse events of abatacept (ABT) using multiple medical cohorts

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Conflict of interest: Yes

[Objectives]We developed SNP algorithms with the aim of enabling the prediction of responders or non-responders, remission or non-remission and adverse events in ABT-treated patients. **[Methods]**The first cohort included 46 RA patients, the second 50 patients for a total of 96 patients from five hospitals in different regions of Japan. Efficacy was assessed by DAS28 (CRP) at 48 weeks after the initial treatment. Any adverse events that may have been related to ABT administration and observed at 48 weeks of this long-term administration and during phase II were considered to be side effects. We selected 10 SNPs associated with ABT-responsiveness, remission, and adverse events which were common in both analyses of the first and second cohort ($p < 0.05$). We scored the relationship between each SNP and responsiveness, the estimated total score of 10 SNPs, and then examined relationships between responders and non-responders. **[Results]**Accuracy, specificity, and sensitivity of the algorithm for responsiveness, remission or adverse events of ABT ranged from 90-96%. **[Conclusion]**These highly accurate algorithms using SNP analysis may be useful in the prediction of responsiveness, remission and adverse events before treatment with ABT.

P1-144

A comparison of usefulness between abatacept and other biologics

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Conflict of interest: None

[Objectives] We report here on a comparison of usefulness between abatacept and other biologics. [Methods] DAS28 and joint ultrasonography findings were compared between patients administered abatacept and those administered infliximab, etanercept, and tocilizumab. [Results] 1. There was a tendency for pain, swelling, the inflammatory markers, VAS, and DAS28 to improve gradually until Week 16, and they were maintained thereafter for a long period. 2. There was also a trend of gradual decrease in joint ultrasonography, which continued to improve for 6 months or more. 4. No difference was found in the responsiveness to the first biologics and others. 5. Once the remission criteria were achieved, that condition tended to be maintained. 6. Discontinuation due to inefficiency occurred in 20% of patients. Discontinuation due to adverse reactions occurred in 10% of patients, indicating a smaller proportion than with other biologics. [Conclusion] Abatacept can be characterized by the tendency that the onset of its effects is slow and they persist for a longer period compared to those in multidrug treatment, although early improvement was not observed. The results also suggested the possibility that abatacept may be effective in treating RA with multidrug resistance to biologics.

P1-145

Assessment of usefulness of abatacept in rheumatoid arthritis at Week 48

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Conflict of interest: None

[Objectives] To conduct a clinical assessment on patients who received abatacept (ABT) for rheumatoid arthritis (RA) [Methods] ABT was used at five institutions in Chikugo Region of Fukuoka Prefecture from October 2010; and the therapeutic efficacy, safety, and therapeutic adherence were assessed in 37 RA patients in whom observation was possible until 48 weeks after administration. [Results] The patients were 8 males and 29 females, average age was 56.6±16.1 years, disease duration was 110±116.5 months, Stage I+II and Stage III+IV comprised 48.6% and 51.4%, respectively. Bio-naïve vs. switch was 12:25, and 80% of patients previously administered biologics took ABT as a secondary drug. MTX was combined in 81% of patients. SDAI remission was achieved in 21.6% of patients at Week 24 and 37.8% at Week 48, showing an increasing tendency over time. The rate of high disease activity based on SDAI decreased from 29.7% before treatment to 13.5% at Week 4, and 2.7% at Week 24. The rate finally reached 0% at Week 48. Treatment adherence was 81.1% at Week 48, and discontinuation due to adverse reactions only occurred in 1 patient. [Conclusion] ABT has an excellent long-term safety and is considered to be a drug with a therapeutic effect that can be expected to increase over time.

P1-146

Clinical outcome of abatacept in RA patients in our facility

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Conflict of interest: None

[Objectives] To clarify the clinical outcome of abatacept (ABA) in rheumatoid arthritis (RA) patients in our facility. [Methods] Nine RA patients were administered with ABA. The average age was 64 years old (48-80 y.o.) and the average disease duration was 15.3 years (2-32 yrs). Only 1 patient was bionaive case, and the others had been treated with other biologics before ABA. The average dose of methotrexate was 3.3 mg/week and the average methylprednisolone dose was 4.1 mg/day. The retention rate, disease activity score (DAS28(4)-ESR), EULAR response, and adverse events were examined. [Results] The retention rate was 100%. Before ABA treatment, DAS28(4)-ESR was 5.4 on average. Then it was significantly decreased to 3.8 and 3.4 at 3 and 6 months after treatment. At 6 months, 4 cases were good response and 5 were moderate response. No severe adverse event was detected. Nasopharyngitis was observed in a few cases. Of moderate response cases, 2 cases showed knee joint swelling. [Conclusion] The retention rate was 100% and high efficacy was detedted in our case series. Especially, almost all cases were not bio-naive, suggesting that ABA is effective even in refractry RA to other biologics in our cases.

P1-147

A case report: Use of abatacept to a rheumatoid arthritis patient with nontuberculous mycobactelial infection

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Conflict of interest: None

[Object] To report an improvement of disease activity by using abatacept (ABT), to a rheumatoid arthritis (RA) patient with non-tuberculous mycobactelial infection (NTM), which was never possible with internal medicines like methotrexate (MTX). [Case] 58 years old female was diagnosed as RA at a different clinic 14years ago and was started medicine. After 6years of treatment, she was introduced to our hospital. 2years after the first admission, we found NTM in her as well. Cautiously examined, non-biological treatments such as MTX, tacrolimus, leflunomide were given. Still joint symptoms remained and MMP-3 was kept high due to pneumonia and liver enzyme elevation. 10 month from now, with doctors from respiratory internal medicine, started ABT. Now joint symptoms are improving and MMP-3 has lowered to77.2. NTM has not worsened as well. [Conclusion] Biological treatment to a NTM patient is stated 'to be avoided'. ABT is said, has lower risk of infection than TNF inhibitor or IL-6 inhibitor. Careful examination is needed, but ABT might be a fairly safe biological treatment for RA patient with NTM.

P1-148

Ankle arthrodesis with external fixation for ankle deformity in rheumatoid arthritis

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Conflict of interest: None

[Background] Ankle arthrodesis is common in rheumatoid ankles, but long-term cast immobilization and non-weight bearing are needed to obtain bone union. As rheumatoid arthritis (RA) shows joint disorders in contralateral extremities, disorders of other joints under non-weight bearing are feared. We have thus performed operations not directing non-weight bearing by using Ilizarov external fixators. [Subjects] Four patients (1 man and 3 women; mean age, 61.3 [58-68] years) underwent surgery (arthroscopic fixation in 2, anterior sliding bone graft in 1, and post-fixation nonunion surgery in 1). Postoperative follow-up period was 21 (13-38) months. Biological drugs were used in 3 patients. [Results] All patients obtained bone union. Except for 1 patient with nonunion surgery, walker-assisted gait was achieved at 9.3 (7-14) days, T-cane gait at 20.7 (13-33) days, and they were discharged on day 39 (33-42). Those on biological drugs had no complications of external fixation. [Discussion] Conventional procedures needed long-term cast immobilization and non-weight bearing. Combined external fixation, allowing early weight-bearing and low load on the contralateral joints and upper limb joints, was effective for the treatment of RA.

P1-149

Two Cases of Persistent Arthritis Localized in Ankle Joint

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Conflict of interest: None

We reported two cases of arthritis in the ankle joint periphery. Case 1; 48 -year-old female had six-months persistent swelling in right ankle. anti-CCP 0.8U/ml; CRP 0.53mg/dl. With Xp and CT images, bone erosion was recognized talus and joint space narrowing was recognized subtalar joint. With enhanced MRI, synovitis was recognized around the talocrural joint. Arthroscopic synovectomy was performed for the talocrural joint and the subtalar joint. Pathological findings showed stratification of synoviocytes and inflammatory cell infiltration. We make a diagnosis RA and MTX 6 mg/week was administered. Case 2; 59-year-old female had five-years persistent swelling in right ankle. anti-CCP 1.9U/ml; CRP 0.99mg/dl. With XP, CT, and MRI, joint space narrowing and bone erosion was recognized in the ankle joint. Arthroscopic synovectomy was performed for the talocrural joint, and pathological findings showed tissue images compatible with RA. MTX 10 mg/week was administered. Neither of two cases met the criteria for 2010 RA classification by ACR/EULAR. RA was diagnosed from histological examinations. Although pain-relief effects were obtained from synovectomy and MTX, image findings showed progression of arthropathic changes. We thought that early diagnosis and treatment are necessary.

P1-150

An examination of hindfoot deformity of ryeumatoid atrhritis operated arthrodesis

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Conflict of interest: None

[Objectives] Biological agent change treatment of rheumatoid arthritis. Forefoot deformity are many reported cases,but hindfoot deformity report a few case. Three cases of hindfoot deformity by rheumatoid arthritis report foot joint arthrodesis. [Methods] After 2003 foot joint arthrodesis of hindfoot are three cases,one case operate triple arthrodesis,two cases operate arthrodesis of subtaler joint and calcaneocuboid joint. [Results] All cases are female,the average age 54. Rheumatoid arthritis contract over 10 years, and other joint operation history,and used biological agent.(infliximab 1case,adalimumab 1case,tochilizumab 1caes) It was possible gait,but foot weight bearing was pain ful.Arch support is not effective. After operation improve VAS25mm from to VAS 70mm. [Conclusion] Forefoot deformity of rheumatoid arthritis is strong pain. Biological agent effect for rheumatoid arthritis,arthrodesis of the foot joint works well for forefoot deformity of rheumatoid arthritis

P1-151

A case of isolated talonavicular joint arthrodesis in rheumatoid arthritis patient

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Conflict of interest: None

[Objectives] We report a case of isolated talonavicular joint arthrodesis in a rheumatoid arthritis (RA) patient, who had a gait disturbance due to the destruction of the joint, despite reached to DAS clinical remission. [Case] A 69-year-old woman at the onset of RA in 2007 started a treatment at our hospital from September 2010. She had a difficulty to walk due to severe pain of her left foot, despite reached to DAS clinical remission with MTX therapy. Swelling and tenderness were showed only in the talonavicular joint of her left foot. We performed isolated talonavicular joint arthrodesis in August 2012. She had a limb cast immobilization without weight bearing for 6 weeks after surgery. Prolonged healing of the wound, it healed conservatively. Now she is able to walk without

pain. [Conclusion] In RA patient, foot lesions are common. Failure of talonavicular joint is one of the factors to proceed foot deformity. We have a good result to perform fixation of the joint. Talonavicular joint fixation contributes not only to improvement of walking function associated with pain relief but also to prevention of the progression of foot further deformation.

P1-152

The first MTP joint arthrodesis by a newly designed Surf Plate

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Conflict of interest: None

【Objectives】Fore foot deformities in patients with rheumatoid arthritis (RA), hullux valgus (HV) and osteoarthritis (OA) might cause gait dysfunction and lead to disability. Here we report the retrospective study of arthrodesis of the first MTP joint using a newly designed Surf Plate.【Methods】We examined antero-posterior radiographs obtained from 61 feet of 51 patients (RA 39, HV 10, OA 2 cases). And we measured the hallux valgus angle (HVA) pre- and postoperatively, and during follow-up on antero-posterior radiographs. We also assessed the union rate of the postoperative first MTP joint.【results】The average of pre- and postoperatively, and during follow-up HVA was 48.1, 9.0 and 14.6 degree, respectively. And the union rate of the postoperative first MTP joint was 73.2%.【Conclusions】The average HVA significantly improved when compared between preoperation and the follow-up period. And the union rate was also good. Therefore, arthrodesis of the first MTP joint using Surf Plate was effective for the treatment of severe deformity of the first MTP joint in patients with RA, HV, and OA.

P1-153

Postoperative complications in joint preserving surgery and resection arthroplasty for lessor toe in patients with rheumatoid arthritis (RA)

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Conflict of interest: None

[Objectives] In our institution, total arthroplasty with Swanson flexible hinge toe was performed for metatarsophalangeal (MTP) joint of the 1st toe, and resection arthroplasty was performed for the lessor toes (group A). However, we performed joint preserving surgery of metatarsal bone for the lessor toes (group B). In this sturdy, we examined the relationship between the length from tarsometatarsal joint to MTP joint and the postoperative complications, also whether the crossing forefoot deformities increased postoperative complications. [Methods] 46 patients with 66 feet were included, 35 feet in group A, and 31 feet in group B. Anteroposterior radiographs of the foot were taken preoperatively, immediate postoperatively, and 6 months after surgery. The length from tarsometatarsal joint to MTP joint (a), and the second cuneiform (cuneiform length, b) were measured. [Results] No significant differences in (postoperative a/b) / (preoperative a/b) were seen between the both groups. Postoperative complications were occurred 22 feet. There were no correlation between crossing foot and postoperative complication. [Conclusion] In this study, no correlation were concluded between postoperative complications and the length from tarsometatarsal joint to MTP joint around the surgery.

P1-154

Operation technique for rheumatoid forefoot deformity

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Conflict of interest: None

[Objectives] Postoperative results of arthrodesis for 1st MTP joint and resection arthroplasty for lesser toes and joint preserving surgery for RA patients were evaluated. [Methods] 19 feet performed operation for rheumatoid forefoot deformities were followed up over 6 months. 15 feet were performed arthrodesis for 1st MTP joints and resection arthroplasty for lesser toes (Destructive group). 4 feet were performed modified Mann method for the big toe and shortening oblique osteotomy for the lesser toes (Preserving group). [Results] The JSSF score and the HVA significantly improved postoperatively in both groups. The recurrence of corns was seen in 2 feet from the Destructive group. 1 foot was diagnosed as a deep infection of the MTP joint of the big toe, and 3 feet had delayed healing of the wound from the Destructive group. Superficial infection was seen in 1 foot and delayed healing of the wound in 2 feet from the Preserving group. [Conclusion] The post operative result of arthrodesis for 1st MTP joint and resection arthroplasty for lesser toes for rheumatoid forefoot deformity was acceptable. Because short term results of 4 feet which were performed by joint preserving surgery was good, this method is proven if the control of inflammation is stable.

P1-155

Combined surgical therapy with MTP joint Swanson implant arthroplasty and proximal open wedge osteotomy using BOW plate for hallux valgus in rheumatoid arthritis

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Conflict of interest: None

【Objectives】To evaluate the clinical result of MTP joint replacement with Swanson implant and proximal open wedge osteotomy using BOW plate for hallux valgus in rheumatoid arthritis (RA).【Materials and Medods】Nine feet, one male, eight female, of hallux valgus of RA patients, who were treated with MTP joint replacement with Swanson implant and proximal open wedge osteotomy using BOW plate for hallux valgus in RA. Average age was 65.5 years old (range, 53-76 years). The follow-up average 12 months (6-19 months). We evaluated that preoperative and postoperative hallux valgus angle (HVA), the angles between the axes of the first and second metatarsal shafts (M1-M2), AOFAS hallux metatarsophalangeal-interphalangeal scale and complication.【Results】The mean HVA was 48° preoperatively, 16° at follow-up period. The mean M1-M2 angle was 24° preoperatively, 10° at final follow-up. AOFAS scale was improved 32 points preoperatively to 84 points postoperatively. There were no delayed union and infection.【Conclusion】BOW plate fixation for proximal open wedge osteotomy was very rigid and stable to weight bearing walk earlier. The results of this surgical therapy for hallux valgus in rheumatoid arthritis was useful and satisfactory.

P1-156

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

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Conflict of interest: None

[Objectives] Although TNF inhibitors suppress bone destruction in patients with RA, TNFα stimulation alone does not directly induce osteoclasts, bone resorbing cells. With the assumption that the combination of TNFα and a humoral factor X induces differentiation of osteoclast, we aimed to identify factor X and clarify the mechanism of its action. [Methods] We cultured bone marrow derived monocytes/macrophages in the presence of M-CSF, TNFα and various humoral factors in vitro. Expression levels of c-Fos and NFATc1 were analyzed by Western blotting. For in vivo analysis, TNFα and X were administered into the supracalvaria in mice. [Results] The combination of TNFα and X induced TRAP positive osteoclast-like multinucleated giant cells in an osteoclast differentiation factor, RANKL-independent manner. The osteoclast-like cells made resorption pits on dentin slices. Stimulation with TNFα and X significantly up-regulated the expression levels of c-Fos and NFATc1. Bone resorption on the calvaria in mice was significantly increased, once the combination of TNFα and X was administered. [Conclusion] These results suggest that TNF inhibitors might suppress bone destruction caused by the osteoclast-like cells induced in the presence of TNFα and X.

P1-157

Inhibitory effect of IL-17 on chondrogenic differentiation of human mesenchymal stem cells

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Conflict of interest: None

[Objectives] Cell-based therapy with mesenchymal stem cells (MSCs) is a promising approach for joint repair of RA. In the light of cartilage repair, we evaluated the effect of IL-17, known to be involved in pathophysiology of RA, on chondrogenesis. [Methods] Pellet culture was performed with MSCs in chondrogenic induction media containing TGF-β3 (CIM). [Results] The increased expression of cartilage matrix and marker genes (Col2a1/Aggrecan/Col10a1) by CIM culture was inhibited by IL-17. Undifferentiated MSCs expressed low level of IL-17 receptor, whereas pellet culture in CIM increased its expression. Expression and phosphorylation of Sox9, a master transcription factor for chondrogenesis, were up-regulated and sustained up to day 21. Although the Sox9 expression was not altered by IL-17, phospho-Sox9 was decreased at day 7. Analysis of protein kinase A (PKA), a kinase known to phosphorylate Sox9, was induced by CIM and suppressed by the addition of IL-17. Therefore, IL-17 suppress the activity of PKA, which reduces phosphorylation of Sox9 and chondrogenesis. [Conclusion] The inhibitory effect of IL-17 was performed via inhibition of PKA and Sox9 activity. Our results indicate that suppressing IL-17 within the joint is important for effective MSCs-based cartilage repair therapy.

P1-158

Tubular architecture in osteoarthritis cartilage

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Conflict of interest: None

[Objectives] In this study we examined the site specific structure of the OA cartilage using the section of proximal tibia obtained from medial osteoarthritis patients. [Methods] A total of 14 OA tissues from lateral joint surface of proximal tibia was obtained from medial osteoarthritis patients undergoing TKA. (mean age 72.7±6.4) In the OA cartilage from lateral joint surface of proximal tibia, the degenerated softening area (LTS cartilage) and elastic hard area (LTH cartilage) were cut vertically or sagittally and cutting surface was observed under stereomicroscope and Scanning Electron Microscope. [Results] Cutting edge of LTS cartilage shows highly longitudinally oriented tubular architecture, but the cutting edge of LTH cartilage shows low number of tubular architecture.(LTS 54.2±22.2 vs LTH 18.9±19.7 $P<0.001$) In the horizontal section of LTS cartilage, chondrocytes which move to line in row to form the tubular architecture can be observed under stereomicroscope and numbers of small hall like structure was observed under SEM,. [Conclusion] Tubular architecture including some cells in the cavities and in the wall was observed In the degenerated softening area of OA cartilage. These tubular architecture would be constructed by the lining-up and reorganization of chondrocyte.

P1-159

Evaluation of synovial tissue obtained by arthroscopy in patients with elderly-onset rheumatoid arthritis

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Conflict of interest: None

To diagnose the cases in patients with elderly-onset rheumatoid arthritis (EORA), we obtained synovial tissue by arthroscopy. The subjects included 3 females. Abrupt onset occurred in all patients. The macroscopic appearance of arthroscopy was not like RA, but like septic arthritis in two cases. The synovial contains an increased number of neutrophils and the pathological diagnosis were septic arthritis in two cases. These might reflect a difference in the etiology of synovitis of these disease entities, RA and EORA.

P1-160

Effects of T cells on the induction of osteoclasts(OC) from human monocytes

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Conflict of interest: None

Objectives Activated T cells express RANKL and have been considered to pomote OC differentiation. Alternatively, activated T cells were suggested to suppress OC differentiation via the production of IL-4 and IL-10. In a mouse model, T cells were reported to drive monocytes to differentiate into dendritic cells (DCs) through GM-CSF production. We investigated effects of CD4+ T cells or CD8+ T cells on the induction of OC from human monocytes. ***Methods*** After incubation of monocytes with RANKL(50 ng/ml) and M-CSF(20 ng/ml) for 14 days, OC differentiation was evaluat-

ed by the TRAP staining. Additionally, we added CD4+T cells or CD8+T cells with or without IL-2 (20U/ml) at the initiation of the culture. ***Results*** OCs were induced from monocytes by the culture with RANKL and M-CSF. The addition of CD8+ T cells facilitated the OC differentiation. Conversely, the addition of CD4+ T cells with IL-2 inhibited the OC differentiation, with preferential induction of DCs. ***Conclusion*** CD8+ T cells seem to facilitate OC differentiation from monocytes. Irrespective of the presence of RANKL and M-CSF, CD4+ T cells with IL-2 facilitate DC differentiation, thereby resulting in inhibition of OC differentiation. (Collaborator: M Harada M.D. PhD., Dept. of Immunol., Facult. of Medicine, Shimane Univ.)

P1-161

Pentosidine levels in patients with rheumatoid arthritis treated with tocilizumab: an observational study

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Conflict of interest: None

【Objectives】 To investigate whether tocilizumab (TCZ) have an effect on serum pentosidine (Pen), a well-defined advanced glycation end products.【Methods】 This study was a prospective observational study for 24 weeks of 18 rheumatoid arthritis patients who started to receive TCZ. We examined serum MMP-3, DAS28-ESR, and mHAQ as clinical markers, Pen and homocysteine as bone quality markers, TRACP-5b as bone resorption marker, and serum IL-6 at 0, 12, and 24 weeks.【Results】 Each clinical markers have improved significantly with time. On the other hand, IL-6, bone quality markers and bone resorption markers showed no significant change. Although there was no correlation between IL-6 and Pen at 0 week, IL-6 difference, subtracted IL-6 value at 0 week from 12 week, showed strong correlation with Pen at 0 week ($R=0.782$, $P<0.001$). Furthermore, IL-6 difference and Pen difference during 24 weeks showed a moderate positive correlation ($R=0.572$, $p=0.018$).【Conclusions】 Based on the "Bathtub model" proposed by Nishimoto (Blood 2008; 112: 3959-), IL-6 difference implied IL-6 receptor (IL-6R) mediated clearance. This study suggests that Pen rise in proportion to IL-6R related clearance, and reduction of Pen may be obtained by TCZ particularly in patients with high IL-6R related clearance.

P1-162

Longitudinal assessment of lumbar spine bone mineral density in patients with rheumatoid arthritis

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Conflict of interest: None

[Objectives] To evaluate the risk factors for bone mineral density loss in patients with rheumatoid arthritis (RA). [Methods] In a longitudinal study, lumbar spine bone mineral density (BMD) was measured at baseline and after average 1.2 years. Data of RA disease activity, treatment agents towards RA and osteoporosis, dietary and physical status were collected. [Results] 218 patients were examined at baseline and follow-up time. Usage of drugs for osteoporosis was associated with decreased risk for lumbar spine BMD loss. Among current user of drugs for osteoporosis, smoking and shortage of calcium intake were associated with bone loss, while among patients without drugs for osteoporosis, low body mass index was associated with lumbar spine BMD loss. [Conclusion] Results of this longitudinal study suggest that management of osteoporosis, including drugs and education towards life style, is important in RA patients.

P1-163

The Bruton tyrosine kinase suppresses osteoblastic differentiation

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Conflict of interest: None

Objectives The Tec family of nonreceptor tyrosine kinases have been shown to play a key role in inflammation and bone destruction. Bruton tyrosine kinase (Btk) has been the most widely studied due to the critical role of this kinase in B-cell development and recent evidence showing that blocking Btk signaling is effective in ameliorating lymphoma progression and experimental arthritis.The role of Btk in osteoblast (OB) differentiation has not been well elucidated. We report herein the role of Btk in OB differentiation. **Methods** We investigated the effects of Btk inhibitor and knockdown of Btk on OB differentiation in MC3T3-E1 cells and primary murine calvarial osteoblasts. **Results** Expression of Btk was detected in these cells. Btk inhibitor stimulated ALP activity and mRNA expression of OB markers. Mineralization was also promoted by treatment with Btk inhibitor. Knockdown of Btk caused increased ALP activity and mRNA expression of OB markers. Btk inhibitor suppressed phosphorylation of MAPK and Akt. Our results indicate Btk might regulate OB differentiation through MAPK and Akt. Btk inhibitor would be of potential use for the treatments of osteoporotic change in RA patients since it possess not only anti-inflammatory effect which has been reported but also pro-osteoblastic effect.

P1-164

Efficacy and safety of treatment with monthly minodronate in osteoporotic RA patients

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Conflict of interest: None

[Objectives] The aim of this study is to evaluate the efficacy and safety of treatment with monthly minodronate in osteoporotic RA patients. [Methods] Minodronate was monthly administrated to 36 osteoporotic RA patients at a dose of 50 mg for 24 weeks. 10 RA patients were treated with no bisphosphonate (group I) before minodronate treatment. In contrast, 16 or 10 RA patients were treated with weekly or daily risedronate (group II, or group III), respectively, and changed to monthly minodronate. [Results] The percentage change from baseline in lumber and total hip bone mineral density was increased in group I and III at 24 week. In contrast, bone mineral density in group II at 24 week was not changed compared with baseline (0 week). In addition, TRACP-5b and uNTx at 24 week were significantly decreased in group I and III and BAP was weakly decreased in all groups at 24 week. Moreover, serum concentration of PTH was increased in group I, but was reduced in group II and III. [Conclusions] Monthly administration of minodronate was effective in osteoporotic RA patients. Furthermore, monthly minodronate was strong compared with daily risedronate. Especially, the effect of minodronate on the induction of secondary hyperparathyroidism might be weak as compared to that of risedoronate.

P1-165

Erroneous Bone Mineral Density in Patients with Decreased Renal Function

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Conflict of interest: None

[Objectives] Bone mineral density (BMD), an indicator of osteoporosis, is affected by various factors. We studied the effect of decreased renal function on BMD. [Methods] We retrospectively analyzed BMD, measured by dual-energy X-ray absorptiometry (DEXA), of 97 male patients having serum creatinine values and BMD both of femoral necks and of lumbar spines (62.9±13.8 y, eGFR 53.9±33.5 ml/min/1.73m^2). Females were excluded due to the effect of menopause. [Results] Right femoral neck BMD (R-BMD; T-score, -1.38±1.08) correlated with left femoral neck BMD (L-BMD; -1.38±1.07)(R=0.961, P<0.0001). However, lumbar spine BMD (S-BMD, -0.31±1.50) was less associated with R-BMD (R=0.616, P<0.0001) and L-BMD (R=0.637, P<0.0001). Age-dependent decline in BMD was observed in femoral necks but not in lumbar spines. T-score of S-BMD was higher than those of R-BMD by 1.09±1.27 and of L-BMD by 1.10±1.23. When eGFR was less than 45 ml/min/1.73m^2, the odds ratio for the highest quartile of the discrepancy (deltaT-score>1.7) was 9.92 [95%CI: 2.90-46.32] (non-adjusted) and 8.97 [95%CI: 2.40-46.60] (age-adjusted). Vascular calcification of abdominal aorta might account for erroneously high BMD of lumbar spine. [Conclusion] Lumbar spine should not be used to evaluate BMD in patients with decreased renal function.

P1-166

Comparison of the effect of eldecalcitol and alfacalcidol on the bone density of distal radius in osteoporotic patients

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Conflict of interest: None

[Objectives] Distal radius (DR)_DXA is a device spreading most widely in the clinical setting. We compare the effects of ELD and alfacalcidol (ALF) on DR_BMD in osteoporotic patients, and examine whether the curative effect of drugs on the DR using DXA is possible. [Methods] Eighty-four primary osteoporotic patients who visited our hospital from 2011 to 2012 were enrolled. All patients were given calcitonin together. We compared the effects of 6-month treatment of ELD (n=40) and ALF (n=44) on DR_BMD, serum TRACP-5b and adjusted serum Ca. [Results] In ELD group, DR_BMD significantly increased from baseline (p<0.05), while ALF group showed a significant decrease (p<0.05). The difference in BMD change between the two groups was also significant (p<0.01). As the result of subgroup analysis of the effect of ELD, there was no interaction between treatment effect on BMD and baseline age. In the both groups, TRACP-5b significantly decreased to normal range (p<0.001). When patients were stratified into tertile, ELD normalize TRACP-5b regardless of their baseline levels. The adjusted serum Ca maintained the normal range in both groups. [Conclusion] ELD therapy could increase DR_BMD and inhibit bone resorption superior to ALF, suggesting the therapeutic advantage over ALF therapy.

P1-167

Efficicacy of menatetrenone(Vitamin K_2) in patients with autoimmune diseases under glucocorticoid therapy with bisphosphonate: an observational study

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Conflict of interest: None

<Purpose> To clarify the clinical significance of effect of menatetrenone (Vitamin K_2, VK_2) on bone metabolism in patients with autoimmune diseases under glucocorticoid (GC) with bisphosphonate (Bis). <Method> Sixty five patients with autoimmune diseases who were started to received predonisolone at 30mg or higher daily and regular dose of Bis were included in this study. Twenty of these patients received VK_2 from 2 weeks after GC. The bone metabolism markers included osteocalcin (OC), undercarboxylated OC (ucOC), and procollagene type I N-terminal peptide (PINP) and bone-specific alkaline phosphatase (BAP) as bone formation markers and collagen I N-terminal telopeptide and tartrate-resistant acid phosphatase isoform 5b as bone resorption markers, were measured before GC and after 1, 2, 3 and 4 weeks. Changes in BMD were also evaluated. <Result> The serum levels of OC, ucOC and PINP were decreased from 1 to 4 weeks after GC, while the serum BAP and bone resorption markers did not changed during 4 weeks. The mean BMD after a year was not changed by VK_2. <Conclusion> Serum OC and ucOC were decreased by GC, however serum OC was significantly increased by addition of VK_2. Additional use of VK_2 to Bis might be useful for stimulation of bone formation in GC-induced osteoporosis.

P1-168

Changes in serum Dickkopf1 and Sclerostin levels after glucocorticoid therapy in systemic autoimmune disease: a prospective study

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Conflict of interest: None

[Objectives] The purpose of this study is to clarify whether serum Dickkopf-1 (DKK1) and Sclerostin, Wnt pathway inhibitors, play a role in the pathogenesis of glucocorticoid (GC)-induced osteoporosis in patients with systemic autoimmune diseases. [Methods] Forty patients (female 26, postmenopausal 16) with systemic autoimmune disease who received initial therapy with 30-60 mg prednisolone daily dose were prospectively included in this study. Regular doses of bisphosphonate were co-administered in all the patients. We measured serum RANKL, OPG, and bone formation markers at 0, 1, 2, 3 and 4 weeks after GC therapy. [Results] The serum levels of bone formation markers, osteocalcin and procollagene type I N-terminal peptide were significantly decreased from 1 to 4 weeks after GC therapy. The serum DKK1 levels was significantly decreased from 2 to 4 weeks after GC therapy. In contrast, serum sclerostin levels did not changed during 4 weeks. [Conclusion] The bone formation markers were significantly decreased at early phase by GC administration. However, Wnt pathway inhibitors, serum DKK1 was decreased rather than increased by GC therapy. It is suggested that GC-induced reduction of bone formation was not caused by inhibition of Wnt pathway.

P1-169

Adalimumab, a fully human anti-tumor necrosis factor monoclonal antibody,may increase bone density of lumber spine in men with active psoriatic arthritis

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Conflict of interest: None

[Objectives] We investigated whether adalimumab treatment modifies bone density (BMD) and metabolism in PsA patients under prospective condition. [Methods] Adalimumab was dosed as 40mg every two weeks.From March 2010 to December 2010, thirteen patients were eligible for the study (all males), and the average age and affected period (psoriasis/psoriatic arthritis) were 45.9 years old and 16.5 / 8.0 years, respectively. Clinical results for 1-year treatment in 13 patients was evaluated. BMD (%YAM) of lumbar vertebrae(L-spine) and left side of the femoral neck on DXA and bone metabolic markers (TRACP-5b,BAP, serum Calcium, ucOC) were measured at baseline and 24 and 52 weeks after treatment. LOCF method was used for the analysis. Wilcoxon signed rank test was used and significance level was set at 0.05. [Results] The mean %YAM in L-spine increased significantly from 99.7±17.2% at base line to 102.7±18.2% at week 52 ($p<0.05$). The mean BAP increased significantly from 18.0±7.4 at baseline to 21.1±9.1 at week 24 ($p<0.05$), whereas no significant difference was observed 17.4±7.2 at week 52. The mean ucOC increased significantly from 2.3±1.4 at baseline to 5.3±4.0 at week 52 ($p<0.01$). [Conclusion] Adalimumab may improve BMD in L-spine in men with PsA.

P1-170

Severities of vertebral fractures evaluated with semiquantitative analysis(SQ) in glucocorticoid-induced osteoporosis(GIO)

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Conflict of interest: None

[Purpose] To clarify situation of severities of vertebral fractures and correlation with clinical variables. [Methods] 137 patients with connective tissue disease other than RA were recruited and obserbed for 3 years. Patients backgrounds ; age 61±15 yo, disease duration 13±12 years, total PSL dosage 34±34g, daily PSL dosage during the study 8±6mg/day. Grading with the SQ method (Genant et al. JBMR 1993) was used for evaluation of severities of vertebral fractures. [Results]1) At the beginning of the observation, 42(30%), 15(11%) and 6(4%) patients revealed the grade (G) 1, G2 and G3, respecitively. 2) Deteriorated grades during 2 years were seen in 47% of the patients. 38% of patients with incident fractures showed oner-grade deterioration. 3) The number and severities of prevalent fractures correlate with incident fractures ($P<0.05$). The number and severities of SQ grade of prevalent fractures correlate with the severities of incident fractures. 4) Logistic regression analysis showed the age, total and daily PSL dosage and BMD as independent risk factors, and treatments with Bis and Vit K as preventing factors($P<0.05$). [Conclusion] Evaluation of severities of vertebral fractures with the SQ was suggested to be an important aspect in pathogenesis and prevention of GIO.

P1-171

Risks to Visit Emergency Room in patients with Systemic Lupus Erythematosus: A Four-Year Retrospective Study In Japan

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Conflict of interest: None

[Objectives] The aim of this study is to describe the characteristics of systemic lupus erythematosus (SLE) patients who visit emergency room (ER) and to identify the risks to visit ER in SLE patients. [Methods] A four-year retrospective study was performed at Tokyo Metropolitan Tama Medical Center using electric medical record. We identified all emergency room visits in SLE patients from April 2008 to March 2012. [Results] Total 269 events were identified in 118 patients. Of 269 events, 91 (33.8%) events were infection; 41 events (15.2%) were neurological diseases; 36 (13.4%) events were orthopedic problems; and 11 (4.1%) were cardiovascular events. “ER user group” and “ER non-user group” were 118 and 87 patients. The dose of glucocorticoids (prednisolone equivalent, 9.18±0.63mg, 5.19±0.72mg), use of cyclophosphamide (6/118(5.08%), 0/87(0%)), presence of neuropsychiatric lupus (23/118(19.5%), 6/87(6.9%)) and presence of lupus nephritis (49/118(41.5%), 21/87(24.1%)) were higher in ER user group than ER non-user group. [Conclusion] In persons with SLE, infection was the most reasons for using ER. Higher glucocorticoids dose, use of cyclophosphamide, presence of neuropsychiatric lupus and presence of lupus nephritis were higher in ER user group, compared with ER non-user group.

P1-172

Investigation of pathological and clinical features of 10 male patients in autopsied cases with systemic lupus erythematosus (compared with 70 female patients)

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Conflict of interest: None

[Objectives] To analyze the pathological and clinical features of male patients with Systemic Lupus Erythematosus (SLE) and examine the association between sex difference, pathological condition, treatment and prognosis. [Methods] Autopsy studies of 10 male patients with SLE carried out between 1960 and 2009 and their pathological and clinical features and treatment were investigated by comparing with 70 female patients. [Results] Age at onset of male is older (38.5 vs 28.4), and daily dose of steroid is higher than female (58.7mg vs 25.3mg). Lupus nephritis was detected in almost all cases. Fatty liver was detected in 40.0% of male, 71.4% of female patients. Other findings were onion-skin lesion (70.0% vs 61.7%), interstitial pneumonia (IP, 40.0% vs 22.9%), cardiomegaly (40.0% vs 18.6%) and myocardial infarction (30.0% vs 14.3%). Male patient didn’t have gastrointestinal ulcer, gastritis and esophagitis. Gastrointestinal bleeding was detected only one case. [Conclusion] Male patients with SLE have more of cardiovascular disease and IP than female patients, but less of gastrointestinal disease. We should pay attention to these organ complications with male patients at clinical field.

P1-173

Clinical characteristics of elderly-onset systemic lupus erythematosus

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Conflict of interest: None

[Objectives] SLE often affected in women of reproductive age. Elderly-onset SLE has been defined as onset of SLE more than 50 years old, and reported to occur in 10-20% of all patients. It has been hard to diagnose elderly-onset SLE different from those of young-onset SLE. We clarify the difference of clinical characteristics between elderly-onset and young-onset SLE. [Methods] We compared clinical and serological data in 15 cases of elderly-onset SLE with those in 12 cases of young-onset. [Results] Percentage of male was higher in elderly-onset (33.3%) than in young-onset (8.3%). Malar rash was less observed in elderly-onset (13.3%) than in young-onset (41.7%). Serositis and neurologic disorders occurred in 33.3% and 26.7% of elderly-onset, in contrast to in 25.0% and 8.3% of young-onset, respectively. Higher ANA titers, C3 and C4 were observed in elderly-onset (741±110, 80±7 and 19±3 mg/dl) than in young-onset (340±120, 50±8 and 11±3 mg/dl) (P= 0.002, P=0.01 and P=0.04), respectively. Anti-ds DNA antibody was higher in elderly-onset (163±33 IU/ml) than in young-onset (43±29 IU/ml). [Conclusion] Elderly-onset SLE have higher frequency of male, serositis and neurologic disorders than young-onset. Higher complements and anti-ds DNA antibody were found in elderly-onset than in young-onset.

P1-174

Association of *UBE2L3* with systemic lupus erythematosus in a Japanese population

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Conflict of interest: None

[Objectives] Recently, association of *UBE2L3*, which encodes a ubiquitin-conjugating enzyme, with systemic lupus erythematosus (SLE) was identified by genome-wide association study. *UBE2L3* was found to be a shared susceptibility gene for various autoimmune diseases. We previously reported the association of *UBE2L3* with systemic sclerosis. In this study, we analyzed whether *UBE2L3* is associated with SLE in a Japanese population. [Methods] Association study was conducted on the SNPs located in *UBE2L3* region (rs463426, rs131654, rs2298428) in 414 Japanese SLE patients and 562 healthy controls. [Results] rs2298428 located downstream of *UBE2L3* was associated with SLE in Japanese (T/T frequencies, SLE: 17.1%, control: 10.1%, P=0.0013, odds ratio [OR] 1.83). In addition, rs131654T/T was increased in SLE (30.9%) compared with controls (24.6%, P=0.027, OR 1.38). rs131654 was in moderate linkage disequilibrium with rs2298428 (r^2=0.43). The association of rs2298428 remained significant after adjustment by rs131654. On the other hand, the association of rs131654 disappeared after adjustment by rs2298428, suggesting that the association of rs131654 was caused by linkage disequilibrium with rs2298428. [Conclusion] The association of *UBE2L3* with SLE is shared across populations.

P1-175

Discovery of protein biomarkers in plasma from active systemic lupus erythematosus patients by gel-based proteomics

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Conflict of interest: None

Systemic lupus erythematosus (SLE) exhibits an aggressive clinical phenotype with severe complications and overall poor prognosis. The goal of this study was to identify candidate protein biomarkers to help to diagnose SLE patients from Taiwan. The SLE plasma samples were collected from Cathay General Hospital, Taipei, Taiwan. They, one male and eighteen female patients, were also diagnosed with renal involvement. The average age is 32.1±11.5. The patient protein profile in the plasma was randomly compared to that from twelve healthy controls from three male and nine female with average age at 41.9±12.2. The total protein in plasma was separated by one-dimensional and two-dimensional SDS-polyacrylamide gel electrophoresis. The up- and down-regulated proteins compared to healthy plasma ($p < 0.5$) were cut from the gels and digested with trypsin followed by the amino acid sequencing with both MALDI-TOF/TOF and ESI-MS/MS. Five proteins are found to be up-regulated in patient plasma: apolipoprotein B-100, alpha-2-macroglobulin, haptoglobin, retinol-binding protein 4 and transthyretin. The identified proteins are potential biomarkers that can be further confirmed by statistic analysis and clinical testing.

P1-176

Examination of the cytokine profile of the cerebrospinal fluid in Neuropsychiatric systemic lupus erythematosus

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Conflict of interest: None

[Background] Neuropsychiatric systemic lupus erythematosus (NPSLE) is serious complications as with lupus nephritis in systemic lupus erythematosus (SLE). [Objectives] We examined a cytokine profile in a cerebrospinal fluid (CSF) of NPSLE and the useful marker for the diagnosis. [Methods] We used the CSF of multiple sclerosis (MS) and the optic nerve myelitis (NMO) patient as a disease control group. We examined 27 kinds of cytokine, chemokines, growth factor with NPSLE group (N=27), MS group (N=10) and NMO group (N=10) patient using Bio-Plex Pro Assays. [Results] SELENA-SLEDAI score was 13.3±5.86. Anti ds-DNA antibody was 23.3±58.6 U/ml. The percentage of anti phospholipid antibody syndrome, anti ribosomal P antibody-positive

and abnormality of brain MRI are 4/27 (14.8%), 5/27 (18.5%) and 9/27 (33.3%), respectively. The concentration of Basic FGF, IL-1ra, IL-5, IL-7, IL-9, IL-15 and IL -17 were significantly higher in comparison with other two groups in NPSLE group. According to multivariate analysis, the protein levels of IL-5 ($p<0.036$), IL-9 ($p<0.0005$), IL-15 (<p0.0065) and IL-17 ($p<0.0336$) were significantly correlated with IL-6. [Conclusion] The diagnosis of NPSLE would be enabled by examining various kinds of cytokine profiles and contribute for elucidation of its mechanism.

P1-177

Three cases of lupus enteritis

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Conflict of interest: None

【**Case 1**】A 35-year-old female, who had been receiving treatment for lupus nephritis (type V) since she was 27 years old. She came complaining of abdominal pain in late May, 2010. CT imaging showed significant hypertrophy of the intestinal wall, leading to a diagnosis of lupus enteritis (LE). 【**Case 2**】A 55-year-old female, who developed lupus nephritis (type IV) at the age of 32. Renal function deteriorated gradually, and was started on peritoneal dialysis at 52 years of age. At 52 years of age, she started complaining of anorexia and nausea, and significant hypertrophy of the intestinal wall was found on CT imaging. LE was suspected. 【**Case 3**】A 54-year-old female, who diagnosed with SLE at the age of 48. She came complaining of abdominal pain and diarrhea at the age of 53, and after detailed examination was found to have bilateral hydronephrosis. We placed a ureteral stent for her hydronephrosis. On abdominal CT, there was hypertrophy of the intestinal wall, which led to a diagnosis of LE. 【**Conclusion**】Gastrointestinal complications of SLE may include the disorders caused by infections as well as by medications. Despite occurring with low frequency, it is important to keep LE in mind when encountering SLE patients complaining of gastrointestinal symptoms.

P1-178

SLE-transverse myelitis; two intractable cases and two cases that responded to MMF

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Conflict of interest: None

Case 1: A 24-year-old female had a fever for 4 days and abrupt lumbago with longitudinal myelitis on spinal magnetic resonance imaging (MRI). Paraplegia and sphincter dysfunction developed despite high-dose steroids and intravenous cyclophosphamide (IVCY) therapy. *Case 2*: A 39-year-old female developed a high-grade fever for 1 week and meningitis followed by progressive paraplegia, sphincter dysfunction, drowsiness, and hiccups caused by extensive myelitis. She recovered unassisted walking after combination therapy with high-dose steroids, IVCY, and plasma exchange. *Case 3*: A 35-year-old female developed recurrent paraplegia and hiccups when myelitis presented; this responded partially to high-dose steroids and IVCY. Remission occurred with the addition of mycophenolate mofetil (MMF) therapy. *Case 4*: A 33-year-old female who had transverse myelitis 5 years earlier developed progressive numbness of the legs and spinal fluid abnormalities, which were treated successfully with moderate-dose steroids and MMF. These four patients developed isolated myelitis in the setting of long-standing systemic lupus erythematosus (SLE). Acute myelitis might be intractable despite intensive therapy, while mild recurrent myelitis might respond to MMF therapy.

P1-179

Organzing pneumonia associated with Systemic lupus erythematosus : Two cases report

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Conflict of interest: None

Pleuropulmonary manifestations with systemic lupus erythematosus (SLE) are numerous and include acute pneumonitis, interstitial pneumonia, alveolar hemorrhage, pleuritis, and diaphragmatic dysfunction. However, organizing pneumonia (OP) is a rare complication of SLE. We report two cases of OP. First case, A 58 year-old woman who had been diagnosed with SLE for 33years complained of fever and chest pain at the time deep breath. Second case, A 48 year-old woman who had been diagnosed with SLE for 15 years complained no significant respiratory symptoms, but slightly dry cough. Their symptoms were different, but it is clearly that they had radiographic abnormalities by chest X-ray test and chest computed tomography. Their respiratory symptoms, fever, and radiologic findings were showed significant improvement after treatment with high-dose oral corticosteroid. OP has been associated with several connective tissue disease, including dermatomyositis-polymyositis, mixed connective tissue disease, and rheumatoid arthritis.Although, OP is a rare complication among the pleuropulmonary manifestation with SLE. We should pay more attention for OP, when the patients showed fever, dyspnea, and radiographic abnormalities.

P1-180

A case of lupus myelitis with perimedullary arteriovenous fistula

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Conflict of interest: None

[Case] 35 F [Present history] The patient was diagnosed as having SLE in 2003 by the presence of butterfly rash, arthritis, leucopenia, anti-cardiolipin antibody and anti-ds-DNA antibody, and stably treated with daily PSL of 5mg. Her lupus deteriorated in February 2012 with the new symptomincluding fever, rash, myalgia and left cervical lymphadenopathy and the elevated titer of anti-ds-DNA antibody. The dosage of daily PSL was increased to 15mg, but she started to feel dysuria and wobbled in walk in April. We recognized her muscle weakness of lower extremities, sensory impairment below Th10 and bladder disturbance with positive pyramidal tract signs. The number of cell, IL-6 and anti-ribosomal P antibody in CSF were elevated. She was diagnosed as lupus myelitis and treated with steroid pulse therapy followed by 60mg of PSL daily along with the anticoagulant therapy. On the 3rd day of treatment, MRI showed the perimedullary AVF at Th10-12. The symptoms improved after steroid therapy. To date, the dosage of daily PSL was gradually decreased without the recurrence of the symptoms of myelitis. [Discussion] The extremely high level of anti-ribosomal P antibody in CSF and the response to the steroid therapy indicated that the myelopathy was caused by lupus myelitis.

P1-181

Clinicl study of lung involvement associated with systemic lupus erythematosus (SLE) in our hospital

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Conflict of interest: None

[Objectives] We have investigated the relationship of pulmonary disease associated with SLE and the activity, laboratory data of the onset, intercurrent illness and treatment. [Patients and methods] 103 patients (male10, female93) with SLE who had diagnosed in our hospital, during January 2005 to September 2012, were enrolled. [Results] The average age was 41.4, SLEDAI point was 2 to 34 (median 11). On an onset time, patients for lung involvement were 25 cases (24.2%). The type of manifestations included infection 3 cases (12%), interstitial lung disease 11 cases (44%), pulmonary hypertention 2 cases (8%), pleuritis 12 cases (48%), bronchitis 1 cases (4%) respectively. The intercurrent autoimune diseases were dermatomyosis, Sjögren syndrome, rheumatoid arthritis and primary biliary cirrhosis. They presented in 8 cases of interstitial lung disease. Lung involvement group showed significant difference of the high level WBC, IgG and decrease of the value of Hb, although there was no difference of SLEDAI. The steroid therapy had started in 22cases (88%). [Conclusion] Our data showed that interstitial lung disease and pleuritis associated with SLE occured nearly same frequency. Moreover there was the tendency that interstitial lung disease was associated with other rheumatic disease.

P1-182

A case of CNS lupus presented limbic encephalitis with subacute progression

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Conflict of interest: None

【Case report】A 27-year-woman who was diagnosed with SLE at 12 was admitted to our hospital in April, 2012. Then she was controlled with prednisolone (PSL)5mg/day and cyclosporine (CyA)200mg/day stably. In February 2012, she had new onset of headache,decline in spontaneity, and impaired orientation and they developed subacutely. In April 2012, visual field test revealed light homonymous hemianopsia and brain MRI revealed high intensity area of light frontal lobe and limbic system. We examined carefully and infection and paraneoplastic disorder were ruled out.The progress in her medical course and the findings of brain MRI or cerebrospinal fluid (CSF) were atypical for CNS lupus, however we treated with steroid pulse therapy followed by oral administration of 50mg/day of PSL. Headache and impaired orientation were slowly improved as well as the findings of MRI and CSF.【Discussion】We experienced a rare case of CNS lupus that presented limbic encephalitis with subacute progression. It also made us difficult to make definite diagnosis that it required some more time to impair her symptoms. Afterward it was reported that cerum and CSF concentration of anticytoplasmic antibody increased before steroid pulse therapy and they lowered after that.

P1-183

A case of systemic lupus erythematosus(SLE) complicated with malignant lymphoma(ML) and hemophagocytic syndrome(HPS)

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Conflict of interest: None

A 65-year-old female patient was diagnosed as having SLE on the basis of thrombocytopenia, proteinuria, antinuclear antibody and antiphospholipid antibody in February 2012.Her disease was well controlled with low dose of prednisolone (PSL) therapy. However, she presented with high fever and severe thrombocytopenia in October 2012. Considering the disease exacerbation, she was admitted to our hospital and treated with 1mg/kg of PSL. Although bone marrow (BM) specimen showed hemophagocytosis and elevated soluble IL-2 receptor level was found, there was no obvious malignant cell in her BM initially. She was then treated with methyl PSL pulse therapy, diagnosed as having autoimmune-associated HPS, but the efficacy was temporary and limited without improvement of fever amd thrombocytopenia. Futhermore, markedly elevated levels of LDH and ferritin were found, and FDG-PET showed increased FDG accumulation in the spleen and BM. We therefore performed a BM puncture again and found findings compatible with ML. We started the treatment for ML, which led to improvement of the disease. Here, we report the present case in which it was difficult to distinguish ML-associated HPS from HPS with SLE.

P1-184

Two cases of neuropsychiatric SLE developing during induction therapy with initial sign of arthritis

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Conflict of interest: None

[Introduction] Neuropsychiatric lupus is one of the most severe disease manifestations, and is difficult to predict. [Case report] Patient 1 was a 27-year-old woman with a history of alopecia, arthritis, photosensitivity and oral ulcer of 5-month duration. Anti-ds DNA antibody was 138 IU/mL, CH50 0 U/mL and SLEDAI 16. Six days after treatment with 0.8 mg/kg/day of prednisolone (PSL), headache and vertigo developed. MRI showed multiple cerebral infarctions and hemorrhages, and IL-6 level in spinal fluid was high. She was diagnosed with SLE-associated vasculitis. Patient 2 was a 28-year-old woman, with an 11-year past history of bipolar disorder, with present initial manifestation of one and a half months of arthritis. Anti-ds DNA antibody was 1845 IU/mL, CH50 21 U/mL and SLEDAI 9. Initial therapy with 0.3 mg/kg/day of PSL and tacrolimus was not effective. Two weeks after treatment started, high grade fever, depression and suicide ideation became apparent. MRI showed meningitis, and IL-6 level in spinal fluid was high. Steroid pulse therapy improved these signs in both cases. [Conclusion] Although the initial disease manifestation was mild in both cases, high anti-ds DNA and hypocomplementemia may be predictive of severe complications in such patients and require careful monitoring.

P1-185

Endometrial Tuberculosis Causing Amenorrhea And Abnormal Uterine Bleeding in a Lupus Patient Treated with Cyclophosphamide

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Conflict of interest: None

BACKGROUND: Amenorrhea may occur in patients with lupus treated with cyclophosphamide. This is usually attributed to primary ovarian failure, a known complication of cyclophosphamide. Urogenital tuberculosis (TB) can be a rare cause of amenorrhea in lupus patients. **OBJECTIVE:** To present a case of endometrial TB causing amenorrhea and abnormal uterine bleeding in a patient with lupus nephritis treated with cyclophosphamide. **CASE:** A 32-year old Filipino female who was diagnosed with lupus nephritis was managed with high dose steroid and IV cyclophosphamide, with improvement of renal flare. She subsequently developed amenorrhea and vaginal spotting for two months. Premature ovarian failure due to cyclophosphamide was considered. Transvaginal ultrasound showed thickened endometrium, normal ovaries and uterus. Dilatation and curettage was performed. Histopathology of endometrial curetting revealed chronic granulomatous endometritis with Langhans giant cells. Endometrial tuberculosis (TB) was diagnosed, and anti-Koch's therapy was started. The patient showed a favourable response, with resumption of normal menstruation. **CONCLUSION**: It is important to consider a wide range of differentials for gynecologic symptoms in lupus patients. TB should be considered in areas of high endemicity.

P1-186

The correlation of the disease activity in the patients with lupus nephritis and the expression of Kim-1 (kidney injury molecule-1)

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Conflict of interest: None

[Objectives] Kim-1 (kidney injury molecule-1) is expressed by injured tubules, it is the transemembrane domain. Tubular (t-Kim-1) and urinary Kim-1 (u-KIm-1) expression are increased in various kinds of kidney disease. We investigate to clarify the correlation with t-Kim-1+ cells/u-Kim-1 levels and the disease activity in lupus nephritis (LN) patients. [Methods] LN patients are clarified by ISN/RPS and counted the score of activity/chronicity index. We performed the multiple analysis of Kim-1 expression, renal damagein the histology, and the laboratory parameter. [Results] T-Kim-1+/ u-Kim-1 in class IV are increased compared with those in other class of ISN/RPS. T-Kim-1 was correlated with mesangial proliferation, glomerular sclerosis, crescent formation, and interstitial fibrosis. However, there are no correlations with C4, anti-dsDNA antibody titer, SLEDAI, and activity index even though t-Kim-1 correlated with u-Kim-1 levels. [Conclusion] Kim-1 expression is not necessary correspond to the disease activity. However, Kim-1 expression showed the correlation with the disease activity of the chronic phase, but not acute phase in LN. By understanding the Kim-1 has characteristic, Kim-1 could be the useful biomarker in the chronic LN.

P1-187

The co-expression of P-glycoprotein and CXCR3 on $CD4^+$ cells and its relevance to kidney damage in lupus nephritis

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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 patients. We investigated the relevance of expression of P-gp and Th1-chemokine receptors (CXCR3, CCR5) on $CD4^+$cells to tissue damage in lupus nephritis (LN). [Methods] Immunohistochemistry and flow cytometry were performed using $CD4^+$T cells in SLE patients. [Results] CXCR3 and P-gp on peripheral $CD4^+$cells in SLE were increased. P-gp on $CXCR3^+$cells was positive correlation with CXCR3 on $CD4^+$cells in LN. When LN progressed despite the suppression of humoral immunity by high dose corticosteroid (CS) with biweekly IVCY, $P\text{-}gp^+CD4^+$cells infiltrated in renal interstitial tissue and peripheral $P\text{-}gp^+CXCR3^+CD4^+$cells increased. Therefore, the poor control of Th1-mediated cellular immunity was indicated. MTX-IVCY therapy eliminated $P\text{-}gp^+CXCR3^+CD4^+$cells, resulted in clinical remission, renal dysfunction improvement and CS tapering. [Conclusion] $P\text{-}gp^+CXCR3^+CD4^+$cell might induce drug resistance and tissue damage. Reduction of $P\text{-}gp^+CXCR3^+CD4^+$cell is necessary for overcoming treatment resistance in LN. Measurement of P-gp on lymphocytes is useful to assess drug-resistance and tissue infiltration, and is a good maker for treatment strategy.

P1-188

Therapeutic response of lupus nephritis based on pathological findings

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Conflict of interest: None

[Objectives] To clarify the relationship between pathological evaluation and therapeutic response in lupus nephritis (LN). [Methods] Histopathological findings of renal biopsy from 51 patients with LN were calssified by ISN/RPS classification. Besides, Tubulointerstitial involvement (TII), thorombi were also evaluated. Therapeutic responses were assessed by SLICC renal activity and response index score at 6 months, 1, 2 and 5 years. [Results] The histopathological findings were classified into Class I/ II/ III/ IV/ V/ VI (1/5/10/26/9/0). High dosage of corticosteroids including pulse therapy and intravenous cyclophosphamide (IVCY) were selected as an induction therapy for Class III and IV especially after 2004. Complete response (CR) rate at 2 years was 70.0% and 46.2% in class III and IV, respectively. TII and thrombi were found in 60.8% and 58.8% of the specimens, respectively. TII significantly decreased the CR rate at 6 months, whereas presence of thrombi was a significant poor prognostic factor at 2 years. [Conclusion] Therapeutic outcomes based on ISN/RPS classification were expected as shown in previous reports. Tubulointerstitial involvement contributed to poor response of an induction therapy, whereas thrombi is implicated in unfavorable long-term outcome.

P1-189

Optimal treatment strategy for lupus nephritis based on the analysis of renal pathological findings

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Conflict of interest: None

[Objectives] To investigate optimal treatment strategy for lupus nephritis (LN) based on the analysis of renal pathological findings. [Methods] We performed a retrospective analysis of 43 LN patients who had received immunosuppressive therapy from January 2007 to August 2012 and had been followed up for 6 months. Definition of complete remission of LN was as spot urine protein/creatinine ratio <0.5g/gCr or qualitative test under plus-minus and normal GFR or improvement of GFR according to the EULAR/ERA-EDTA recommendation. Renal pathological findings were assessed according to the 2003 ISN/RPS classification. [Results] The classification were as follows; II: 9, III: 4, IV: 28, V: 2. Fifteen of 32 cases (46.9%) with III/IV had crescents or extracapillary proliferation, and chronicity as well. Cyclophosphamide (CY) was initiated in 24 cases with III/IV. 13 cases were maintained thereafter by other immunosuppressants and 11 cases were combination with tacrolimus (CY+Tac group). The complete remission rate at 6 months was 53.8% and 54.5%, respectively. Chronicity was observed more commonly in CY+Tac group, which was statistically significant (p=0.032). [Conclusion] Multi-target therapy such as CY+Tac may be effective for refractory LN with chronicity in renal pathological findings.

P1-190

Cases of lupus nephritis treated without study of renal biopsy findings

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Conflict of interest: None

Objective: To verify the usefulness of renal biopsy in the treatment of LN. **Methods:** We studied 135 SLE patients attending our hospital in 2011, selected those clinically-diagnosed as LN and compared the clinical features between those undergone renal biopsy and those not undergone, retrospectively. **Results:** Among 37 patients of LN, renal biopsy was performed in 24 cases(group A) and not performed in 13(group B). The reasons why biopsy could not be performed were thrombocytopenia, pregnancy and restlessness due to NP-SLE. As for treatment, initial dose of oral prednisolone, incidence of corticosteroid pulse therapy and combined immunosuppressants were as follows : group A vs B; 52.8 mg/day vs. 47.3 mg/day, 7/24 cases vs. 3/13 cases, and 6/24 cases vs. 6/13 cases, respectively. As for laboratory findings after treatment, mean levels of serum creatinine were 0.7 mg/dl vs. 1.3 mg/dl, and proteinuria was found in 4/24 cases vs 5/13 cases respectively. These data suggest that group A patients were more effectively treated than group B ones. **Conclusion:** Usefulness of renal biopsy in the treatment of LN was verified. We should treat LN patients more strictly when renal biopsy cannot be performed.

P1-191

A case of long-term lupus nephritis associated with Collapsing glomerulopathy

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Conflict of interest: None

A 45-year-old female with a pre-existing diagnosis of systemic lupus erythematosus with lupus nephritis (WHO V) presenting massive proteinuira. A renal biopsy gave the histological diagnosis of collapsing glomerulopathy in diffuse proliferative lupus nephritis with evidence of "full-house" immunostaining. Collapsing glomerulopathy is a rare form of glomerular injury, characterized by segmental or global collapse of the glomerular capillaries, wrinkling and retraction of the glomerular basement membrane, and marked hypertrophy and hyperplasia of podocytes. Prognosis is usually poor, with most cases developing end-stage renal disease, in spite of treatment. The association of collapsing glomerulopathy and systemic lupus erythematosus is very unusual. In this report, we describe a case of simultaneous diagnosis of collapsing glomerulopathy and diffuse proliferative lupus nephritis. The case presented nephrotic syndrome and evolved with partial remission of nephrotic syndrome after aggressive treatment with intravenous methylprednisolone.

P1-192

Two cases about phosphatidylserine-dependent antiprothrombin antibody positive antiphospholipid syndrome

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Conflict of interest: None

【Case 1】31-year –old female was diagnosed intrauterine fetal death and treated, three months before hospitalization. Then, for the appearance of fever, polyarthritis, she came to our department, and was diagnosed as SLE, and admitted. Though anti CLβ2GP I antibody and lupus anticoagulant (LAC) were negative, we suspected APS because of APTT elevation and her history of miscarriage. We consulted with Hokkaido university about detecting anti PS/PT antibody and LAC in aPTT mixing assay and she was diagnosed as anti PS/PT antibody positive APS.She hasn't developed thrombosis since she was administrated the warfarin potassium. 【Case 2】25-year-old female was diagnosed as SLE in other hospital, eight years before hostapilazation, she achieved a remission with PSL. Recently, she had admitted for splenic infarction in our hospital. Altough her anti CLβ2GP I antibody was negative, we suspected the complication of APS because of positive LAC and her history of thrombosis. Further, examination revealed that her anti PS/PT antibody was positive. She haven't experienced a recurrence of thrombosis, since she was administrated aspirin and cilostazol.【Consideration】Think of these two cases, we report the feature, complication and treatment of anti PS/PT antibody positive APS.

P1-193

A patient with antiphospholipid syndrome whom intra vena cava filter penetrated the duodenum

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Conflict of interest: None

A 72-years old woman has been treated with steroid because of systemic lupus erythematosus (SLE) and antiphospholipid syndrome (APS) since 1996. She was admitted to our hospital in Au-

gust, 2012, complaining of diarrhea, gaining about 10 kg and appetite loss. These symptoms had been continued since mid-July 2012. Physical examination revealed legs edema. Laboratory data revealed anemia and low protein. After the admission, she had a melena, so we examined upper gastrointestinal endoscope and colonscope. It showed ischmic enteritis. In spite of conservative treatment, anemia worsened, therefore we examined capsule intestinal endoscope in September. Endoscopic examination showed that an alien steel substance evaginated out of the duodenum. Enteroscopic examination was conducted with a fluoroscope again. An inferior vena cava (IVC) filter was detained preventing the pulmonary embolism due to APS in the past. Consequently, we diagnosed that IVC filter penetrated the duodenum. The operation was not done, considering the age. When the patient who detained IVC filter preventing the relapsing pulmonary embolism for APS complains an abdominal pain and had a melena, we must rule out that IVC filter penetrate or perforate through and around organs.

P1-194

Successful combination therapy of Ambrisentan and immunosuppressants in MCTD with interstitial pneumonia and pulmonary hypertension

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Conflict of interest: None

A 69-year-old female saw a doctor at a nearby general hospital with dyspnea and cough in March 2011.And she diagnosed as interstitial pneumonia May in the same year. Then she was transferred to our hospital because she had scleroderma and edema of her forearm, and in blood examination, she had antinuclear antibody (ANA) and anti centromere antibody.She was diagnosed as Mixed connected tissue disease (MCTD), Pulmonary arterial hypertension (PAH) and Interstitial pneumonia (IP). Oxygenation and Anticoagulation were started, and 0.3 mg/kg/day of prednisolone (PSL) and 3.0 mg/kg/day of Cyclosporine (CSA) were initiated on her 11th hospital day and Ambrisentan on the 26th hospital day too.On the 35 hospital day she had a relaps of IP with an elevation of the levels of NTpro-BNP. 500 mg/body of intravenous cyclophosphamide (IVCY) was initiated and CSA was changed to 3.5 mg/kg/day from 3.0 mg/kg/day. After IVCY, her clinical and laboratory findings of IP and PAH gradually improved. We should treat carefully patients of collagen vascular disease with IP and PAH.

P1-195

A case of mixed connective tissue disease with encephalipathy induced by tacrolimus

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Conflict of interest: None

A 64-year-old woman, who had been diagnosed with mixed connective tissue disease and lupus nephritis at 60 years of age, remained in a stable condition while receiving prednisolone and tacrolimus. Before admission to our department, she developed fever, pancytopenia and consciousness disorder. Brain MRI examination indicated the presence of leukoencephalopathy, presumably induced by tacrolimus. Blood concentration of tacrolimus was not examined at disease onset. Discontinuation of this immunosuppressant resulted in an improvement of her consciousness disorder. Bone marrow aspiration revealed hemophagocytosis and high-dose steroid therapy ameriorated it. <Clinical significance> Tacrolimus has been approved for use worldwide in organ transplantation and for treating autoimmune diseases, including inflammatory bowel disease, lupus nephritis, and rheumatoid arthritis. Leukoencephalopathy is rare, but critical side effect for patients treated with tacrolimus. We emphasize that careful monitoring of the blood concentration and clinical status for the detection of initial symptoms are required.

P1-196

The analysis of TCR Vδ1$^+$ NKT cells in systemic sclerosis patients with interstitial pneumonitis

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Conflict of interest: None

[Objectives] Interstitial pneumonia (IP) is one of the critical complications in patients with systemic sclerosis (SSc). The purpose of this study is to determine the role of TCR Vδ1$^+$ NKT cells in the pathogenesis of IP. [Methods] (1)PBMCs were isolated from healthy controls (HC, n=22) and SSc patients (n=35). Cells were analyzed by flow cytometry and the correlation between TCR Vδ1$^+$ NKT cells in PBMCs and serum KL-6 values among IP-positive SSc patients was analyzed. (2)Cytokine secretion (IFN-γ, TNF-α, IL-4, IL-17) from TCR Vδ1$^+$ NKT cells in HC and SSc patients was analyzed by FCM. (3)CD161$^-$ Vδ1$^+$ γδT and CD161$^+$ Vδ1$^+$ γδT cells (TCR Vδ1$^+$ NKT cells) in PBMCs sorted out from HC (n=3). We performed GeneChip analysis using those two cell populations. [Results] (1)TCR Vδ1$^+$ NKT cells significantly increased in IP-negative SSc patients compared with IP-positive SSc patients and HC. IP-positive SSc patients had negative correlation between KL-6 values and TCR Vδ1$^+$ NKT cells. (2)In HC and SSc patients, TCR Vδ1$^+$ γδT cells produced higher levels of IFN-γ. (3)The expressions of CCL3 and CCL4 genes in TCR Vδ1$^+$ NKT cells were markedly higher than those in CD161$^-$ Vδ1$^+$ γδT cells. [Conclusion] TCR Vδ1$^+$ NKT cells might play a regulatory role in the pathogenesis of IP in SSc patients.

P1-197

Frequency and diversity of pulmonary hypertension due to left heart disease in patients with connective tissue disease

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Conflict of interest: None

[Objectives] The aim was to clarify the pathogenesis and frequency of pulmonary hypertension (PH) due to left heart disease (LHD) (LHD-PH). [Methods] The 39 connective tissue diseases (CTD) patients had suspected PH at our clinic from February 2012 to July 2010 and underwent right heart catheterization (RHC). Evaluation of LHD was performed by cardiac troponin T (Trop T), echocardiography (UCG), myocardial scintigraphy, MRI, and myocardial biopsy. [Results] By RHC, 8 patients had PH (mPAP>=25 mmHg), 6 had PAH (PCWP<15 mmHg), 2 had LHD-PH (PCWP>=15mmHg). 9 had borderline PH (20 mmHg<=mPAP<=24mm Hg). When PAH and LHD-PH was defined as PVR>=160 and<159, 9 had PAH and 8 had PVH among

total of 17 patients. Among 8 LHD-PH patients, 1/5 (20%) had positive cardiac trop T, 7/8 (88%) had abnormalities in UCG, 2/3 (67%) had decreased accumulation of myocardial scintigraphy, 2/4 (50%) had diastolic dysfunction by MRI and 2/3 (67%) had myocardial fibrosis by biopsy. 7/8 (88%) patients had left ventricular dysfunction caused by systolic dysfunction in 1/7 (14%), diastolic dysfunction in 4/7 (57%) and both in 1/7 (14%). [Conclusion] The causes of LHD-PH varies widely. Treatment strategies, which are completely different from PAH, should be established based on pathogensis of LHD-PH.

P1-198

Cardio-pulmonary function to predict Pulmonary Hypertension (PH)

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Conflict of interest: None

[Objectives] Collagen diseases often develop pulmonary hypertension (PH). But the factors which can predict PH have not been well characterized. We started prospective study to develop early diagnosis of PH and detect the prognosis factor. [Methods] We examined echocardiogram, 6 minutes distance walking test, pulmonary function test for the patients with collagen diseases (n: 70, male: 11, female: 59, 55.4yo). [Results] The 52 patients have SSC, 11 patients have SLE, and 7 patients have MCTD. The number of anti RNP antibody positive patients is 23. Echocardiogram : EF 71.1%, LVDd 43.1%, TRPG 22.9 mmHg. 6MD : 422.8m, SPO2 96.5%, Minimum SPO2 92.6%, Pulmonary function test : VC% 104.1%, FEV1.0% 97.6%, DLco% 88.1%, [Conclusion] One patient developed PH. We are going to detect the prognosis factor of PH.

P1-199

The clinical picture of pulmonary hypertension in patients with diffuse cutaneous systemic sclerosis, limited cutaneous systemic sclerosis and mixed connective tissue disease

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Conflict of interest: None

[Objectives] Pulmonary hypertension (PAH) is one of the life threatening symptoms in the collagen disease but until now the frequency of its occurrence is not exactly sure. Then, we evaluated its frequency and the clinical picture of pulmonary hypertension in patients with diffuse cutaneous systemic sclerosis (dcSSc), limited cutaneous systemic sclerosis (lcSSc) and mixed connective tissue disease (MCTD). [Methods] We measured the estimated systolic pulmonary artery pressure using echocardiography with Doppler measurement of the tricuspid jet and investigated the clinical pictures. [Results] 7 out of 18 dcSSc (38.8%) patients, 6 out of 43 lcSSc (13.9%) patients and 2 out of 27 MCTD patients (0.07%) showed the pressure gap between right atrium and ventricle was more than 25 mmHg. 14 out of 18 disc patients, 3 out of 43 patients and 6 out of 27 patients were associated with interstitial pneumonia. [Conclusion] PAH associated with dcSSc may often worsen because of the acute exacerbation of the interstitial pneumonia therefore we should care about the pulmonary involvement.

P1-200

Morbidity and mortality of patients with pulmonary hypertension (PH), associated with systemic sclerosis (SSc)

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Conflict of interest: None

[Objectives] SSc associated PH reduce the survival rate. It was reported in 24 months after diagnosis of PH that the mortality rate of SSc associated PH was about 50%. Recently the pulmonary vasodilatation medicine comes to be introduced and contributes for improvement of their outcome. We have retrospectively estimated the survival of SSc associated with PH for 5 years. [Methods] We have selected the SSc patient form chart list that have not visited our hospital, and asked the survival to their family by telephone based questionnaire. We also discussed the risk factor for death. [Results] Mean survival was 60±17. Ratio for male to female was 1:5. In dead case, 83% of patients were associated with interstitial pneumonia. 70 % of patient was diagnosed with PH by cardiac ultrasound aft! er appearance of dyspnea. Cause of death was heart failure and arrhythmia directly induced by PH (34%) and infection (34%). 80% cases were treated by steroid based therapy. 80% cases were treated by immunosuppressive therapy including cyclophosphamide. Survival of PH case was much longer than previous reports. [Conclusion] Prognosis of SSc has been improving by the progress of new treatment intervention strategy. We think early diagnosis is important for improvement of prognosis.

P1-201

Long-term follow-up of esophageal dysfunction in patients with anti-centromere antibody

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Conflict of interest: None

[Objectives] Anti-centromere antibodies (ACA) are characteristic autoantibodies observed in systemic sclerosis (SSc) and primary Sjögren's syndrome (pSS). We previously reported that ACA are an important factor of esophageal dilatation in SSc patients (EULAR2010, JCR2010). The aim of this study was to examine the effect of ACA on esophageal dysfunction in patients with SSc and pSS by long-term observation. [Methods] Twelve pSS patients with ACA(ACA+/pSS) and 20 SSc patients with ACA(ACA+/SSc) were studied. The esophageal function was examined by barium esophagogram. The esophageal dilatation was assessed by the maximal diameter at lower esophagus. [Results] The mean durations of follow-up period were 7.04 years. Esophageal dilatation (≧30mm) was noted in 18.8% of all patients at the initial evaluation and 34.4% at the end of follow-up. ACA+/SSc showed significant increase of esophageal dilatation during follow-up when compared with ACA+/pSS (95.3% vs 119.5%, $p<0.05$). [Conclusion] The present study demonstrated that esophageal dilatation was progressive during long-term follow-up of patients with ACA.

However, the severity of dilatation was different depending on the underlying diseases. ACA seem not to be an independent factor contributing to esophageal dysfunction.

P1-202

Six cases of scleroderma renal crises

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Conflict of interest: None

[Objectives] Scleroderma renal crises (SRC) was observed in 10-20% of diffuse cutaneous systemic sclerosis (dcSSc) and 1% of limited cutaneous SSc (lcSSc). Despite of ACE inhibitors (ACEIs) treatments, SRC remains poor kidney outcome and mortality. [Methods] We analyzed the clinical features of six SRC. ANCA positive or thrombotic microangiopathy cases were excluded from this study. [Results] Clinical features of SRC at onset; mean age; 50.6±9.6 years, disease duration of SSc; 60.4±42.9 months, systolic blood pressure (BP); 200±30mmHg, diastolic BP; 116±24mmHg and serum levels of creatinine; 1.6±1.3mg/dl. Five cases were dcSSc, and one case was lcSSc. Five cases took prednisolone (mean 14.4±7.7mg/day) before SRC onset. Three cases had interstitial pneumonia (IP), and two cases had pulmonary hypertension (PH). Five cases took ACEIs at SRC onset. One case died under dialysis therapy. One lcSSc case with anti-centromere antibody abruptly progressed IP, PA and SRC at the time of anti-topoisomerase 1 antibody positive. [Conclusion] We experienced five dcSSc cases of six SRC. One lcSSc case progressed to dcSSc. Regardless classification, BP should be carefully checked in early stage of SSc for detection of SRC.

P1-203

Efficasy and safety of bosentan on Raynaud's phenomenon in patients with connective tissue diseases

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Conflict of interest: Yes

[Objectives] To analyze the efficacy and safety of bosentan on Raynaud's phenomenon in patients with connective tissue diseases. [Patients] Three males and 15 females, with a mean age of 61.4 years were studied. Mean disease duration was 16.4 years. systemic sclerosis; 13 cases, mixed connective tissue disease; 3, systemic lupus erythematosus; 1, overlap syndrome (systemic sclerosis & polymyositis); 1. [Methods] Effects of bosentan on Raynaud's phenomenon were assessed by diary cards. Evaluation points in the card were included number of occurrence, duration of Raynaud's phenomenon during a day and patient's visual analog scale of its accompanying symptom (cold sensation, numbness and pain). The improvement (≧20%) more than 2 out of 3 points was judged as "effective". Thermography of hands & feet was additionally performed. [Results]1) Number and duration during a day of Raynaud's phenomenon were significantly improved after the administration of bosentan. 2) Cold sensation and numbness were also significantly improved, but not pain. 3) Adverse events: Liver dysfunction; 4 cases, Nasal bleeding; 1, EB virus reactivation; 1. [Conclusion] It was suggested that bosentan was effective and well-tolerated for Raynaud's phenomenon in patients with connective tissue diseases.

P1-204

PRES (Posterior Reversible Encephalopathy Syndrome) and RCVS (Reversible CerebralVasoconstriction Syndrome) in a Patient with Scleroderma Renal Crisis

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Conflict of interest: None

A 43-year-old woman admitted to our hospital. She had been aware of Raynaud' phenomenon for twenty years. In January 2012, she had developed digital-tip ulcers. She had severe hypertension and renal disfunction, and chest radiograph showed cardiomegaly. Since head T2-weighted MRI scans showed hyperintense signals in the cebral and brain stem white matters, she was diagnosed of PRES. Nicargipine was given as continuous intravenous infusions, however, she produced the unconsciousness. MRI+MRA showed newly narrowings and obstructions of internal carotid and vertebral artery-posterior multiple cebral arteries. Taken together, positive anti-nuclear antibody/anti-centromere antibody, she was diagnosed as scleroderma renal crisis (SRC) and ACE inhibiter imidapril was started. Two weeks later, diffusion-weighted MRI scans showed right occipital and left parietal lobe infarctions, while MRA showed the disappearance of segmental narrowings of cebral arteries. As a result, she was diagnosis of RCVS. RCVS caused the reversible spasm of cerebral blood vessels and it is often complicated with PRES. The pathology of SRC is associated with the disorder of renovascular endothelium, and spasm of renal medium and small-sized artery. We report a case of severe SRC complicated with PRES and RCVS.

P1-205

A case of mononeuritis multiplex associated with scleroderma and Sjögren syndrome successfully treated with intravenous immunoglobulins

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Conflict of interest: None

A 69 year old woman was admitted to our hospital because of numbness of her extremities. Six month before, she had been diagnosed scleroderma and Sjögren's syndrome because of skin sclerosis, interstitial pneumonitis, Raynaud phenomenon, malignant hypertension, positive of anti-nuclear antibodies, anti-Ro/SS-A antibodies and anti-Ro/SS-B antibodies, decreased salivary gland function. As for numbness of the extremities, she was diagnosed mononeuritis multiplex with scleroderma and Sjögren's syndrome. Intravenous immunoglobulin therapy (IVIg) was selected for her numbness. IVIg was very effective not only for her nembness but also for her skin sclerosis and improvement of her slivary gland function.

P1-206

Clinical heterogeneity of Incomplete Jo-1 antisynthetase syndrome-a retrospective case series of 20 patients

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Conflict of interest: None

To determine the clinical and serological features of patients with autoantibodies against the aminoacyl-transfer RNA synthetase (ARS)- Jo-1 (histidyl-tRNA synthetase). The medical records of 20 consecutive patients with autoantibodies against Jo-1 detected by line immunoassay, from 2011 august to 2012 September were reviewed. Females were more commonly affected than males (M: F = 7:13). The median age of onset was 40 (range 11-54) years and the Mean disease duration was 21.6 (range 5-60) months.Concurrence of autoantibodies against Ro-52 with Jo-1 was seen in 4 patients (20%). ILD was present in 5(25%), fever in 8(40%), mechanic hands in 3(15%), Raynaud's phenomenon in 2(10%), polyarthritis in 15(75%) and positive anti-nuclear antibody (ANA) in 16(80%) of patients.2 patients had carpal tunnel syndrome as presenting symptom.2 patients had only ocular symptoms –one has bilateral granulomatous uveitis and the other presented with nodular posterior scleritis. One patient had dermatomyositis. Five patients (25%) had overlap syndromes (sjogren syndrome=2, limited scleroderma=1, SLE=1, APLA =1). The clinical presentation of Jo-1 ASS is very diverse.Carpal tunnel syndrome and ocular features were not been previously reported in patients with anti-synthetase syndrome.

P1-207

Evaluation of myositis associated with systemic lupus erythematosus

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Conflict of interest: None

[Objective] To evaluate the myositis occurring in systemic lupus erythematosus (SLE). **[Method]** Five SLE patients with myositis were analyzed. **[Result]** All females. Mean onset age of SLE was 32±17 and mean onset age of myositis was 46±20 years old. Four of 5 had juvenile onsets of SLE and high SLE disease activity including low complement and high anti-DNA antibody levels at the onset of myositis, whereas a patient with an aged onset did not have active SLE. CK levels were 169 ~ 4,548 IU/L (the highest in an aged patient). The elevated CK levels were accompanied with high levels of serum transaminase dominant in AST (GOT) except an aged patient. Two of 5 patients with anti-RNP antibody were able to have mixed connective tissue disease (MCTD), and the rest patients could be diagnosed SLE/myositis overlap. Myositis, however, was frequently considered a manifestation of SLE in Europe and the USA. Myositis is also adopted to an item of SLE Disease Activity Index of ACR and given a higher score than complement and anti-DNA antibody levels. **[Conclusion]** Since individual connective tissue disease (collagen disease) has a distinct disease entity, myositis associated with SLE should not be considered as a manifestation of SLE, but as an overlap syndrome including MCTD.

P1-208

Examination of the usefulness of the muscle ultrasonography in newly developing myositis patients

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Conflict of interest: None

[Background] It is established that magnetic resonance imaging (MRI) is useful for detecting the muscle inflammation in polymyositis (PM)/dermatomyositis (DM). On the other hand, theusefulness of muscle ultrasonography (US) is not generally accepted in PM/DM. [objects and methods] There were 11 newly developing PM/DM patients who examined by US in the period from June, 2011 to September, 2012 in our hospital. We compared the results of US, MRI, needle electromyogram (NEMG), and muscle biopsy. [Result] In US, the high echoic leasion in muscle were detected in 9 cases (Positive Group; PG), and it did not detected in 2 cases (Negative Group; NG). Among 9 cases of PG, 8 cases showed positive findings in MRI (89%), and 8 cases showed myogenic change in NEMG (89%). Biopsy was performed in 6 cases of PG, and the pathological findings of myositis was detected in 5 cases. Both 2 cases of NG had positive findings in MRI and NEMG. [Conclusion] US showed the high coincidence rate as compared with MRI or NEMG. We expect that it is useful for US not only in diagnosis of PM/DM, but in determination of the biopsy position. At present, US is an auxiliary test in diagnosis of PM/DM, and we need to compare the results of US, MRI, NEMG, or biopsy in more cases.

P1-209

A case of paraneoplastic syndrome with advanced ovarian cancer which could not be detected by PET, Ga-scintigraphy, nor enhanced-CT

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Conflict of interest: None

In March 2012, a 55-year-old woman recognized peripheral sensory disturbance in her extremities, fever, arthritis, dysphagia, following with muscle weakness, skin rash. She was diagnosed Churg-Strauss syndrome in previous hospitals. She underwent steroid pulse and oral steroid (prednisolone) therapy, yet still, her symptoms remained and she visited our hospital in late August. As she had a severe dysphagia, nasogastric nutrition intake was needed. From clinical symptoms of muscle and skin, dermatomyositis was suspected. prednisolone dosage was increased to 40mg/day, and she was treated with intravenous immunoglobulin. Peripheral sensory disturbance slightly improved, but muscle weakness including dysphagia remained. Paraneoplastic syndrome was also considered, and various image examinations, gastrointestinal, and colon endoscopy were performed, but suspected underlying malignancy was not detected. However, the result of cervical cytology was class V and ovarian cancer was strongly suspected. Operation followed by chemotherapy was performed in early October due to the results of pathology: appendix and peritoneal dissemination metastasis. After few weeks, the dysphagia and muscle weakness of the extremities clearly improved, and nasogastric tube was no more necessary.

P1-210

Pathological findings of anti-CADM140 antibody positive acute interstitial pneumonia with clinically amyopathic dermatomyositis at an early stage

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Conflict of interest: None

[Background] Anti-CADM140 antibody positive acute interstitial pneumonia (AIP) with clinically amyopathic dermatomyositis (CADM) is characterized by lower consolidation on chest CT findings and diffuse alveolar damage (DAD) in autopsy findings. However, it is unclear that whether DAD is found from an early stage. [Case] The patient was a 45-year-old man. He had fever, exertional breathlessness, lower consolidations on chest CT and underwent thoracoscopic lung biopsy. We diagnosed CADM and AIP with poor prognosis (fever, palmar papule, hyperferrtinemia, normal CK level, anti-CADM140 antibody positive), and started treatment with PSL, IVCY, and TAC. IVIG was added with reference to serum ferritin 4 weeks later, and clinical course was improved. [Pathological findings at the site of lower consolidation] There were polypoid granulation tissues in alveolar space accompanied by abundant infiltration of macrophages and lymphocytes, suggesting organized pneumonia (OP). However, these were absolutely different from OP, since alveolar epithelium was injured. It indicated mild form of organizing DAD. Pathological findings of NSIP were not observed. [Discussion] Our case suggests that intensive immunosuppressive therapy prevented to develop irreversible DAD from mild form of organizing DAD.

P1-211

Intractable chronic intestinal psedo-obdtruction(CIPO), successfully treated with octreotide in a case of anti-EJ antibody-positive dermatomyosits

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Conflict of interest: None

A 38-yr-old female patient of dermatomyositis (DM) was admitted to Tokai University Hospital because of the relapse of myositis and ileus-like symptoms in January,2012.Her DM has been treated with corticosteroid and immunosuppressants since 2004 when she developed muscle weakness,heliptope rash and erythema overlaying the knee and elbows.Autoantibody screening showed positive for anti-EJ antibody by an RNA immunoprecipitation procedure.Abdominal X-ray revealed gaseous distention of the small intestine, but abdominal US and CT scan did not demonstrete mechanical obstruction.The diagnosis of CIPO was made but gastrointestinal decompression by the ileus tube failed to improve her symptoms.Then,continuous administration of octreotide was started subcutaneously.Abdominal symptoms were markedly improved and the octreotide regimenn was reduced.Thereafter she has been well with the maintenance therapy of i.m. administrarion of octreotide monthly.This is an interesting case of anti-EJ antibody positive dermatomyositis presenting intractable CIPO,successfully treated with octreotide.

P1-212

Successful treatment of steroid pulse and intravenous immunoglobulin for parvovirus B19-dermatomyositis

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Conflict of interest: None

We report a 36-year old woman, who was admitted to our hospital because of rash, arthralgia, general fatigue and fever. The blood examination showed myogenic enzyme elevation and appearance of atypical lymphocyte. After admission cervical lymphadenopathy, erythema nodosum, muscle weakness and myalgia were appeared and the serum IgM of parvovirus B19 (PVB19) and PVB19 DNA-PCR were positive, so we diagnosed dermatomyositis with PVB19 infection. We treated her with steroid pulse and intravenous immunoglobulin (IVIG) for six months, her symptoms were improved and she was discharged. Although we gradually decreased steroid, after one and half months she relapsed with muscle and skin symptoms and myogenic enzyme also got worse, so she was admitted second time. However PVB19 DNA-PCR remained positive, we treated with steroid pulse and IVIG again. Since the readministraion was effective, her muscle symptoms recovered and myogenic enzyme improved. After two months admission she was discharged. More two months later, PVB19 was disappeared. There are many reports which describe the relationship between PVB19 infection and autoimmune diseases, but a few reports in association with dermatomyositis. In our case the treatment with steroid pulse and IVIG was effective.

P1-213

A case of antisynthetase syndrome associated with pulmonary arterial hypertension

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Conflict of interest: None

A 65-year-old female had been suffering from dry mouth and Raynaud's phenomenon and visited our hospital in 2008. She was diagnosed with Sjögren syndrome and had been followed up at our outpatient clinic. She had been developing arthritis in wrist joints, proximal interphalangeal joints and so on from July 2010. We diagnosed the arthritis as ealy-onset rheumatoid arthritis, and started low-dose oral pulse methotrexate and other DMARDs. The arthritis had been lasting, so she was admitted because of refractory arthritis and exertion. The laboratory tests showed elevation of aldolase (6.4U/l), NTpro-BNP(611pg/ml), KL-6 (844 U/ml). Antinuclear antibody was positive (cytoplasmic pattern). We investigated myositis-specific autoantibody, and obtained a positive reaction for serum anti-PL12 antibody. There were no bone lesions or articular narrowing on radiographs of the fingers. The chest CT showed linear and reticular shadow and ground-grass opacity in the bilateral lung fields. Right heart catheterization showed that mean PAP was 25 mmHg. We diagnosed antisynthetase syndrome complicated by pulmonary arterial hypertension, and initiated tacrolimus for interstitial pneumonia, and ambrisentan and beraprost sodium for pulmonary arterial hypertension.

P1-214

A case of muscular dystrophy who had been treated as intracatable polymyositis

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Conflict of interest: None

The patient is 52 year-old woman. She noticed muscle weakness in 2001. Elevation of CK level was pointed out in 2002. She was diagnosed as polymyositis and treated with prednisolone (PSL) 80 mg/day. CK level was normalized, but increased when PSL was 45 mg/day. MTX, CY, AZA, CyA could not be continued because of ineffectiveness or adverse effects. She was introduced to our department and retreated with PSL 60 mg/day. PSL seemed to be effective, but CK level was increased at her first outpatient visit. CyA or MMF was not effective. PSL was increased up to 60 mg/day in 2011. She developed gall bladder adenomyomatosis and os-

teonecrosis of femoral head. PSL decreased as fast as possible for surgical operation but CK level was stable until PSL was 10 mg/day. Thereafter she received IVIG therapy, but it was not effective. It was considered that CK level was decreased when she takes rest. Finally, she was diagnosed as muscular dystrophy at national center of neurology and psychiatry. Certain type of muscular dystrophy is difficult to distinguish from polymyositis. This case indicates the importance of reevaluation in case of intractable polymyositis that shows resistance against multiple medications.

P1-215

A case of rapid progressive interstitial pneumonia with dermatomyositis remained stable after discontinued Cyclosporine

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Conflict of interest: None

A 65-year-old female was diagnosed as rheumatoid arthritis in 2005, and treated with bucillamine, salazosulfapyridine, or methotrexate. In November 2009, she was diagnosed as dermatomyositis (DM) because of proximal muscle weakness, the elevated level of serum CK, myogenic change in the electromyogram, heliotrope rash, and Gottron sign. 0n the 9th day after admission she felt dyspnea, and interstitial shadows appeared on her chest CT. She was diagnosed as rapid progressive interstitial pneumonia with DM (DM-IP) and initiated with prednisolone (PSL 55mg/day), cyclosporine (CyA 200mg/day), and intravenous cyclophosphamide pulse therapy with favorable response. In November 2010, hepatic damage was developed. Because there was a possibility of CyA induced hepatic damage, CyA was stopped and the dose of PSL was increased from 14mg to 30mg. Liver biopsy showed military, and antituberculotic drugs was initiated. Interstitial pneumonia has been stable for two years without CyA. This case of rapid progressive DM-IP suggested that CyA could not be necessary for maintenance therapy.

P1-216

Analysis of clinical features of microscopic polyangiitis

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Conflict of interest: None

【Objective】We conducted a retrospective study of clinical features of patients with MPO-ANCA-positive MPA admitted to our hospital between 2000 and 2012.【Methods】We assessed the organ involvement, laboratory findings, and treatment in 93 MPA patients.【Results】The age of the patients was 71.8 years and the sex (M:F) was 39:54. The organ involvements included kidney involvement (78.5%), interstitial pneumonia (49.5%), alveolar hemorrhage (10.8%), and peripheral nervous involvement (25.8%). The initial dose of PSL was 33.3±11.8 mg. Patients treated with PSL+cyclophosphamide (CPA) were 35 (37.8%). The median serum Cr at onset was 1.3 mg/dl and the mean CRP was 8.4±7.5 mg/dl. Comparing the patients treated with PSL+CPA and PSL alone, there was no significant difference in the organ involvements. The age and serum Cr were lower in patients treated with PSL+CPA. In patients admitted to the Clinical Immunology, serum Cr was relatively low, and CRP was high. The patients with renal involvement tended to receive PSL+CPA.【Conclusion】MPA patients treated with PSL+CPA were relatively young age and mild renal dysfunction. In patients with severe renal dysfunction, steroid monotherapy was selected.

P1-217

The clinical characteristics and prognosis of patients with microscopic polyangiitis (MPA)

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Conflict of interest: None

[Objectives] To evaluate the clinical characteristics and prognosis of patients with microscopic polyangiitis (MPA). [Methods] We analyzed retrospectively 42 cases of MPA according to the Watts' algorithm from 2003 to 2011 at our hospital including the clinical characteristics and prognosis. [Results] The mean age of the 42 patients (20 males and 22 females) was 74.2±7.5 year-old. 23 of 42 patients received corcisteroid (CS) alone, and 19 patients were treated with CS and cyclophosphamide or azathioprine in combination as induction therapy. In Kaplan-Meier survival analysis, the survival rates at 6 months was 85.7%, 83.7% at one year, and 70% at five years. 14 patients died during the observation period (seven due to infection, six due to alveolar hemorrhage, two due to acute exacerbation of interstitial pneumonia).

P1-218

A case of microscopic polyangitis (MPA) presenting with dysphagia and dysphonia based on cerebral vasculitis and cranial neuropathies

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Conflict of interest: None

A 73-year-old female was diagnosed as MPA affecting fever, renal involvement, pericarditis and pleuritis with myeloperoxidase anti-neutrophil cytoplasmic antibody (MPO-ANCA) positive in February 2010. She was treated with methylprednisolone (mPSL) pulse therapy followed by prednisolone (PSL) 50mg/day for the initial treatment, after which the symptoms and laboratory findings showed improvement. In May 2012, she developed dysphagia, dysphonia and MRA, SPECT and spinal fluid examination revealed cerebral vasculitis. She was started to treat again with mPSL pulse therapy followed by PSL 30mg/day. Although her symptoms disappeared temporally, dysphagia and dysphonia recurred on a day taking PSL 20mg/day in September 2012. Examinations showed paralysises of both right recurrent laryngeal nerve and glossopharyngeal nerve without cerebral vasculitis at this time. She was given a single course of high dose intravenous immunoglobulin (IVIg) treatment and it made dramatic improvement for paralysises. After IVIg treatment, she is taking azathioprine in addition to PSL and she does not suffer a relapse of any neuropathies. It is possible that the IVIg is good option not only for peripheral neuropathy of MPO-ANCA vasculitis but also for cranial neuropathy of it.

P1-219

A fetal case of microscopic polyangiitis with diffuse alveolar hemorrhage following legionella infection

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Conflict of interest: None

A 75-year-old woman was admitted to the hospital because of rapidly progressive dyspnea, hemoptysis and renal disorder. Chest radiographs and CT scan demonstrated diffuse, bilateral consolidations with interstitial shadow. Tracheal intubation was performed promptly, with the institution of mechanical ventilation. Her laboratory data revealed anemia, renal disorder, and elevated level of MPO-ANCA(640U/ml). Intriguingly, urinary antigen test for legionella was positive. From these results, she was clinically diagnosed with diffuse alveolar hemorrhage (DAH) and rapidly progressive glomerulonephritis associated with microscopic polyangiitis (MPA), and legionella infection. Despite rapid induction of high dose methylprednisolone, antibiotics, plasmapheresis, and cyclophosphamide therapy, she died of respiratory failure on the 25th day. To date, much of the mechanism of acute exacerbation of primary vasculitis remains unknown. It is inferred that she owed subclinical ANCA vasculitis at least 3 month before admission because she presented with renal dysfunction for three-month. It is of great interest that acute exacerbation of DAH was concurrent with legionella infection, suggesting infection-related-immune-response in host trigger the aggravation of vasculitis directly, or indireclty.

P1-220

A case of microscopic polyangitis with thrombotic microangiopathy

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Conflict of interest: None

A 77-year-old woman had fever and leg edema for 3 weeks. On laboratory examination, antinuclear antibody and rheumatoid factor was positive, and MPO-ANCA was negative. Chest CT showed interstitial pneumonia and nerve conduction velocity study revealed mononeuritis multiplex. Hematuria, proteinuria and elevated serum creatinine level were observed. Based on these findings, she was diagnosed with microscopic polyangitis (MPA). She was treated with 40mg/day of prednisolone. Because the disease activity still remained, high-dose methylprednisolone (1g×3days) was administered. After the therapy, thrombocytopenia with red blood cell fragmentation was observed in peripheral blood, and the serum level of haptoglobin was remarkably decreased. She was diagnosed as thrombotic microangiopathy (TMA) with MPA. After IVCY therapy, her leg edema, thrombocytopenia, and hemolytic anemia were improved. In the present case, the activity of ADAMTS13 was slightly decreased and ADAMTS13 inhibitor was negative. The mechanism of TMA independent of ADAMTS13 activity was thought to be due to the impaired vascular endothelial cell. We report a rare case of MPA with TMA and discuss the pathogenesis of TMA.

P1-221

A case of granulomatosis with polyangiitis diagnosed by nasal and epidural lesions which developed in a remission state of previously diagnosed microscopic polyangiitis

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Conflict of interest: None

This case report describes findings in a 64-year-old man who had previously been diagnosed with MPO-ANCA related microscopic polyangiitis by renal biopsy. When he was in complete remission with negative serum myeloperoxidase anti-neutrophil cytoplasmic antibody (MPO-ANCA) levels, he developed postnasal drip, headache, and epidural lesion. On the base of clinical features and results of pathologic examination of the paranasal mucosa, the patient was diagnosed with granulomatosis with polyangiitis. The symptoms and remaining lesions resolved with steroid pulse therapy.

P1-222

Characteristics of chest HRCT findings in ANCA-associated vasculitis

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Conflict of interest: None

[Objectives] The aim of this study was to assess the characteristic chest HRCT findings in ANCA-associated vasculitis (AAV) whom were registered “Observational cohort study of remission induction therapy in Japanese patients with AAV and rapidly progressive glomerulonephritis: (RemIT-JAV-RPGN)”. [Methods] Between August 2011 and November 2012, 62 patients were diagnosed as AAV. HRCT findings were assessed in each of the three parts on aortic arch, carina and 1cm above the diaphragm. Interstitial Pneumonia (IP) pattern of CT images were classified into UIP, possible UIP and inconsistent with UIP according to the diagnostic criteria of IP by the Official ATS/ERS/JRS/ALAT statement. [Results] Among 62 patients with AAV, 58 had pulmonary involvement. HRCT showed ground glass opasity in 34, bronchial wall thickening in 15, nodule and/or small nodule in 14, consolidation in 13, pleural effusion in 13, emphysema in 12, bronchiectasis in 11, centrilobular granular shadow in 8, IP in 22 (UIP in 5,possible UIP in 5,inconsistent with UIP in 12) and Combined pulmonary fibrosis and emphysema (CPFE) in 6, respectively. [Conclusion] The characteristics of HRCT findings of AAV was various such as nodule, bronchiolitis and pleuritis with predominance of non-UIP pattern.

P1-223

A patient with antineutrophil cytoplasmic antibodies associated vasculitis complicated by fasciitis, cerebral infarction and rapid progressive glaneulonephritis

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Conflict of interest: None

A 67-year-old male has pain of left lower leg and general malaise at the beginning of August 2012. Pyrexia, polyarthralgia, weight loss, purpura, increased level of CRP (14.94 mg/dl) and renal dysfunction were pointed out by home doctor. He was referred and admitted to our hospital. Antineutrophil cytoplasmic antibodies (ANCA) associated vasculitis (AAV) was diagnosed by increased levels of proteinase (PR) 3-ANCA (>3000 EU), and rapid progressive glaneulonephritis (RPGN). MRI of left lower leg showed Fasciitis. Steroid pulse therapy (methylprednisolone 1 g/day) and sustained injection of heparin (12,000 units/day), and hemodialysis was initiated. At the 4th hospital day, dysarthria developed suddenly, MRI of brain showed multiple cerebral infarction. Cilostazol (100mg/day) was srarted. Prednisolone 60mg/day and azathioprine 25mg/day were administered from the 13th hospital day. Fasciitis, arthralgia and purpura were improved, and the levels of CRP and PR3-ANCA decreased. Hemodialysis was finished because of im-

provement of renal function. We report a rare case of AAV complicated by fasciitis, cerebral infarction and PRGN.

P1-224

ADL of treated AAV

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Conflict of interest: None

(Purpose) AAV often fall into the state of very serious. To assese risk factors of low ADL in AAV patients. (Method) Retrospective, standardized collection of data from 54 AAV patients (5 EGPA, 39 MPA, 10 GPA) of first admission at our center was studied. The relationship of ADL levels to BVAS score, age, CRP, MP-ANCA titor, duration from appearance of symptom to start of treatment, neuropathy, renal involvement and lung involvement was examined. 9 Death patients was excluded. We use Kruskal Wallis test and chi-squared test. (Result) Patients who have maintained good ADL was 31, and who required assistance of others was 14. Significant correlation was observed between ADL levels and BVAS score, age. (Conclusion) Elderly or high BVAS patients may be low ADL in AAV patients.

P1-225

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

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Conflict of interest: None

[Objectives] MPO-ANCA is an autoantibody against neutrophil myeloperoxidase (MPO), which were frequently detected in patients with ANCA-associated vasculitides. Alteration of post-translational modifications (PTMs) of autoantigens is thought to be involved in the autoantibody production. In this study, we investigated PTM of MPOs obtained from neutrophils of the MPO-ANCA-positive patients. [Methods] Peripheral blood polymorphonuclear cells (PMN) were collected from MPO-ANCA-positive patients and healthy donors. MPOs in the cells were detected by 2D-western blot (2D-WB). The detected spots were compared between the two groups. *In vitro* reactive oxygen species (ROS) treatment was performed by incubating PMN proteins with 2-10mM H_2O_2 and 5 mM $FeCl_2$. [Results] By 2D-WB, MPO was detected as multiple spots, indicating the complicated modification of the protein. The volume of the heavy chain spots with higher p*I* values (> 9.4) and higher MW (> 53kDa) were significantly greater in the patients group. *In vitro* ROS treatment of myeloperoxidase increased the p*I* and MW values of the heavy chain. [Conclusion] This study indicated that MPO heavy chain was oxidatively modified by ROS in PMN of the patients, and this oxidative modification might participated in the production of MPO-ANCA

P1-226

Clinico-radiological features of interstitial pneumonia complicated by dermatomyositis with preceding pulmonary lesions

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Conflict of interest: None

[Objectives] Clinico-radiological features of interstitial pneumonia complicated by dermatomyositis (DM-IP) with preceding pulmonary lesions were investigated in patients. [Methods] The subjects were 7 of these in whom pulmonary lesions preceded. [Results] The mean age was 59 years. CADM was noted in 5, and all patients were negative for anti-Jo-1 antibody. The mean KL-6 was 1,847 U/ml (440-2,770). The mean time of treatment initiation after the diagnosis was 12.3 days (48-60) in DM and 475.4 days (47-2,550) in IP. The mean prednisolone dose was 45.7 mg/day (20-70). Regarding concomitant immunosuppressors, cyclosporine and mizoribine were administered to 6 and 1 patient, respectively. One patient died and 5 survived. On comparison with patients without a preceding pulmonary lesion (n=27), the KL-6 level was significantly higher in patients with preceding pulmonary lesions (1,847.4±238.9 vs. 835.0±121.7, P=0.0007). On chest HRCT, distribution along the bronchial vascular bundle, traction bronchiectasis, and linear shadows were noted in many patients. [Conclusion] The incidence of chest HRCT findings suggesting structural alteration and fibrosis was higher in DM-IP patients with preceding pulmonary lesions than in those without a preceding pulmonary lesion.

P1-227

The change of CT score in actute/subacute progressive interstitial pneumonia with dermatomyositis treated with Cyclosporine-A and prednisolone

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Conflict of interest: None

[Objectives] To evaluate the change of CT score in actute/subacute progressive interstitial pneumonia with dermatomyositis (DM-A/SIP) treated with Cyclosporine-A (CyA) and prednisolone (PSL). [Methods] We assessed the change of CT score of 24 DM-A/SIP patients initiated with CyA (4mg/kg) and PSL (0.75-1mg/kg), and the association between CT score and serological factors. The CT score was calculated separately by two physicians from GGO on chest CT performed before the treatment (Pre) and about 2 weeks (2w), 4 weeks (4w) and 1 year (1y) after the treatment. Total CT score was defined as sum of each lobe score. [Results] The mean of age, initial PSL and CyA dose were 51.8±9.5 years old, 51.2±8.6mg/day, 212±34mg/day, respectively. Of the 24 patients, 4 patients were dead. The reduction of total CT score from Pre to 2w and 4w to 1y was shown (p=0.0025 and P=0.0124, respectively). Total CT score of the patients with anti-Jo-1 antibody (N=8) between Pre and 1y was significantly reduced compared with that of the patients without anti-Jo-1 antibody (p=0.0296). [Conclusion] In DM-A/SIP patients,the combination of CyA and PSL showed a significant improvement in GGO about 2 weeks. Anti-Jo-1 antibody positivity could be a predictive factor for favorite response of CT images to the treatment.

P1-228

Successful combination therapy of cyclosporine A and azathioprine in a recurrent case of interstitial lung disease in dermatomyositis assoiciated with anti Jo-1 antibody

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Conflict of interest: None

Although corticosteroids have been the initial agent for the treatment of interstitial lung disease (ILD) in inflammatory myositis (IM) assoiciated with anti Jo-1 antibody(Jo-1 Ab), substantial number of patients were reccured. Addition of immunosuppressive agents such as azathioprine (AZP), cyclophosphamide, cyclosporine A (CsA) or tacrolimus resulted in almost satisfactory result with the exception of recalcitrant cases. On the other hand, the efficacy of combination therapy of calcineurin inhibitor (tacrolimus or CsA) and immunosuppressive metabolite (mycophenolate mofetil, AZP or mizoribine), called multitarget therapy, has been proven in refractory lupus nephritis without serious side effects. However, in recalcitrant ILD in IM with Jo-1 Ab, the experience of such a therapy is very limited, and has not been described. Here, we report a 49 year old female patient with recalcitrant ILD with Jo-1 Ab who was successfully treated with the combination therapy of CsA and AZP. At first, the ILD did not respond satisfactory by the monotherapy of AZP or CsA, and frequently recurred when the dose of corticosteroid was tapered. However she was succesfully treated by the combination therapy of CsA and AZP without any recurrence and her vital capacity was remarkably improved.

P1-229

Clinical features of organizing pneumonia (OP) associated with RA: OP develops independently to RA activit

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Conflict of interest: None

[Objectives] To clarify clinical features of OP associated with RA [Methods] We extracted patients who experienced OP from consecutive 350 RA patients visiting our clinic in December 2010. OP was diagnosed by findings of chest CT and biopsy samples. When biopsy samples were not obtained, OP was diagnosed by CT findings, resistance to antibiotics and good response to glucocorticoid. [Results] Nineteen patients had developed OP, prevalence of which was 3.8%. Most patients (14/19) developed OP after the onset of RA. OP developed simultaneously to RA in 3 patients and OP preceded RA in 2 patients. At time just before onset of OP, 63% of patients achieved less than low disease activity. Biologics was given to 6 patients that controlled RA activities. At the onset of OP, only 2 patients showed exacerbation of arthritis, Respiratory symptoms were found in 11 cases, and fever was developed in 15 patients. All patients revealed elevation of serum CRP levels. Disappearance of lung infiltration was found in 8 cases. Glucocorticoid therapy was required for 11 cases, which improved their symptoms. In 3 patients, recurrence of OP was observed in 3 cases. [Conclusion] OP is developed in RA patients without increase of disease activity.

P1-230

Basic analyses for development of novel therapeutic strategy for pulmonary hypertension associated with collagen vascular disease by HEXIM1

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Conflict of interest: None

[Objectives] To establish a new therapeutic strategy for pulmonary hypertension (PH) associated with collagen vascular disease (CVD), we propose a unique approach that directly blunts right ventricular hypertrophy (RVH) by HEXIM1, which suppresses P-TEFb a key molecule for development of cardiac hypertrophy. [Methods] We infected HEXIM1-expressing adenoviruses (HEXwt or mt; lacking P-TEFb suppressive ability) into neonatal rat cardiomyocytes (NRCM), stimulated the cells with endotheline-1 (ET-1), and examined the effects of HEXIM1 on P-TEFb, ERK, and S6K activation and hypertrophy of NRCM. Using cardiomyocyte-specific HEXIM1-Tg mice (HEXCTg), we examined the effect of HEXIM1 on hypoxia-induced PH model. Moreover, we explored the drugs that induce protein expression of HEXIM1 in NRCM. [Results] HEXwt could inhibit ET-1-induced activation of P-TEFb but not phosphorylation of ERK and S6K. HEXwt but not mt could inhibit cardiomyocyte hypertrophy. HEXCTg attenuated hypoxia-induced RVH, cardiomyocytes hypertrophy, and RV dilatation. A PH drug PGI2 could induce expression of HEXIM1 protein in NRCM. [Conclusion] HEXIM1 may be a candidate for preventing RVH/RV failure with PH by inhibiting P-TEFb activity and HEXIM1 inducer might act as a novel therapeutic bullet in PH associated with CVD.

P1-231

Evaluation of effect for interstitial lung disease with collagen vascular disease using ambrisentan for pulmonary arterial hypertension

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Conflict of interest: None

Background: Phase 3 clinical trial of ambrisentan in patients with idiopathic pulmonary fibrosis (IPF), due to lack of efficacy. Objective: To evaluate the effect for interstitial lung disease with collagen vascular disease using ambrisentan for pulmonary arterial hypertension. Patients and methods: 6 patients with collagen vascular diseases (3 dermatomyositis, 2 scleroderma and one overlap of dermatomyositis and scleroderma, mean age was 51.5 year-old) were analyzed. Results: Before using ambrisentan, all patient showed NSIP type radiological findings and no honeycombing were seen in all patients. WHO classification were 4 class II, 2 class III and no class IV. There were already had two oxygenation patients. After receiving ambrisentan, there were no patient worsening of respiratory symptoms and radiological findings of chest HRCT. There were two patients with slight increasing of serum KL-6 levels, and rest of 4 patients showed no change of KL-6 levels. Conclusions: Further study is needed to evaluate the safety for interstitial lung disease with collagen vascular disease using ambrisentan for pulmonary arterial hypertension.

P1-232

Severe pulmonary hypertension associated with SLE ; A case report

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Conflict of interest: None

We describe a 40-year old who developed severe pulmonary hypertension (PAH) with systemic lupus erythematosus (SLE). she had been diagnosed as SLE five years before based on malar rash, discoid rash, ANA-positive, and arthritis. She was suffering from progressive dyspnea on effort(WHO functional criteria IV), abdominal distention, and appetite loss gradually for two month. Her past history included type C hepatitis(child pugh-A), and psoriasis. Physical examination showed jugular vein dilatation and significant ascites. She was diagnosed with PAH based on enlarged main pulmonary arteries on chest x-ray, marked elevated brain natriuretic peptide (BNP) level of 1077pg/ml, an estimated right ventricular pressure exceeding 70mmHg on echocardiography, and elevated mean pulmonary artery pressure of 42mmHg on right heart catheter. The contrast enhanced CT showed no evidence of pulmonary embolism. Her symptoms was relieved dramatically with intravenous cyclophosphamide and high-dose prednisolone, and maintained in good condition with beraprost sorium, tadarafil, and bozentan. This case indicates that both immunosuppresive therapy and pulmonary vasodilation therapy is needed for severe PAH with SLE.

P1-233

Characteristics of pulmonary hypertension in patients with collagen disease in our hospital

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Conflict of interest: None

[Objectives] This study aims to examine retrospectively the characteristics of pulmonary hypertension (PH) patients with collagen disease in our hospital. [Methods] There were 64 patients with connective tissue diseases (CTD) (7 SLE, 38 Systemic Scleroderma, 12 Mixed CTD (MCTD), 2 Sjögren Syndrome (SjS) and 5 others) who underwent right heart catheterization from Jan. 2011 to Aug. 2012 in our hospital.PH is defined as mean pulmonary artery pressure (PAP) ≧25 mmHg and we consider mean PAP of 20 to 24 mmHg as borderline type. [Results] 9 of 64 patients showed mean PAP ≧20 mmHg. Definite PH patients were one SjS and one SLE patients, and borderline types were five SSc and two SLE patients. The time to right heart catheterization from the onset of the CTD was more than 10 years in the two definite PH patients, and in the 7 borderline type patients, that was more than 10 years in the two patients and within 5years in the others. 2 SLE and one SjS were treated with pulmonary vasodilators (PV) (PGE5 inhibitors and endothelin receptor antagonists) in addition to immunosuppressive therapy (IT). While the five SSc were treated with PV without IT. [Conclusion] We report about the characteristics and treatment of PH patients with CTD in our hospital, including a discussion of the literature.

P1-234

A case of limited scleroderma that died of severe pulmonary arterial hypertension(PAH) suddenly

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Conflict of interest: None

A 50-year old man developed nonproductive cough, shortness of breath and Raynaud's phenomenon. Chest radiograph revealed cardiomegaly and dilated pulmonary artery at initial visit in our hospital. Sclerodactylia and subnugual hematoma were observed. Contrast-enhanced CT scan showed no evidence of pulmonary thromboenbolism. Findings such as enlarged chamber of the right side of heart and septal shift were observed by echocardiogram. Pulmonary artery systolic pressure estimated by echocardiogram was 53mmHg suggesting PAH. Antinuclear antibodies in the serum were negative. Skin biopsy from the forearm revealed no obvious histological findings. In addition to oxygenation, administration of PDEIII inhibitor, anticoagrants, bosentan, catecholamine and beraprost natrium were performed. Although we considered whether to introduce epoprostenol, the patient suddenly died of respiratory failure on the 9th hospital day. We here report a case of limited scleroderma associated with PAH.

P1-235

Eighteen cases of Lung shadow with suspected non-tuberculosis maicobacterium pneumonia patients complicated rheumatoid arthritis

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Conflict of interest: None

[Objective] The importance of nontuberculous mycobacterial infection (NTM) and its association with RA are being recognized. We assessed cases of NTM or suspected NTM in association with RA in our hospital. [Methods] We investigated 18 RA patients, whose thoracic CT and thoracic X-ray image diagnosis suggested NTM. The criteria included the presence of nodular and small nodular shadows, spread of reticular shadows, etc. [Results] All 18 patients were women, 15 patients were determined to have Stage 4 RA. In all patients, shadows were observed after the onset of RA, in 13 patients, were observed on the first CT screening, and in 5 patients, were found after subsequent CTs showed worsening of the conditions. Five patients fulfilled the NTM diagnostic criteria; 7 patients showed positive results once for sputum cultures; and bacteria could not be detected in 6 patients. In terms of an association with anti-rheumatoid drugs during diagnosis, 15 of 18 patients were using steroids; 11, methotrexate. Five patients received additional treatment for NTM, whereas 8 patients showed no signs of disease conditions. [Conclusions] We believe that extra caution during diagnosis and treatment is necessary, given the high activity of RA and the need for patients to rely on immunosuppressant drugs.

P1-236

Relationship between Non-tuberculous Mycobacteria (NTM) from drinking water in-house and chance of opportunistic infection

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Conflict of interest: None

[Objectives] In terms of the possibility of NTM infection during the rheumatoid therapy, we are considering the NTM viability

in water outlet. [Methods] Samples were collected by the scraping using the sterilized cotton swab. These samples were analyzed by the Gram stain and Ziehl-Neelsen method. In addition, PCR and NTM isolation by the 2% Ogawa medium were tried to detecting the gene and NTM, respectively. [Results] We analyzed the 30 water outlet by bacterial staining, and there are no bacteria founded in the smear. For the PCR to find the gene existing 2 swab positive. Since one of two samples is positive in twice, we believe this water outlet may have the NTM, and all of 30 samples were incubated with 2% Ogawa medium. Unfortunately, there are no colonies in these cultures. In the same time, we tried to analyze the water outlet of another University; we founded the 2 NTM in the water outlet. Then, we founded there are no NTM in water outlet in-house. [Conclusion] Since there are many chances to use the anti-cytokine therapy to rheumatoid patients, there are many chance to meet the opportunistic infection. This research will be the important to analyze the route of the NTM infection, and cleaning activity in-house may be better way to decreasing NTM.

P1-237

Two cases of rheumatoid arthritis with bronchiectasis treated by biologic DMARDs: how about surgical treatment?

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Conflict of interest: None

Bronchiectasis (BR) is not typical pulmonary manifestation of rheumatoid arthritis (RA). However, RA patients suffering from concomitant BR are not rare. Coexistence of BR and RA causes frequent and severe pulmonary infections, and it may interfere with continuation of medication by biologic and non-biologic DMARDs. BR with RA which causes repetition pneumonia may be indication for surgery.

P1-238

Clinical characteristics of patients with combined pulmonary fibrosis and emphysema (CPFE) in connective tissue disease (CTD)

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Conflict of interest: None

[Objectives] The aim of this study was to assess the clinical characteristics of CPFE in CTD. [Methods] Between 2005 and 2007,17 patients were diagnosed as CPFE associated with CTD. We retrospectively investigated the laboratory data,the results of pulmonary function test (PFT),high resolution computed tomography (HRCT) findings and prognosis in these patients.Moreover,we compared the prognosis between 2 groups(36 patients with CPFE/IPF vs.8 patients with CPFE/UIP in CTD). [Results] Among 17 patients,underlying disorders were rheumotaid arthritis (RA) in 7,microscopic polyangitis (MPA) in 7,systemic sclerosis (SSc) in 2,systemic lupus erythematosus in 1,respectively.Among 17 patients(15 males and 2 females,mean age were 68.4 ± 8.5 years),16 were current or former smokers.The mean smoking index were 1105±594.PFT at the first visit revealed 2.94±0.97L of FVC.Systolic pulmonary artery pressure were 37.2±17.8 mmHg on UCG. HRCT showed UIP pattern in 8 and non-UIP pattern in 9.The median survival time (MST) was 36 months in UIP and 72 months in non-UIP(p=0.19) Moreover, the MST was 53 months in CPFE/UIP in CTD and 19 months in CPFE/IPF(p=0.16). [Conclusion] Clinical characteristics in CPFE in CTD showed male predominance with high smoking index.The MST of CPFE/UIP in CTD was as worse as CPFE/IPF.

P1-239

Pneumocystis jirovecii pneumonia associated with rheumatoid arthritis, a report of 4 cases

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Conflict of interest: None

Pneumocystis jirovecii pneumonia (PCP) has been observed in 0.1-0.4% of patients with Rheumatoid arthritis (RA) treated with biological agents in Japan. PCP has been also reported in RA patients during low-dose methotrexate (MTX) therapy has been reported. We report four patients (three females, one male, average age 68.5 years old) who developed PCP during RA treatment in our department. The average disease duration of RA was 7.5 years. All patients had been treated with low dose MTX (average 8.0 mg / week). Biological agent (etanercept) was used in only one patient. After the onset of the symptom, PCP was diagnosed by Pneumocystis jirovecii PCR. In spite of steroid pulse and trimethopurim / sulfamethoxazole therapy, two in four patients died. PCP is a serious complication in patients with RA, and the mortality is high in this series similar to other reports. Early diagnosis and intervention is important. Physicians should consider the possibility of PCP developing, and careful monitoring is needed during immunosuppressive therapy in RA patients.

P1-240

Clinical characteristics of rheumatoid arthritis (RA) concomitant with pneumocystis pneumonia (PCP)

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Conflict of interest: None

The object of this study is to clarify the clinical characteristics of RA concomitant with PCP. We experienced five RA patients who developed PCP during April through September 2012. PCP was diagnosed when all three of the following features were present: 1) rapidly progressive respiratory failure, 2) bilateral diffuse interstitial shadow on chest X-ray, and 3) serum β-D-glucan > 20 pg/ml. The average age of the five patients were 69.6 years and the average disease duration of RA was 18.6 years. All the five patients received methotrexate (MTX) and one of them have TNF inhibitor added. In three of the five patients, MTX had been increased from ≤ 8mg/w to 10-14 mg/w in the dosage due to poor control of RA and PCP developed after an average of 6.6 months after the dosage increased. PCP was improved with trimethoprim-sulfamethoxazole in all patients. Although previous studies have shown that advanced age, glucocorticoid use, interstitial pneumonia and diabetes mellitus are clinical risk factors for PCP in RA, high-dose MTX is a possible risk factor. Physicians should particularly be aware of this complication when the MTX dose had been increased in RA patients.

P1-241

A study of the Clinical Features of 12 patients with Adult-onset Still's disease

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Conflict of interest: None

Twelve patients with Adult-onset Still's disease (AOSD) who visited our division from 2006 to 2012 were assessed for their clinical features. Out of 12 patients with AOSD, 4 were male, 8 were female. The mean onset age was 55.9 years (21-87). Fever (100%), arthralgia (83%), dermatographism (75%), sore throat (50%), splenomegaly (42%), abnormal levels of liver enzyme (83%), leukocytosis (10,000/ml or greater) with at least 80 percent granulocytes (67%), high serum ferritin values (100%), elevated levels of serum ferritin more than 5-fold of upper limit of normal range (83%), negative results of both rheumatoid factor and antinuclear antibody (83%), and mean CRP levels are 10.1±7.8mg/dl. The duration from the onset to the time of diagnosis is 1.3 (0.5-4.0) months. Seventeen percent of the patients had macrophage activation syndrome. Seven patients were treated by glucocorticoids alone, and the remaining 5 patients had DMARDs or immunosuppresants such as with methotrexate, cyclosporine, or tacrolimus. As the duration from the onset to the time of diagnosis was still long, development of specific test or combination of tests is required.

P1-242

Report on the diagnosis upon 12 cases of adult onset Still's disease in our hospital

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Conflict of interest: None

【Objectives】There are several criteria for adult onset Still's disease (AOSD), but positive diagnostic criteria have yet to be established. We aimed to gain the helpful insight for the diagnosis from biochemical studies.【Methods】We examined 12 patients diagnosed as AOSD in the past 20 years from the perspective of clinical as well as serological point of view.【Results】Mean age at diagnosis was 43.9 years. Two males and 10 females were identified. Ten patients met the Yamaguchi criteria. The most common clinical manifestation included fever(100%), lymphadenopathy or splenomegaly(83.3%), arthralgias(75%). Characteristic laboratory abnormalities exhibited were elevated liver enzyme(100%), negative studies for antinuclear antibody and rheumatoid factor(75%). Four patients received bone marrow aspiration because of possibilities for malignant lymphoma (ML) and tuberculosis (TB). One patient received liver aspiration biopsy, and another received lymph node biopsy, respectively. Mean serum ferritin level was 3017ng/ml.【Conclusion】The Yamaguchi criteria and elevated serum ferritin level were very helpful combination for diagnosis of AOSD as previously reported. However, some patients had to receive invasive tests such as biopsy because of possibilities for ML, TB etc.

P1-243

A case of adult-onset Still's disease accompanied by macrophage activation syndrome successfully treated with Dexamethasone palmitate

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Conflict of interest: None

A 43-year-old man was admitted to our hospital due to adult onset Still's disease. His disease was refractory to high dose glucocorticosteroids and steroid pulse therapy. The serum ferritin and transaminase levels were markedly elevated and her bone marrow smear showed hemophagocytosis. We made a diagnosis of macrophage activation syndrome. Therefore we started cyclosporine therapy and plasmapheresis, and changed prednisolone into dexamethasone. His symptoms significantly improved, however serum ferritin, AST, ALT and LDH levels elevated again after tapering the dose of dexamethasone. Then, we started liposome-incorporated dexamethasone, Dexamethasone palmitate, instead of dexamethasone. It improved his condition rapidly. Dexamethasone palmitate may be a good treatment option of refractory adult-onset Still's disease accompanied by macrophage activation syndrome.

P1-244

A case of adult-onset Still's disease complicated by malignant lymphoma

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Conflict of interest: None

A 43-year-old man was diagnosed with adult-onset Still's disease (AOSD) because of pyrexia, skin rash, arthritis, leukocytosis and elevated serum ferritin levels in August 2003. Administration of oral prednisolone (PSL) and methotrexate was started and symptoms improved. The dose of PSL was reduced slowly. However, pyrexia and elevated serum ferritin levels flared up again in October 2012. The serum soluble interleukin-2 (sIL-2R) level was extremely high (15,565 IU/ml). A computed tomography scan showed a generalized lymphadenopathy. We suspected a relapse of AOSD, however, treatment with methylprednisolone pulse therapy had a partial effect. The inguinal lymph node biopsy specimen revealed diffuse large B-cell lymphoma (DLBCL). R-CHOP chemotherapy was thus started and patient's condition significantly improved. Lymph node biopsy should be considered for patients with AOSD with high serum sIL-2R levels and a generalized lymphadenopathy.

P1-245

A case of thyroid papillary cancer having symptoms similar to Adult Onset Still's Disease (AOSD)

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Conflict of interest: None

[Case] 69 y.o. Female. **[Current medical history]** In August 2012, she was admitted to the previous hospital because she developed symptoms such as fever, sore throat, and polyarthralgia. Infectious diseases were unlikely because she did not bring down fever in spite of administration of antibiotics. In late that month, she was transferred to our hospital. She had leukocytosis, liver dysfunction, mediastinal lymph node swelling, splenomegaly, and dorsal salmon pink rash. The levels of ferritin (28419 ng/mL) and CRP (10.27 mg/dL) elevated. Although the level of soluble IL-2 receptor modest elevated (841 U/mL), malignant lymphoma was ruled out from findings of bone-marrow examination and skin biopsy. The thyroid swelling was pointed out on echography, and thyroid papillary cancer was diagnosed cytologically. We started the treatment using oral prednisolone (PSL) 40 mg/day for AOSD

like symptoms. Her symptoms and serum ferritin and CRP titers gradually improved with the combination of steroid and immunosuppressive agent (methotrexate). **[Consideration]** We experienced an elderly case of asymptomatic thyroid papillary cancer with hyperferritinemia and AOSD like symptoms. We reported this suggestive case since the etiology and the strategy of the treatment should be considered.

P1-246

Two cases of adult onset Still's disease associated with hemophagocytic syndrome and agranulocytosis

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Conflict of interest: None

Case 1 ; 38 y.o. female. At 21 y.o., the patient developed sore throat, fever and rash, then was diagnosed as adult onset Still's disease (AOSD). She was admitted because of fatigue and fever. She was diagnosed as a relapse of AOSD associated with infection. Then, meropenem and steroid pulse therapy were started. On 5th day, neutrophils decreased and G-CSF was started. On 7th day, hemophgocytosis was confirmed by bone marrow aspiration. Plasmapheresis was performed and neutrophils started to increase on 29th day. Case 2 ; 47 y.o. male. The patient developed sore throat, myalgia, rash and fever. He was diagnosed as AOSD and admitted to the hospital. In spite of steroid pulse therapy, pancytopenia progressed. On 29th day, hemophgocytosis was confirmed by bone marrow aspiration. After plasmapheresis, pancytopenia was not improved and agranucytosis was developed on 34th day and G-CSF was started. Neutrophils started to increase on 47th day. Discussion ; Although hemophagocytic syndrome was reported to develop in AOSD due to hypercytokinemia, agranulocyotosis is very rare. In these 2 cases, it took 2 weeks for neutrophils to recover in spite of administration of G-CSF. In this period, we should pay attention to infection and its prophylaxis in addition to AOSD treatment.

P1-247

Refractory adult onset Still's disease (AOSD) successfully treated with etopiside (VP-16) and tocilizumab (TCZ) : 2 case reports

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Conflict of interest: None

It is reported that TCZ has good efficacy to refractory AOSD, but hemophagocytic syndrome (HPS) is possibly complicated after TCZ in the highly active disease. We report 2 cases of refractory AOSD treated with VP-16 for induction therapy and TCZ for maintenance therapy. [Case 1] A 38-year-old woman with AOSD was treated with steroid pulse therapy, prednisolone (PSL) and cyclosporine (CSA) with unfavorable response, and referred to our hospital. Intravenous immunoglobulin (IVIG), plasma exchange (PE) and intravenous cyclophospamide were not effective (ferritin 15,276 ng/ml). A pulse therapy of VP-16 (150mg/m^2) was initiated on the 43rd hospital day, followed by TCZ (8mg/kg/week) on the 158th day. The level of ferritin was decreased to 215 ng/ml. [Case 2] A 60-year-old woman with AOSD was treated with PSL with unfavorable response, and referred to our hospital. Steroid pulse therapy, CSA, IVIG and PE were not effective. She was suffered from high fever. Splenomegaly, hyper triglyceridemia, hypofibrinogenemia, high ferritin level (279,237 ng/ml) and hemophagocytosis on the bone marrow were shown. HPS was complicated. A pulse therapy of VP-16 (150mg/m^2) was initiated on the 17th hospital day, followed by on the 52th day. The level of ferritin was decreased to 1,024 ng/ml.

P1-248

A rare case of adult onset still disease preceding sarcoidosis

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Conflict of interest: None

A 70-year-old woman had high fever for 14 days accompanied by pharyngalgia, polyarthralgia with bone erosion including fingers and erythema concentrated on extremity. Skin biopsy at an erythema revealed the neutrophil infiltration in the epidermis, the neutrophil filling at small blood vessels and extravasations. Titer of antinuclear antibody was eighty times, whereas rheumatoid factor and anti-cyclic citrullinated peptide antibody were negative. We diagnosed as AOSD rule out infection and malignancy. Therefore, the HLA type was defined as A24, B52, B54, DR13, and DR15. With the diagnosis of AOSD, corticosteroid therapy by predonisolone 45mg daily was given, and it improved her symptom. This case meets a clinical criterion for sarcoidosis and AOSD, which is not only the low activity of sarcoidosis but also an atypical AOSD. HLA-B54 is one of the criteria of neuro-Sweet disease (NSD), but our case is atypical eruption of NSD as a painful erythematous papule with edema. We confirm the neutrophil infiltration without a necrotizing vasculitis, but not satisfied NSD. However it is compatible main item as fever, neutrophil-based peripheral leukocytosis, and elevation of CRP, we think overlapping one of sweet disease. We diagnosed AOSD based on polyarthralgia with bone erosion.

P1-249

Two successful cases of the adult Still's disease that achieved a steroid withdrawal after induction of the tocilizumab therapy

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Conflict of interest: None

[Case 1] A 69 years old woman who showed fever, developed polyarthralgia and general fatigue admitted our hospital after the diagnosis of seronegative rheumatoid arthritis by the previous doctor. We couldn't reduce prednisolone (PSL) less than 30mg/ day because of the repetitive flare. Inspite of the lack of typical rash, we clinically concluded that her diagnosis was adult Still's disease on the basis of her symptoms and hypercytokinemia. Because she also showed the resistance to some immunosuppressant, we started tocilizumab(8mg/kg/4 week). Finally her symptoms were improved, so we could stopped PSL. [Case 2] A 27 years old man. He showed fever, polyarthralgia and elevation of serum ferritin level, and consequently was diagnosed as adult Still's disease. Although these symptoms were improved by high-dose steroid treatment, his fatigue and arthralgia were relapsed with elevation of CRP level after the reduction of PSL dosage.We decided the induction of tocilizumab (8mg/kg/4 week) and finally achieved steroid withdrawal. [Conclusion] Recently, some reports showed the effect of tocili-

zumab therapy for adult Still's disease. We succeeded to finish steroid therapy with tocilizumab introduction in these 2 cases and could mitigate the side effect of steroid therapy.

P1-250

A case of adult-onset Still disease (AOSD) initially associated with myocarditis

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Conflict of interest: None

A 24-year-old man suffered from fever, general malaise and sore throat in December 2011. Ten days later in January 2012, he was admitted to a neighbor hospital. Laboratory findings revealed leukocytosis, liver dysfunction, elevated levels of ESR, CRP and serum ferritin. RF and ANA were negative. He had anterior chest pain on the 2nd hospitalized day. Serum CK and troponin T were found to be elevated. Electrocardiogram (ECG) showed ST-T segment abnormalities and cardiac ultrasonography (UCG) showed cardiac hypofunction(EF47%). On the 7th day, he was referred to our hospital for further evaluation. Chest pain had already disappeared and the titers of CK and troponin T were normal. Myocardial perfusion scintigraphy showed decreased blood flow at the inferior wall and interventricular septum. Coronary CT angiography revealed no pathological lesion. UCG showed improvement of cardiac function prior to treatment. He was diagnosed as AOSD associated with transient myocardial damage and PSL treatment of 60mg daily were started on the 14th day. Then, systemic symptoms rapidly disappeared. Further improvement of cardiac function was found by UCG, but follow-up myocardial scintigraphy revealed the same results. Now we consider that his myocardial damage was self-limited myocarditis.

P1-251

A Case of the Adult onset Still Disease whose Steroid Dosage was able to reduce rapidly using Tocilizumab Combination

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Conflict of interest: None

[Objectives] Tocilizumab (TCZ) is one of the biologics for active rheumatoid arthritis (RA) and juvenile idiopathic arthritis (JIA). The macrophage activation syndrome (MAS) in adult onset Still disease (AOSD) is refractory clinical condition to need high-dose steroid. We presented the case that steroid was able to reduce by TCZ rapidly for this clinical condition. [Case] A 39 year-old man ran a fever and liver dysfunction in August/X. We had a diagnosis of MAS by AOSD, and started steroid pulse therapy. After that, he took PSL 100mg/ day. The days of hospitalization become long, and the occurrence of adverse event with the steroid is concerned about more when we reduce steroid doses as before. Therefore we gave TCZ one week after steroid pulse therapy was provided. We gave TCZ in the same way as treatment in JIA. As a result, the patients were able to reduce PSL to 2 mg/day in November/X without showing relapse of the condition. [Conclusion] The combination therapy of TCZ for the MAS of AOSD became able to reduce steroid doses rapidly, and it was thought that we contributed to the prevention of the adverse event.

P1-252

Two cases of adult onset Still's disease (AOSD) that were diagnosed after polycyclic disease course

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Conflict of interest: None

Adult onset Still's disease (AOSD) is a rare systemic inflammatory disorder characterised by spiking fever, salmon pink rash and arthritis. We experienced two cases of AOSD that were diagnosed after polycyclic disease course. <CASE1> Seventy-one years old man. He had spiking fever, poly-arthritis, wight-loss 35 years ago. After that, he also had fever episode several times that resolve in a few days. Four years ago, he was hospitalized with unidentified fever, thrombocytopenia and elevated levels of serum ferritin. But he recovered in a week without any diagnosis. In this time, he had high fever, elevated levels of serum ferritin and carpal ankylosis on X-ray. He was diagnosed with AOSD by exclusion. <CASE2> Seventeen years old woman. She had fever and rashes three years ago and diagnosed with chronic urticaria. In this time, she had high fever and general rashes. She also had abnormal liver enzyme and leucocytosis with 80% granulocytes. So she was diagnosed with AOSD by exclusion. <Clinical implication> There are three courses in AOSD; monophasic, intermittent, chronic. We experienced two AOSD cases which followed intermittent pattern before diagnosis. Atypical symptom doesn't lead to diagnosis at first episode and diagnosis may be lengthy.

P1-253

Successful treatment of refractory adult-onset Still's disease (AOSD) complicated by ARDS with tocilizumab (TCZ)

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Conflict of interest: None

A 43-year-old man was diagnosed as having AOSD in 1999. Treatment with prednisolone (PSL) was effective, and he has been followed up without medication after 2000. He developed fever, arthralgia, and sore throat in January 2012. He was suspected as suffering from bacterial infection and admitted to another hospital. Despite of antibiotics administration, his respiratory symptom worsened gradually. Therefore, he was diagnosed with the exacerbation of AOSD complicated by acute respiratory distress syndrome (ARDS) and treated with methyl PSL pulse therapy and cyclosporin. However, he developed respiratory failure and was transferred to our hospital on January 31. After admission, with a use of BiPAP support for ARDS, TCZ (8mg/kg) was started for treatment of steroid-resistant refractory AOSD. With the reduced administration interval of TCZ (once every 3 weeks), his respiratory symptom as well as serum disease marker such as CRP or ferritin was improved subsequently, and remission state was eventually obtained. Recently, there are increasing reports showing the effectiveness of TCZ for treatment of AOSD. We report the present case as an important case showing the efficacy of TCZ for severe AOSD complicated by ARDS.

P1-254

Successful treatment with infliximab for two patients with skin manifestations associated with undifferentiated spondylarthritis

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Conflict of interest: None

We present two cases of spondilarthritis with two different cutaneous manifestations. One case of 40-year-old woman with erythema nodosum (EN)-like lesions, and an another case of 59-year-old woman with pyoderma gangrenosum (PG). The first case presented with right ankle arthritis and left heel enthesitis shown by MRI and bone scintigraphy, and she exhibited many EN-like lesions on her lower extremities. Skin biopsy specimen from the cutaneous lesion showed lymphocytic vasculitis with fibirinoid necrosis without typical panniculits. The second case presented with right heel enthesitis shown by MRI without bone erosion by plain radiography. She also exhibited erythematous ulcer on the left lower extremity. Skin biopsy specimen from the cutaneous lesion showed extensive sterile dermal abscess with neutrophilic infiltration with nuclear dusts. We initiated the administration of infliximab in combination with MTX. In both patients, not only arthritis and enthesitis, but also cutaneous lesions were rapidly improved. EN-like lesions and PG are very rare complications of SpA, and these results suggested that TNF may play an important pathogenic role in both cutaneous manifestations and arthritis / enthesitis of SpA.

P1-255

Coexistence of ankylosing spondylitis (AS) and rheumatoid arthritis (RA) -a case report-

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Conflict of interest: None

We present a case with coexistence of AS and RA. [Case Report] At 13 yo, he noticed shoulder pain just after vaccination and the subsequent gymnastic exercise. At 15 yo, he complained of bilateral hip joint pain. At 20 yo, he was bothered by severe neck pain and became unable to bend his head. He saw a nearby doctor regularly from 13 to 30 yo, and was subscribed oral NSAIDs as having RA. At 53 yo, his right hip pain worsened and received the total hip replacement. At 55 yo, he had bilateral wrist pain and swelling. Since two months ago, he developed knee pain and visited our hospital. He showed polyarthritis in his wrists and hands. From X-ray of PIP and MP joint erosions and positive anti-CCP antibody, he was diagnosed as RA. His spinal X-ray showed severe ankylosis of cervical spine and sacroiliac joints and he was positive for HLA-B7 and B27. From these findings we considered he developed AS in his teenage and secondly RA at 55 yo. We prescribe MTX and follow him. Coexistence of RA and AS is rare and there have been only one Japanese case reported so far. The findings of HLA type and strong ankylosis of cervical spine were similar between both cases. The estimated prevalence of coexistence of RA and AS is $7x10^{-5}$% in Japan, which may have been overlooked in the past.

P1-256

Clinical features of 113 patients with Behcet's disease

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Conflict of interest: None

[Objectives] To assess the clinical features of Behcet's disease (BD). [Methods] We investigated retrospectively our Behcet's patients from April 2008 to October 2012. We assessed sex, age of onset, classification, symptoms, complications, type of HLA and medications. [Results] In our departments, 113 patients were diagnosed with BD. The male-to-female ratio was 51:49. Median age of onset was 37.1 years. Eleven-point-five percentage of them have oral ulcerations, urogenital lesions, cutaneous lesions and ocular lesions. Fifty six-point-six percentage of them did not have those 4 clinical manifestations. Thirty six (31.9%) patients had either gastrointestinal lesions, neurologic lesions or vascular lesions. And 8 patients showed both gastrointestinal and vascular lesions. And rheumatic complications were spondyloarthropathy, giant cell arteritis and systemic sclerosis. The prevalence of HLA-B51 and HLA-A26 were 32% and 22%, respectively. Colchicine was most commonly used for treatment of BD (48.7%). [Conclusion] The male-to-female ratio and median age of onset were similar to the existing reports. Eight patients had gastrointestinal and vascular lesions.

P1-257

Clinical Characteristics of Behçet's disease in our hospital

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Conflict of interest: None

[Objectives] We investigated the clinical manifestation of Behçet's disease (BD) patients from initial manifestation to diagnosis in our hospital. [Methods] Forty patients fulfilled with the Japanese criteria for BD admitted from January 2009 to September 2012. Sixteen males and twenty-four females were involved, including two with complete type, twenty-seven with incomplete type, six with enteric type, three with neurogenic type, and two with vascular type. [Results] Oral ulcers were the most common manifestation (90%), followed by skin involvement (30%), genital ulcers (25%), and ocular involvement (7.5%) among initial main manifestations. The mean ± SD duration between the onset symptom and the fulfillment of diagnostic criteria was 88.1 ± 125.3 months. Especially, ocular involvement and oral ulcers preceded to diagnosis, the mean duration were each 70.2 ± 105.9 months and 64.4 ± 101.2 months respectively. The patients without skin involvement were associated with HLA-B27 positive statistically. [Conclusion] Mucocutaneous lesions are the hallmarks of the disease, and precede other manifestations. Further assessment may allow the detection of early predictions of the more aggressive disease, which requires more intensive treatment.

P1-258

Long-term analysis of Japanese BD patient with HLA-B27-associated HLA factors

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Conflict of interest: None

[Introduction] Human leukocyte antigen (HLA)-B27-associated HLA factors include HLA B7, Bw22, B39, B42, B54, B55,B56, B60, B61and B73. It was reported that HLA-B27-associated HLA factors were related with ankylosing spondylitis. Uveitis and arthritis are symptoms of ankylosing spondylitis, similar to Behcet Disease (BD). We investigated whether HLA-B27-associated HLA factors are nevel genetic factors associated with BD. [Methods] The samples were obtained from 46 Japanese BD patients for more than three years (average:5.7 years). We examined HLA type and their symptoms during treatment. [Results] 30.4% of BD patients had HLA-B51 and 19.6% had HLA-A26. 78% of the remaining BD patients had an HLA-B27-associated HLA factors. Only four patients (8.6%) were without either of the three afore mentioned antigens (HLA-B51, A26 and B27-associated HLA factor). 53.8% of HLA-B27-associated HLA factor-positive patients had arthritis had arthritis. However, no patient had spondylitis. [Conclusions] In contrast to previous studies, it was shown that BD patients did not only occur in patients with HLA-B51 and A26, but also with B27-associated HLA factors. While the HLA-B27-associated HLA factor positive patients tend to have synovitis, all patients didn't show symptoms of spondylitis.

P1-259

Serum exosomes carrying mitochondrial DNA drive inflammatory responses

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Conflict of interest: None

[Objectives] To assess serum level of mitochondrial DNA (mtDNA) associated with celler damage and the influence to inflammatory responses. [Methods] Serum mtDNA were measured among patients with Behçet's disease (BD), systemic lupus erythematosus, systemic sclerosis, polymyositis/dermatomyositis, rheumatoid arthritis and healthy controls. The influence of mtDNA was assayed by neutrophil and monocyte migration, cytokine production by macrophage. [Results] Serum levels of mtDNA were elevated in various immunological disorders especially in BD and mtDNA was included in the serum exosomes. Esosomes with rich mtDNA prepared from sera of BD patients enhanced migratory activities of human and mouse neutrophils and IL-1b, IL-12 and TNF-a synthesis by mouse macrophages. These phenomena were inhibited in neutrophils and macrophages from TLR9-/- and MyD88-/- mice. [Conclusion] Among various immunological disorders, serum levels of mtDNA were relativily high. Exosomes carrying mtDNA drive immune responses.

P1-260

Two cases of intestinal Behcet's disease associated with myelodysplastic syndrome with Trisomy-8

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Conflict of interest: None

Myelodysplastic syndrome is a disease characterized with quantitative and qualitative abnormalities of blood cells by abnormal hematopoietic stem cells.In myelodysplastic syndromes with trisomy 8, it may develop intestinal Behcet's disease-like pathology. One example is 42-year-old man eyes. At the age of 28, He had been diagnosed with Behcet's disease from intestinal symptoms such as abdominal pain, stomatitis, and melena. He had been in medical treatment with steroids. At the age of 38, he had cause intestinal perforation. In the course of this time, there were pancytopenia. Underwent a bone marrow aspirate was there, he was led to the diagnosis of myelodysplastic syndrome with trisomy-8. The second case was 64-year-old man's one. Chron's disease was initially suspected from high fever, multiple oral ulcers, and many ulcerations of the large intestine. However, he had macrocytic anemia. Underwent a bone marrow aspirate was there, he showed a myelodysplastic syndrome with trisomy-8.From the fact that the certain chromosomal abnormalities have resulted in status ecific connective tissue disease, they are very interesting cases in considering the pathogenesis of connective tissue disease.

P1-261

Three cases of Behçet's disease who developed non-bacterial meningitis with high level of cerebrospinal fluid (CSF) interleukin-6 (IL-6)

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Conflict of interest: None

[Background] CSF IL-6 is considered to be useful to evaluate neuro-Behçet's disease activity. Here we report 3 cases of Behçet's disease who developed non-bacterial meningitis with high level of CSF IL-6. [Case 1] A 59-year-old man, who developed neuro-Behçet's disease 6 years ago, showed headache and meningeal signs after tapering steroid. His symptoms were improved by increasing the steroid dose. CSF IL-6 changed from 233 to <8 pg/ml. [Case 2] A 33 year-old woman, who developed Behçet's disease 3 years ago, had headache for 2 months. Brain MRI (T2-weighted) revealed high signal intensity lesions. Steroid and methotrexate therapy improved her symptoms. CSF IL-6 changed from 231 to 156 pg/ml. [Case 3] A 67 year-old male, who developed Behçet's disease 9 years ago, initiated cyclosporin A therapy due to myelodysplastic syndrome 3 months ago. A week ago, he developed fever, headache and signs of meningitis. Acyclovir was initiated and he was later diagnosed with herpes meningitis based on a positive result of CSF HSV-DNA. CSF IL-6 changed from 346 to <8 pg/ml. [Discussion] Because viral meningitis also shows increased level of CSF IL-6, careful consideration, including a review of clinical history, is required for the diagnosis of neuro- Behçet's disease.

P1-262

Screening autoantibodies in Behçet disease

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Conflict of interest: None

[Objectives] There were few reports about autoantibodies specific for Behçet disease (BD). The objective is to identify novel autoantibody for BD and evaluate its clinical usefulness. [Methods] Serums were collected from patients with some immunological disorders and healthy controls. Samples from BD and controls were analyzed by Protein Microarray assay. Significant autoantigens were selected, and autoantibodies against them were measured by ELISA in many samples from BD, controls, SLE and RA. [Results] Samples were collected from 27 BD patients, 19 controls,

19 SLE patients and 19 RA patients. Six samples from BD and 3 from controls were analyzed, and claudin1, which plays an important role to tight junction, was extracted as a candidate. Titers of the antibody were 10.3 ng/ml [2.7, 18.0] in BD, 2.6 [0.9, 8.3] in controls, 8.5 [4.9, 24.1] in SLE and 2.2 [0.8, 5.4] in RA. Thus, anti-claudin1 antibody was elevated in BD patients and SLE patients ($p<0.01$) [Conclusion] Anti-claudin1 antibody was elevated in BD. This result suggested that anti-claudin1 antibody may be a clinical marker and contribute to the pathogenesis of BD.

P1-263

Two cases of neuro-Behcet disease with difficulty in early diagnosis

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Conflict of interest: None

[Objectives] It is difficult to diagnose neuro-Behcet disease early in acute phase, lacking typical symptoms. This time, we report two cases of the disease which diagnosis were defined a few years later during the treatments. [Case & Clinical Course] An 18-year-old female presented with fever, unconsciousness and convulsion during the sports day in high school. She had no particular physical findings, but her MRI brain image showed high intensity area at right basal ganglia. She was followed with anticonvulsants without defined diagnosis. Two years later, she had chronic recurrent aphthous stomatitis, pudendal ulcers, and nodular erythema in lower legs, and then led to the diagnosis. Next, 52-year-old female presented with recurrent aseptic meningitis followed by severe headache. She had high level of IL-6 in fluid and her MRI brain image showed high intensity area at both cerebral cortex. Three years later, she had three major symptoms of Behcet disease without eye signs. Both patients got the steroid pulse therapy. The former stabilized with small amount of prednisolone (PSL). The latter did not achieve a remission by PSL therapy alone, and was treated with immunosuppressive drugs. [Conclusion] We experienced two cases of neuro-Behcet disease with difficulty in early diagnosis.

P1-264

A case of massive intestinal hemorrhage due to the rapture of iliocolic aneurysm with intestinal ulcer complicated Behçet's disease

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Conflict of interest: None

[Case] A 32-year-old male had been diagnosed as Behçet's disease (BD) from uveitis, aphthous stomatitis and erythema nodosum on March 2005. On May 2005, he showed massive intestinal hemorrhage from ulcerative lesions in terminal ileum. His manifestations improved after PSL 55mg/day, which was tapered off. Intestinal lesion with melena recurred in 2007. Although IFX and MTX were started, they were not effective. Abdominal pain with melena recurred on July 2009, when PSL was increased into 50mg/day. Since this episode, intestinal disease activity had been well controlled until June 2012, when he presented abdominal pain following the episode of his right leg cellulitis and was admitted. After 11 days from admission, he presented massive intestinal hemorrhage. Abdominal angiography revealed aneurysm in the iliocolic artery, penetrating into the small intestine. An angiographic embolization was performed and PSL was increased into 60mg/day with combination of MTX, after which his symptoms improved. **[Conclusion]** The presence of aneurysm in abdominal feeding artery in our patient indicates that in patients with intestinal BD who show massive intestinal bleeding, the presence of vasculitic aneurysm should be considered.

P1-265

A case of myelodysplastic syndrome-related intestinal Behçet's disease accompanied by tuberculosis

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Conflict of interest: None

Case is 76 year-old male. He has past histories of atrial fibrillation, hypertension, diabetes and colon cancer. Since Sep. 2009, he was prescribed 25mg/d of prednisolone (PSL) due to erythema nodosum (EN). He was referred to us in Jan. 2010. Chest CT showed multiple nodular shadows in upper lobes of the left lung. He was diagnosed with pulmonary tuberculosis. When PSL had been tapered, the EN symptoms relapsed, and continued in spite of successfully completed anti-tuberculosis therapy. As he often suffered from althralgia in Dec. 2010, he was referred to the department of hematology due to the anemia, and diagnosed with myelodysplastic syndrome (MDS). Although we had increased PSL, and added colchicine, cyclosporine A and salazosulfapyridine, periodic fever with EN did not improve. In Nov. 2011, injection site of insulin (lower abdomen) was swollen. Although tocilizumab was introduced and PSL was tapered again, he required emergency surgery in Feb. 2012 because of multiple intestinal ulcer and perforation. There were records of episodic stomatitis in Nov. 2009 and Jul. 2010, which were an important finding for diagnosis of Behçet's disease (BD) as well as EN, althralgia and intestinal lesion. Recently, it is suggested that MDS involved chromosome 8 trisomy is related intestinal BD.

P1-267

A case of juvenile systemic lupus erythmatosis with aplastic anemia

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Conflict of interest: None

[Introduction] We report a case of SLE with aplastic anemia (AA) who responded to combination therapy oral cyclosporine (CyA) and cyclophosphamide pulse monthly therapy (IVCY). [Case]15-year-old girl was diagnosed as juvenile SLE and perfomed methyl prednisolone (mPSL) pulse therapy and treated with prednisolone (PSL) 1mg/kg and mycophenolate mofetil (MMF). As withdrawing of PSL, she presented thrombocytopenia instead of normal serum complement level. Thinking of the possibilityod drug myelosuppression, we changed MMF into azathioprine (AZP). On the course of PSL withdrawing, severe leukocytopenia and thrombocytopenia appeared, then we perfomed bone marrow aspiration and biopsy that reveald hypocellular marrow. She was diagnosed as AA complicated with SLE, and additional mPSL pulse therapy was perfoed. We changed AZP into CyA. To intensity the immunosuppression therapy to SLE, we introduced IVCY. [Discussion] AA is a rare feature of SLE. As previously reported, we perfomed immunosuppression therapy that is equivalent to treatment of SLE. AA should be considered it we experienced SLE patient with pancytopenia that is resistant to several therapy.

P1-268

Eyelid swelling in adult-onset Still's disease: two case reports

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Conflict of interest: None

We report 2 cases of adult onset Still's disease (AOSD) that manifested eyelid swelling. **【Case presentation】 Case1**: 26-year-old female diagnosed with AOSD 2 years ago showed bilateral eyelid swelling followed by fever and arthritis during tapering prednisolone (PSL). Magnetic resonance imaging (MRI) revealed enhanced mass in the bilateral lachrymal regions, which were chronic inflammation on biopsy and resolved by 100 mg/d of PSL therapy for refractory AOSD. Eyelid swelling and febrile condition relapsed when PSL was tapered to 30 mg/d, and remitted by additional tocilizumab therapy. **Case2**: 62-year-old female having AOSD of drug-free remission, which was diagnosed 18 years ago, was admitted because of massive swelling in the left eyelid and scleritis. MRI and 18F-FDG PET/CT revealed inflammation in the left lachrymal gland, skin, subcutaneous tissue, and adjacent extra ocular muscles, which mimicked malignant lymphoma. Lymphadenopathy, fever, arthritis, and skin rash that appeared 2 months later. Biopsy showed fibrotic tissue in the left cervical lymph node and the left eyelid. Relapsed AOSD was diagnosed and successfully treated by 40 mg/d of PSL. **【Clinical significance】** Ophthalmological symptoms, rare complication of AOSD, can be early manifestation of relapsed AOSD.

P1-269

A case of juvenile Sjögren's syndrome with interstitial nephritis and juvenile idiopathic arthritis

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Conflict of interest: None

We report on a 12-year-old girl in whom salivary gland swelling had recurred from the age of 5 years, Sjögren's syndrome was diagnosed at the age of 10 years, and interstitial nephritis developed at the age of 12 years. Laboratory findings were as follows: serum protein, 10.1 g/d; IgG, 3,828 mg/dL; antinuclear antibodies, 1,280-fold; anti-Ro/SS-A antibody, 512-fold; anti-Ro/SS-B antibody, 4-fold; creatinine, 0.45 mg/dL; blood β2-microglobulin, 2.2 mg/L (slightly elevated); and cystatin C, 0.86 mg/L. Urinalysis showed proteinuria and a β2-microglobulin concentration of 11,265 mg/L. Schirmer's test showed decreased tear secretion (5 mm), and fluorescein staining showed marked bilateral superficial punctate keratitis. Light microscopic examination of the renal biopsy specimens showed expansion of mononuclear cell infiltration in the renal interstitium, inflammatory cell infiltration of interstitial areas with edema and mild fibrosis, and tubulitis and mononuclear cell infiltration that included many lymphocytes and plasma cells. Juvenile idiopathic arthritis developed at the age of 13 years,

P1-270

Our research on anti-peroxiredoxin antibodies in patients with Kawasaki disease

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Conflict of interest: None

[Objectives] Prxs with at least six subtypes is a thioredoxin-dependent antioxidant enzyme in the redox system. It has been reported that AECA were detected frequently in patients with vasculitis and were associated with disease activity and vasculitis symptoms. We reported that IgG antibodies to Prx2, a target protein of AECA, were detected in 60% of Kawasaki disease (KD) and may affect the pathophysiology of KD. We investigated clinical importance of IgG antibodies to the other five Prxs. [Methods] We evaluated titers of IgG antibodies to recombinant Prxs by ELISA using 30 KD patients including 3 patients with coronary artery lesions (CAL) before therapy and 15 controls. [Results] IgG antibodies to the recombinant Prx1, Prx3, Prx4, Prx5 and Prx6 were detected in 0%, 10%, 0%, 33% and 4% of KD patients, respectively. Anti-Prx5 IgG antibody was detected in 7% of controls. IgG antibodies to the recombinant Prx3 and Prx6 were detected in one of 3KD patients with CALs and the recombinant Prx5 were detected in two of 3 KD patients with CAL. [Conclusion] The antigenecity of Prx2 was found different from the other five Prxs. IgG antibodies to the recombinant Prx2 were detected frequently in KD. Thus, anti-Prx2 IgG antibody may affect the pathophysiology of both KD and KD with CAL.

P1-271

Juvenile ankylosing spondylitis; a case report

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Conflict of interest: None

[Case] A 17 year-old male with a spastic type of cerebral palsy. When he was 13 years old, he was suffered from left buttock pain and his pain was spontaneously remitted. Then he was diagnosed with irdocyclitis on 17 years of age. During this period, he felt left buttock pain again. Laboratory data showed that high inflammatory response (ESR;70 mm/hour and CRP; 4.4 mg/dl) while neither RF nor anti-CCP antibody was positive. HLA-B27 was positive. On his X-ray, no arthritis, enthesitis, and syndesmophyte was observed. However, osteoarthritic change of sacroiliac joint was remarkable. His pelvic CT showed that the joint space of left sacroiliac joint was irregular, enlarged and osteosclerotic. He was fulfilled one item of the modified New York criteria for ankylosing spondylitis then he was finally diagnosed with juvenile ankylosing spondylitis. He was treated with NSAIDs and oral corticosteroid (2.5 mg/day) and his left buttock pain was gradually relieved. High inflammatory findings became negative 3 months after treatment. [Clinical significance] We experienced a very rare case with juvenile ankylosing spondylitis. Recently new advances in juvenile spondyloarthritis was reviewed, and the induction of methotrexate or TNF-therapy will be considered depending on his disease activity.

P1-272

Six cases of systemic juvenile idiopathic arthritis with the flare of arthritis during Tocilizumab therapy

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Conflict of interest: None

Tocilizumab (TCZ) improved systemic arthritis and active systemic features in systemic juvenile idiopathic arthritis(S-JIA). However, the flare of arthritis occurred in a few patients. Twenty-nine patients of S-JIA received TCZ in our hospital. Six patients (5

boys, 1 girl) had arthritis flare during TCZ therapy. High levels of MMP-3 and serum IL-6 were observed in these patients. These patients were treated with addition of methotrexate. Two patients were observed improvement of arthritis. And, 1 patient was observed improvement of MMP-3 and serum IL-6. The other 4 patients were treated with tacrolimus instead of methotrexate. Three patients were observed improvement of arthritis. And two patients were observed improvement of MMP-3 and serum IL-6. Combination of TCZ and methotrexate or tacrolimus was partially efficacious.

P1-273

Adalimumab (ADA) for clinical remission in a patient with methotrexate refractory juvenile idiopathic arthritis

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Conflict of interest: None

[Back ground] There are some reports about the possibility of bio-free remission in the treatment of rheumatoid arthritis. But we can find a few reports on whether it is possible to maintain the bio-free remission, and even clinical remission off medication (CR) in the treatment of juvenile idiopathic arthritis (JIA). We report a case of methotrexate (MTX) refractory polyarticular JIA (pJIA) who discontinue all medication after achieved clinical remission by the treatment of Adalimumab (ADA). [Case report] We have observed a 11 years old female patient suffering from RF negative pJIA. At age of six, she developed pJIA refractory to MAP therapy (MTX, prednisolone and ibuprofen). At the age of seven she was treated with ADA (20mg, every 2 weeks), and 2 years later she met the criteria for inactive disease (ID) of ACR definition. Over 12 months she had met the criteria of clinical remission on medication (CRM), we stop all medication for pJIA. [Conclusion] For JIA patients, it may be possible to discontinue all medicine after achieving clinical remission by the treatment of anti-TNF agents.

P1-274

A case of 65-year old woman who was diagnosed with neonatal-onset multisystem inflammatory disease (NOMID)

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Conflict of interest: None

NOMID is the most severe form of CAPS, in which high IL-1b is induced by activation of NLRP inflammasome due to its various gene mutations. A 65-year old woman was for the first time diagnosed with NOMID. From birth, she had recurrent episodes of fever, urticarial-like rashes, arthralgia, headache, convulsion and unconsciousness. At high school, she needed a hearing aid due to hearing loss. She had two sons and the second son had the similar symptom. Despite fever, rashes and CNS manifestations, the disease had not been determined in part due to her spontaneous recovery. In 2012 July, she was refereed to our center because of relapsing uveitis. She showed short stature, face with frontal bossing and saddle-shaped nose, and hand deformities with clubbing, but no mental retardation. In August15, she was admitted with aseptic meningitis with high inflammatory lab data, followed by improvement with high-dose steroids. These finding suggested the diagnosis of NOMID, thus the genetic mutation of *NALP* is now under investigation. In October 12, the monoclonal anti-IL-1b antibody canakinumab was given to her, who became better than ever experienced. Our experience indicates that patients with autoinflammatory diseases could be present more among those with unknown fever than expected.

P1-275

Analysis of persistent inflammation in proteasome disability syndrome

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Conflict of interest: None

Nakajo-Nishimura syndrome (NNS) (MIM 256040) is an autoinflammatory disorder that segregates in an autosomal recessive fashion and is caused by a mutation of the β5i immunoproteasome subunit (G201V). The ubiquitin-proteasome pathway might play an important role for persistent inflammation. In this study, we analyzed the role of reactive oxygen species (ROS) using the chemical fluorescence probes. We detected the accumulation of ROS in the fibroblasts derived from NNS patients but not from parents of patients and healthy subjects after 1.5 hour LPS stimulations. This result suggests that the accumulation of ROS might induce persistent inflammation in NNS patients.

P1-276

Cytokine product of PBMC in FCAS patient with novel NLRP3 mutation

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Conflict of interest: None

[Objectives] Familial cold autoinflammatory syndrome (FCAS) is characterized by urticaria and recurrent episode of fever with exposure to cold temperature. The mutations in NLRP3 gene plays an role in the pathogenesis as for cytokine production. We diagnosed a case of FCAS patient to detect a novel NLRP3 mutation, and investigated biology of peripheral lymphocyte in this patient. [Methods] PBMC were obtained from venous blood of FCAS patient (PT) or healthy control (HC), then cultured at 32°C or 37°C with or without LPS stimulation. Cytokines including IL-1β were determined in each supernatant by ELISA. [Results] We identified a heterozygous missense mutation (D303A) at exon3 of NLRP3 in this PT. IL-1β production from PBMC with LPS at 37°C was enhanced significantly in PT. This phenomenon was markedly enhanced at 32°C. Without LPS, IL-1βproduction of PBMC from PT were determined. As for TNF-α, production from PBMC in PT was suppressed compared with that of HC. Additionally, the ASC-dependent NF-κB reporter gene activities were demonstrated in this novel mutant NLRP3. [Conclusion] We identified a novel NLRP3 mutation in FCAS patient. PBMC with this mutation could increase the IL-1β production under the cold stimulation, which could play an important role in the pathogenesis of FCAS patient.

P1-277

Identification of genetic polymorphisms in a Japanese patient with Palindromic rheumatism

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Conflict of interest: None

[Objectives] Palindromic rheumatism (PR) is a autoinflammatory syndrome characterized by episodes of inflammatory phase and non-inflammatory phase with no after effects caused by inflammation. Although *MEFV* and *NLRP3* are susceptible genes in the patients with autoinflammatory syndromes, the details are not clear in the Japanese patients with PR. Here, we performed detailed sequence analysis of *MEFV* and *NLRP3*. [Methods] We sequenced entire exons, a portion of introns and entire region of mRNA in *MEFV* in the case with healthy individuals and a PR patient. Futuremore, we analyzed rs3806265 SNP, located in the *NLRP3*. [Results] In a patient with PR, we found 10 reported polymorphisms in *MEFV* DNA, and rs3806265 homo mutation in *NLRP3*. We also identified *MEFV* exon2 skipping in the mRNA, but not specific in PR patient. Moreover, we detected novel *MEFV* exon2 deletion in the genomic DNA in healthy individuals (Acc. No. AB726085). [Conclusion] One of the polymorphisms identified in a PR patient is rs3743930, which is reported as one of the genetic risk factors of FMF. We also found that rs224204 and rs3806265 were forming haplotype reported as genetic susceptible factor of JRA. These results indicate that these polymorphisms are also associated with pathogenesis of PR.

P1-278

Serum amyloid A triggers the mosodium urate-mediated inflammasome activation and interleukin-1β production from human synovial fibroblasts

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Conflict of interest: None

[Objectives] The cellular pathway of monosodium urate (MSU)-mediated NLRP3 inflammasome activation in synovial tissues, remain elusive. We investigated the effects of MSU on synovial fibroblasts to elucidate the process of MSU-mediated synovial inflammation. [Methods] Human synovial fibroblasts were stimulated with MSU in the presence or absence of serum amyloid A (SAA). The cellular supernatants were analyzed by immunoblotting using anti-IL-1β or anti-caspase-1 antibodies. [Results] Neither SAA nor MSU stimulation resulted in IL-1β or interleukin-1α (IL-1α) secretions and pro-IL-1β processing in synovial fibroblasts. However, in SAA-primed synovial fibroblasts, MSU stimulation resulted in the activation of caspase-1 and production of active IL-1β and IL-1α. The effect of SAA on IL-1β induction was impaired in cells by silencing NLRP3 using siRNA or treating with caspase-1 inhibitor. SAA/MSU-induced IL-1 induction was blocked by Syk inhibitor. [Conclusion] Our data demonstrate that exposure of human synovial fibroblasts to SAA promotes MSU-mediated caspase-1 activation and IL-1β secretion in the absence of microbial stimulation. These findings provide insight into the molecular processes underlying the synovial inflammatory condition of gout.

P1-279

Efficacy and safety of anakinra treatment for patients with cryopyrin-associated periodic syndromes in Japan

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Conflict of interest: None

CAPS (cryopyrin-associated periodic syndrome) is an autoinflammatory disease caused by IL-1 overproduction due to *NLRP3* mutations. Previous studies have demonstrated IL-1-blocking agents are effective for CAPS and anakinra is the first effective drug discovered for CAPS. In Japan, anakinra has not been approved for any diseases, so CAPS patients were treated with anakinra by off-label use through compassionate supply by SOBI or direct import until canakinumab was approved in September, 2011. Although canakinumab has been effective for CAPS so far, its long-term efficacy has not been guaranteed and CAPS patients need to have an alternative therapy once canakinumab fails in any situations. Therefore, in this study, we surveyed the efficacy and safety of anakinra for CAPS to see if anakinra can be a reasonable alternative. We retrospectively collected 12 cases of CAPS patients treated with anakinra nation-wide in Japan. As a result, improvements in symptoms and inflammatory markers were observed in all the patients. All the patients continued to use anakinra, except one patient who had to stop because of allergy reaction to anakinra. Serious adverse effects were not observed. These results indicated that anakinra is an effective and safe alternative for CAPS patients Japan.

P1-280

A case of familial Mediterranean fever identified by periodic fever associated with the menstrual cycle

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Conflict of interest: None

A 56 year-old woman had been experiencing fever and abdominal pain in association with the menstrual cycle. She underwent abdominal CT, and other tests, but no definite diagnosis had been made. Since she visited our hospital presenting with the same symptoms and blood test showed elevated levels of inflammatory markers. As her menstrual periods became less frequent, fever also occurred less frequently to around once every 6 months. However, she recently started suffering from arthralgia and visited our department. Since symptoms subsided without treatment and her father also had periodic fever, familial Mediterranean fever (FMF) was suspected. The genetic test revealed *MEFV* mutation p.Met694Ile, which confirmed the diagnosis. After she started treatment with colchicine, symptoms disappeared, and amyloidosis has not developed. FMF is inherited as an autosomal recessive trait. There are about 300 patients in Japan. Colchicine suppresses the FMF symptoms and prevents amyloidosis. About half of the female patients

have their symptoms in association with the menstrual cycle, to which stress and pain due to menstruation may be attributed. We believe that it is important to differentiate FMF and perform an early genetic test.

P1-281

A case of familial mediterranean fever combined with psoriatic arthritis with different response to adalimumab and infliximab

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Conflict of interest: None

Familial mediterranean fever (FMF) is autosomal recessive disease showing repeated episodes of fever, serositis, and arthritis. Aside from the importance of gene study, FMF has been shown to be overlapped with JIA, psoriatic arthritis (PsA), and others. Here we report a case of FMF overlapped with PsA with different responses to 2 biologics. The case is a 26 year-old woman who affected with psoriasis vulgalis when she was in an elementary school. Episodes of intermittent fever, monoarthritis, and lower abdominal pain with diarrhea developed in 2007 and she was diagnosed as SpA. She was treated with the combination of PSL and SASP, but they did not work well. Finally she visited us in 2009 and the diagnosis of FMF was made based on the gene examination. Colchitine was started resulted in improvement of fever, abdominal pain, and diarrhea. In 2011, because both psoriasis and arthritis worsened, ADA was administrated. PASI score improved but abdominal pain worsened. According to patient's desire, ADA was changed to IFX, resulting in improvement of abdominal pain but in worsening of PASI score and arthritis. Conclusions: Although both ADA and IFX have been thought to be effective for FMF and PsA, the response to these biologics was different in this case.

P1-282

Use of anti-IL-1β monoclonal antibody in a dialysis patient with Cryoprin-associated periodic syndrome: a case report

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Conflict of interest: None

Cryoprin-associated periodic syndrome, CAPS, is one of the autoinflammatory syndromes, caused by the mutations in the *NLRP3* gene. We report our experience of the treatment with canakinumab in a patient with CAPS who receives hemodialysis. The case was a 39-year-old woman who developed periodic urticaria and fever since age 3. She was given a diagnosis of juvenile idiopathic arthritis at the age of 5, and was administered NSAIDs shown to be ineffective. While prednisolone was started at the age of 22, CRP remained elevated. At the age of 32, hemodialysis was started due to renal amyloidosis. When she received a living-donor kidney transplant at the age of 34, CAPS was diagnosed by the genetic testing. Nevertheless, renal function gradually worsened due to amyloid deposition in the transplant kidney. At the age of 37, anakinra, IL-1 receptor antagonist, was introduced by private import, but hemodialysis was reinitiated. In April 2012, anakinra was changed to canakinumab, anti-IL-1β monoclonal antibody. Until now, clinical amelioration is being achieved. Canakinumab was approved as a therapeutic agent for CAPS in December 2011 in Japan. While CAPS was diagnosed at the age 34 in this case, early diagnosis and initiation of the treatment is crucial for the improvement of the prognosis.

P1-283

Treatment of refractory adult-onset still's disease with tocilizumab: report of two cases

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Conflict of interest: None

To date, there have been several publications on the therapeutic use of biologic agents in adult-onset Still's disease (AOSD) patients. Tocilizumab (TCZ) seems to be highly effective for treating patients refractory to TNF antagonists and anakinra. We report two AOSD patients who were treated successfully with TCZ therapy. Patient 1: An 80-year-old man was admitted to our hospital with fever, polyarthralgia, skin eruptions, and sore throat. Laboratory test results were as follows: leukocytes 14800/μl (neutrophils 96.1%), CRP 4.19mg/dl, ferritin 42064ng/ml. He was treated with prednisolone (55mg/day), intravenous methylprednisolone 0.5g/day for 3 days X 2 times, MTX (8mg/week), but his clinical manifestations continued. Patients 2: A 16-year-old man developed pyrexia, polyarthralgia, skin eruptions, sore throat, and polymyalgia. Laboratory test results were as follows: leukocytes 37800/μl (neutrophils 87%), CRP 12.26mg/dl, ferritin 1227ng/ml, AST 62IU/l, ALT 215IU/l. Prednisolone (30mg/day), intravenous methylprednisolone 0.5g/day for 3 days X 2 times, and MTX (6mg/week) failed to induce remission. In both patients, the first treatment with TCZ (8mg/kg) resulted in rapid improvement of symptoms and inflammatory markers. TCZ may be a promising new treatment for AOSD.

P1-284

The first case of dermatomyositis complicated with CNS lesions due to HLH who could successfully treated by modified HLH-2004 protocol

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Conflict of interest: None

<Case>A 17-year-old man with DM complicated HLH was admitted our hospital because of high fever and alteration of consciousness.Labolatory data showed incresased CPK,sIL-2R and ferritin,and decreased WBC and Plt. Bone marrow examinations showed active haemophagocytosis,suggesting simultaneous exacerbation of HLH and DM.Brian MRI images showed bilateral multifocal subcortical leukoencephalopathy.While serum CPK level was improved after methylpredonisolone pulse theray and IVIG,and cyclophosphamide pulse therapy,the CNS lesions were aggravated in concert with worsening of HLH.We considered that the CNS lesions were related to HLH.After initiation of a modified therapy of HLH-2004 protocol using tacrolimus instead of cyclosporine and reduced etoposide,both HLH and CNS lesions gradually improved.<Discussion>This is the first case of successfully treated patient with DM complicated with CNS lesions related to HLH.CNS lesions are very rare in secondary HLH,but rather polu-

lar in familial HLH due to gene mutations.Familial HLH are usually needs agrresive treatment with HLH-2004 protocol.With regard to treatment,this case suggests that CNS lesions due to HLH even in patients with autoimmune disease should be treated in accordance with modified HLH-2004 protocol.

P1-285

Initial dose of prednisolone and clinical course of patients with polymyalgia rheumatica

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Conflict of interest: None

[Objectives] We examined the initial doses of prednisolone (PSL) and clinical course of the patients with polymyalgia rheumatica. [Methods] 12 patients diagnosed by modified Bird's criteria (CRP positive instead of ESR>40) for PMR were studied retrospectively. They presented to our hospital from April 2011 to August 2012 and were followed more than three months. Four of the patients were men. The median age was 74 (64-82). The median body weight (BW) was 44.5kg. The comorbidities were hypertension 5, diabetes mellitus 2, and osteoporosis 1. [Results] All the patients were treated with PSL. Five patients were started PSL with 10 mg/day, 5 with 15mg/day, and 2 with 20mg/day. One of two patients who were started with 20mg/day weighed more than 60kg, and the other was initially treated in another hospital. PSL dosage based on BW was higher in patients weighing less than 45 kg than those with more than 45kg. The median time before PSL tapering was 4 weeks. During the follow-up, two patients were hospitalized with pneumonia or compression fracture, and a patient died of pancreas cancer 15 months after the start of PMR treatment. [Conclusion] It is necessary to review the initial doses of PSL and the timing of PSL tapering, especially in elderly low BW women.

P1-286

A 25-year review of outpatient treatment of rheumatoid arthritis

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Conflict of interest: Yes

[Objective] The treatment of rheumatoid arthritis (RA) has made significant advances in recent years. To examine the changes in RA treatment, a review of 25 years of outpatient practice was conducted. [Methods and results] The author has provided outpatient care for RA for 25 years in total, first at the special outpatient department for RA at Kyushu Medical Center, formerly Fukuoka National Central Hospital which he established in 1987 and Kondo Clinic. The annual number of RA patients treated by the author was 256 in 1987, which increased to 926 after 10 years (1997) and to 1407 after 25 years (2012). Changes in C-reactive protein (CRP) levels over time were examined to assess changes in the control of RA over time. In 1987, CRP was normal in 27.2% of all patients and was 2.0 mg/dL or higher, indicating poor control, in as many as 45.9% of patients. These percentages were 28.2% and 35.4%, respectively, 10 years later, showing a decrease in the proportion of patients with poorly controlled RA. At 25 years, the percentages were 71.9% and 3.6%, respectively, indicating a marked increase in the proportion of patients with normal CRP and a substantial decrease in poor control.The introduction of MTX and biologics is associated with improvement of treatment results.

P1-287

Examination of the efficacy of Kampo medicine treatment for rheumatoid arthritis patients

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Conflict of interest: None

[Background] We examined digestive symptoms of 152 autoimmune patients, symptoms remained in more than 70% of patients. And RA patients often appeal for cold, digestive symptoms and fatigue. In addition most of those are patients in whom Kampo is indicated. There are a lot of case reports that Kampo was effective for RA. We give Ninjinto (eNT) which is used for the purpose of improving cold and digestive symptoms. We examined the efficacy of Kampo treatment for RA patients. **[Method]** We conducted an investigation for RA patients who regularly attended our Hospital and were prescribed eNT. **[Result]** 60 patients were prescribed. There was 19 patients(31.7%) who felt improvement of subjective symptoms and continued to take eNT. Here we present 2 representative cases among 5 cases treated effectively with eNT. **[Case1]** 37y-F. She took MTX 8mg and prednisolone (PSL) 7.5mg, but DAS28 was 3.51. We stopped PSL and MTX after taking eNT in a year, but DAS28 was 1.24. **[Case2]** 62y-F. She was treated with tacrolimus, diclofenac and PSL. Since she appealed for digestive symptoms after taking those drugs, we prescribed eNT. A year later we stopped diclofenac, PSL and tacrolimus, but he is remission state. **[Consideration]** It is suggested that Kampo may be useful as a choice of the RA treatment.

P1-288

Kikuchi disease with skin lesions mimicking lupus erythematosus

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Conflict of interest: None

[Case] We report a case of a 28-year-old woman, who was admitted to our department with high fever, skin lesion lesions, arthritis and left cervical lymphadenopathies. Erythematous plaques were noted on left cheek. On exemination, She had leukocytopenia, thrombocytopenia, low complement, and high level of LDH. Excisional node biopsy was consisted with Kikuchi disease with skin involvement. Skin biopsy showed perivasculor dermatitis with granuloma. Treatment was initiated with oral predonisolone at a dose of 45mg/day. A clinical and analytical involvement was seen within a week. After she stopped predonisolone, fever subsided and the skin rashes disappeared without relapse during a 6-month follow-up period. [Conclusion] Kikuchi disease is histiocytic necrotizing lymphadenitis. It is characterized by cervical lymphadenopathies and fever. Cutaneous Kikuchi diseae can mimic both clinically and histologically skin lesions in lupus erythematosus.

P1-289

CKD in our rhumatoid outpatients

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Conflict of interest: None

[Objectives] We evaluate the new patient of CKD(chronic kidney disease) in our unit, and according to the presence of CKD is influence the treatment of our patients. [Methods] We intended for 81 people (male 20 female 61 mean age 58.6±15.6 years old) who visited our unit from April, 2012 to October, eGFR at the time of the first medical examination divided it into two groups of non CKD more than 60 and CKD under eGFR60, we examined the difference of the cure of RA in each group. [Result] CKD group The CKD group had [20 persons (67±13.2 years old of average age), and a nonCKD group] age at 61 persons (55.9±15.4 years old) ($p< 0.01$). Each group had most RA, the number of primary diseases was 23 by 8 persons (40%) and a non CKD group in the CKD group (38%).Three NSAIDS starts (15%) and a 15-person (25%) MTX start were four persons (20%) and 15 person (25%) biological agents use 4 person (20%) 15 person (21%) about the medical treatment of RA. As for the biologic treatment used by the CKD group, 3 persons (75%) were medicated with TCZ, by a non CKD group, TCZ is 4 persons (27%) [Conclusion] 25% of new patient outpatient hospital rheumatism was CKD. For the treatment the use of MTX and CKD group NSAIDS but tends to lower with respect to the use of biological agents was comparable.

P1-290

A case of patient with rheumatoid arthritis with a episode of autoimmune hepatitis following the discontinuation of methotrexate at the time of introduction of tocilizumab

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Conflict of interest: None

We report a case of autoimmune hepatitis (AIH) during the treatment of tocilizumab (TCZ) in a 59-year-old man with rheumatoid arthritis (RA). He had been previously treated with bucillamine and methotrexate (MTX), and had sometimes revealed the slightly elevation of transaminases. Due to the disease activity, treatment with TCZ was initiated and MTX was stopped on March 2012. After one infusion of TCZ, elevation of transaminases up to ten to twenty times the upper normal limit were noted and treatment with TCZ was terminated. Some kinds of supplement that he had started by himself one month ago was also stopped in suspicion of the cause of elevation of transaminases. Though drug-induced hepatitis was suspected, termination of both TCZ and the supplement did not lead to the improvement of liver disorder. After admission, the patient tested positive for anti mitochondria 2 antibody that suggested the possibility of AIH. Then after liver biopsy, he was administered oral prednisolone (PSL)(50mg/day) and transaminases level decreased to normal limits. PSL was tapered and low dose PSL was continued. After six months later, RA activity increased gradually. Treatment with TCZ was reinstituted. The possibility that MTX had inhibited his latent AIH was considered.

P1-291

Correlation between patient global assessment and psychological aspect and sleep in patients with rheumatoid arthritis

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Conflict of interest: None

Objective: To assess the relation of psychological condition and sleep to PGA in patients with RA. Methods: The patients with RA were divided to PGA remission group (PGA=<1) and PGA non-remission group (PGA>1). Anxiety was assessed utilizing STAI, while depression with CES-D and HADS-D, Self-efficacy with GSES and sleep disturbance with PSQI. These data were compared between 2 groups. Results: Ninety-nine patients (13 males and 86 female) were enrolled and 33% was in PGA remission. There is no significant difference in age and duration between 2 groups. SJC and TJC were significant lower in PGA remission group. STAI was significantly lower in PGA remission group ($p<0.03$). The patients with depression in CES-D and HADS-D were 24% and 17%, respectively, significantly higher in PGA remission group ($p=0.0129$ and $p=0.0083$, respectively). GSES was significant higher in PGA remission group ($p=0.049$). Sleep disturbance was found in 35 % of patients, however, there is no significant difference in 2 groups. Conclusions: The patients with PGA remission are significantly lower in state anxiety and depression, while higher in self-efficacy. This study provides that supports for psychological aspects in RA patients may be effective for improvement of PGA.

P1-292

Correlation of psychological state with sleep and disease activity in patients with rheumatoid arthritis

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Conflict of interest: None

Objective: To assess the correlation of depression with anxiety, self-efficacy, sleep disturbance and disease activity in patients with RA. Methods: The patients with RA were divided to depression group (CES-D>=16) and non-depression group (CES-D<16). Anxiety was assessed utilizing STAI and HADS-A, while self-efficacy with GSES, sleep disturbance with PSQI and disease activity with CDAI. These data were compared between two groups. Results: Ninety-nine patients (13 males and 86 female) were enrolled and 24% was in depression group. There is no significant difference in age, duration, SJC and TJC between two groups. STAI and HADS-A were significantly higher in depression group ($p<0.0001$ and $p=0.0009$, respectively). GSES was significant lower in depression group ($p=0.0007$). Sleep disturbance was found in 35 % of patients, significantly higher in depression group ($p<0.0001$). The proportion of patients with CDAI non-remission was higher in depression group ($p=0.02$) Conclusions: The patients with depression are significantly higher in anxiety, sleep disturbance and disease activity and lower in self-efficacy. These results suggest that supports for psychological state in RA patients may be effective for

improvement of anxiety, self-efficacy, sleep disturbance and disease activity.

P1-293

Correlation between patient global assessment and pain in patients with rheumatoid arthritis

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Conflict of interest: None

Objective: To assess the correlation between global assessments of patient and evaluator and disease activity. Methods: Patient global assessment (PGA) and evaluator global assessment (EGA) and swollen joint count (SJC), tender joint count (TJC) and patient pain (Pain) were assessed in patients with RA. General global assessment of the patients was also examined utilizing with Euro-QOL. The data were analyzed utilizing Spearman's rank correlation coefficient. Results: Ninety-nine patients (13 males and 86 female) were enrolled. Patient characteristics were as follows: average age: 55.1, duration: 11.4 years, PGA: 21.5mm, EGA: 15.9mm, Euro-PGA: 76.8mm, SJC: 2.4, TJC: 2.8, Pain: 21.2mm. PGA was correlated most strongly with pain(ρ=0.91) compared with SJC(ρ=0.46) or TJC(ρ=0.53). Similarly, Euro-QOL was also correlated with most strongly with pain (SJC, TJC, Pain:ρ=-0.35, -0.46, -0.73). On the contrary, EGA showed stronger correlation with SJC (ρ=0.76) and TJC (ρ=0.74) compared with pain (ρ=0.62). Conclusion: Pain gives a great influence on patient global assessment, while evaluator global assessment was influenced strongly by SJC or TJC rather than by pain. Further study for the quality of pain is required to improve patient global assessment.

P1-294

Study for complete implementation of T2T for all RA patients

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Conflict of interest: None

(Objectives) According to our survey for RA patients, it's suggested T2T has been realized for BIO patients, for others, T2T is inadequate. We examined establishing a system for all RA patients to receive T2T. (Method) After T2T workshops were given to healthcare workers, to further the study a survey was conducted; soliciting opinions on how to realize complete T2T implementation. Resultantly, we decided to make an RA patient handbook. (Result) Among 57 participants, 93% answered 'Yes' about patients knowing T2T, and if their prognosis would change. For full T2T implementation, 81% thought 'continued education of patients' is important, 'education for allied health professionals' (66%), 'clarifying goals for advanced RA patients' (59%), and 'making/distributing handbooks' (57%). In making of handbooks, we discussed 3 checklists; one for patient background and others for assessments done by patients and treatment goals decided with doctors. We suggest books have records for health checks, and considered hiring exclusive RA nurses. (Conclusion) Doctors can't spare time for counseling. Patients using biologics are well educated about T2T because they've had 1-to-1 counseling. In promoting T2T education, it's important to have 1-to-1 counseling and handbooks for all patients.

P2-001

Determinants of discrepancies between physician's and patient's global assessment of disease activity in rheumatoid arthritis-analysis based on NinJa 2011 database

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Conflict of interest: None

[Objectives] The discrepancies between RA patient's and physician's global assessment (GA) of disease activity may be a hindrance in clinical practice. The aim of the present study is to explore the determinants for this discrepancy based on NinJa 2011 database. [Methods] We analyzed 8733 RA patients whose pain VAS, physician's and patent's GA were available. Patient's GA - physician's GA was calculated as ΔGA, and ΔGA of $\geq$ 2.5 was grouped as positive discordance (n=1612), and ΔGA of -2.5 to 2.5 as no discordance (n=7018). [Results] Univariate analysis revealed the determinants for positive discordance as elderly, female, long disease duration, high disease activity (tender and swollen joint, pain VAS, CRP and DAS28), artificial joint, HAQ, stage and class, steroid and NSAID use, history of surgery and admission. Multivariate logistic regression analysis revealed that pain VAS and high mHAQ were associated with positive discordance. As for tender and swollen joint counts and CRP, the adjusted odds ratios were less than 1.0. [Conclusion] Pain and high mHAQ were considered to be important for worse estimation of disease activity by the patient than by the physician. The physicians should pay attention to the pain and ADL of their patients to share the recognition of disease activity.

P2-002

Epidemiological study of Methotrexate-associated lymphoproliferative disorder (MTX-LPD) with rheumatoid arthritis -Methotrexate use may increase the frequency of lymphoproliferative disorders in rheumatoid arthritis patients-

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Conflict of interest: None

[Objectives] Methotrexate (MTX) is used as an anchor drug for RA. Lymphoproliferative disorders (LPD) occasionally develop in patients treated with MTX, and are known as MTX-associated

LPD (MTX-LPD). We examined the clinical characteristics of MTX-LPD in RA patients and attempted to determine the risk factors for MTX-LPD development. [Methods] We enrolled RA patients from Kagawa, Japan. In age and gender matched patients, we separated patients who did not develop LPD under MTX treatment (MTX non-LPD group) from those that did (MTX-LPD group), and conducted a comparative examination. Additionally, we examined the clinical characteristics between the group with MTX withdrawal alone and chemotherapy in addition to the discontinuation of MTX. [Results] There were 28 MTX-LPD patients and 125 MTX non-LPD patients. The mean MTX dose was a risk factor for MTX-LPD. In addition, all patients who achieved an early complete remission (CR) in MTX withdrawal group had single extranodal lesions and a "very good risk" or "good risk" status according to Revised International Prognostic Index (R-IPI). [Conclusion] MTX is a risk factor for LPD onset in RA patients. Additionally, the patients with both a single extranodal lesion and a "good risk" status with the R-IPI might be achieved an early CR.

P2-003

Hospitalization and risk of hospitalized infection in patients with rheumatoid arthritis in our hospital

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Conflict of interest: None

[Objectives] We surveyed the hospitalization and the risk factors for hospitalized infection in RA patients. [Methods] Among Japanese RA patients in our hospital, hospitalized patients from April 2008 to September 2012 were extracted based on medical records. We calculated the incidence for each cause of hospitalization and statistically evaluated the background factors between patients who were hospitalized with infection or not. We also analyzed risk factors for hospitalized infection according to the multiple logistic regression model. [Results] Among total of 245 patients were confirmed. The causes of hospitalization were infection, orthopedic diseases, digestive diseases malignancy and circulating diseases. Patients with hospitalized infection were older and had higher disease activity, worse physical dysfunction, lower serum albumin and frequent use of corticosteroids. The risks for hospitalized infection were low serum albumin and corticosteroid use.

P2-004

Persistence rate of biologics In RA patients with pulmonary involvement

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Conflict of interest: None

[Objectives] The purpose of this study is to examine the persistence rate and adverse events of biologics in RA patients with pulmonary involvement. [Methods] From January 2003 through to September 2012, 92 RA patients treated with biologics in our hospital were studied retrospectively and the persistence rate and adverse events were compared between RA patients with and without pulmonary involvement. [Results] Various lung involvements were observed, including interstitial pneumonia, pulmonary fibrosis, chronic bronchitis, pulmonary emphysema, old tuberculosis, pulmonary cavitation, pulmonary nodule, atypical mycobacterial infection. The persistence rate and the dropout rates of biologics were not significantly different between those with and without pulmonary involvement (persistence rate: 60/68 [88.2%], 21/24 [87.5%], dropout rate: 4/68 [5.9%], 3/24 [1.3%], respectively.). In pulmonary involvement group persistently treated with biologics, Etanercept and Abatacept were frequently used (52.4% and 28.6%, respectively). [Conclusion] This study showed that RA patients with pulmonary involvement can be safely treated with biologics under careful observation.

P2-005

Trends in use of biological agents in patients with rheumatoid arthritis: An analysis based on AORA database

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Conflict of interest: None

[Objectives] This study aims at investigating the trends in use of biological agents in patients with rheumatoid arthritis (RA) in Akita prefecture in Japan. [Methods] Based on Akita Orthopedic Group on Rheumatoid Arthritis (AORA) database, we investigate the annual number of RA patients treated with biological agents, along with the continuation rate of each drug, and the switching patterns. [Results] There were 484 patients treated with biological agents (first time), and 459 assessable patients were enrolled. The subjects of the present study consisted of 73 men and 386 women, with a mean age of 58 years and a disease duration of 12 years. The annual numbers of the patients who started biological agents from 2005 to 2008 were 7, 24, 32, and 35, respectively. Since 2008, when four agents became available, the number increased to a peak of 126 patients in 2010, and thereafter slightly decreased. The continuation rates at 36 months were 55% for infliximab (IFX), 75% for etanercept (ETN), 70% for adalimumab (ADA), and 81% for tocilizumab (TCZ).The switching patterns were as follows: IFX (49 patients) was switched to ETN (25 patients) and TCZ (20 patients); ETN (17) to TCZ (7) and ADA (4); ADA (8) to golimumab (4) and ETN (2); and TCZ (3) to ETN (3).

P2-006

Comparison of the effects of Tramadol Hydrochloride/Acetaminophen on eGFR with those of diclofenac sodium in patients with rheumatic diseases

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Conflict of interest: None

[Objectives] Tramadol Hydrochloride/Acetaminophen(T) may be used without impairing renal function due to little COX-inhibitory effect. In this retrospective study, we compared the effects of T on eGFR with those of diclofenac sodium(D) in patients with rheumatic diseases. [Methods] Data from September 1st, 2011 to October 11th, 2012 were obtained from the inpatients and outpatients in our Department, to whom T or D was regularly prescribed. eGFR was calculated with the equation based on serum creatinine. ΔeGFR was obtained by subtracting eGFR before the prescription from that after the prescription. ΔeGFR/Mo (Mo:prescription period) in T was compared with that in D with Mann-Whitney U test.

[Results] In T, 29 female and 8 male cases (RA23 cases, SLE7 cases, others 7 cases), and In D, 48 female and 15 male cases (RA48 cases, SLE2 cases, others 13 cases) were obtained. ΔeGFR/Mo=1.19±6.86 (mL/min/1.73m^2/Mo) in all T cases were not significantly different from ΔeGFR/Mo=0.70±3.56 in all D cases (P=0.64). When only cases over 60 years of age were analyzed, ΔeGFR/Mo in T was lower than that of D (0.24±6.64 vs. 1.15±2.66, P=0.078), although the difference was not statistically significant. [Conclusion] T tends to affect the renal function less than D in the over 60-year-old cases.

P2-007

Cross sectional research on immunosuppressive therapy in 244 patients of systemic lupus erythematosus in Japan

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Conflict of interest: None

[Objectives] To determine actual state of current immunosuppressive therapy for patients with systemic lupus erythematosus (SLE) in Japan in 2012, where hydroxychloroquine, mofetil mycophenolate and belimumab are not ready to be prescribed. **[Methods]** All the outpatients and inpatients with SLE under treatment on April 1, 2012 at our department were studied. Clinical data including total SELENA-SLEDAI instrument score, glucocorticoid (GC) dose, immunosuppressive drugs and its dose were retrospectively collected from the medical records. **[Results]** We extracted SLE 244 patients: female 91%, age (mean±SD) 48.8±16.2 years old, duration of SLE (median) 10 [range 0-48] years, age of onset 36±15 years old, total score (median) 2 [0-16]. GC users were 209 patients (86%): average prednisolone equivalent 8.0±7.4 mg; <5 mg for 43, 5 mg in 49, <10 mg in 62, <15 mg in 39, <30mg in 11 and ≧30mg in 5 patients. Immunosuppressive drugs users were 90 patients (37%): azathioprine in 34, tacrolimus in 28, mizoribine in 24, methotrexate in 9, cyclosporine in 8 and intravenous cycrophosphamide in 3. **[Discussion]** Compared with patients with rheumatoid arthritis, greater dose of GC was used for SLE. We hope further development in treatment of SLE in Japan.

P2-008

An epidemiological survey of fibromyalgia in Japan via the Internet with the 2010 American College of Rheumatology (ACR) Preliminary Diagnostic Criteria for Fibromyalgia

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Conflict of interest: Yes

Objectives: We surveyed to determine the epidemiologic features and symptoms characteristics of Fibromyalgia (FM) in Japan, and compare them with those for chronic pain (CP). **Methods:** An Internet survey was conducted in 2011. The questionnaire consisted of assessments of the Japanese version of 2010 ACR diagnostic criteria for FM, the Japanese Fibromyalgia Impact Questionnaire (J-FIQ) and additional questions regarding pain. **Results:** The questionnaire was completed by 20,407 male and female subjects in Japan. Of the survey population, 2,524 (12.4%) subjects reported symptoms consistent with chronic pain; of these, 425 (2.1%) reported symptoms consistent with FM. There were differences in distribution and trigger of pain, symptoms and QOL between subjects meeting diagnostic criteria for FM and for CP. **Conclusions:** This Internet survey reveals the epidemiologic features and symptom characteristics of FM and CP in Japan in 2011. The incidence of presumed FM was similar to that reported (1.7%) in a study of FM in Japan conducted in 2003, despite the use of the newer, easier to use 2010 diagnostic criteria. These results also reinforce that FM and CP are clearly distinct disorders, and the main clinical differences include the distribution of pain and patient's functionality.

P2-009

Generation of stable human tolerogenic dendritic cells by protein kinase C inhibitors and their clinical application

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Conflict of interest: None

[Objectives] Dendritic cells (DCs) play an important role in induction of tolerance, Some compounds induce tolerogenic DCs (tDCs). In this study, we found that protein kinase C inhibitors (PKCI) generated highly stable tDCs and describe the characterization of PKCI-treated DCs (PKCI-tDCs). [Methods] PKCI-tDCs were generated by adding PKCI during maturation process of immature DCs. We analyzed the cell surface expression, cytokine production, phagocytic ability, and stability of PKCI-tDCs. We also examined allogenic T cell responses, and induction of Tr1 and Treg cells by PKCI-tDCs. [Results] The PKCI-tDCs showed significantly decreased levels of expression of CD40, CD80, CD83, CD86, and MHC class I, but not CD1a, CD11c, and MHC class II, in comparison with mDCs. They also showed CCR7 expression and phagocytic ability. Functionally, PKCI-tDCs produced high amount of IL-10 and TGF-β, and efficiently induced IL-10-producing T cells and functional Foxp3$^+$ regulatory T cells from naïve CD4$^+$ T cells, thus eliciting a strong immunosuppressive function. In addition, PKCI-tDCs were highly stable when exposed to inflammatory stimuli. The tolerogenic mechanism by PKCI was due to NF-kB inhibition and an increase of intracellular cAMP. PKCI-tDCs could be induced antigen specific Treg.

P2-010

Anti-inflammatory effects of lansoprazole on activated macrophages

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Conflict of interest: None

[Objectives] Activated macrophages in many inflammatory diseases produce inflammatory mediators such as nitric oxide (NO) and prostaglandin E_2 (PGE_2). Lansoprazole (LPZ) is a typical proton pump inhibitor used in clinical practice for treatment of gastrointesutinal mucosal disorders. The purpose of this study is to analyze the anti-inflammatory effects of LPZ on macrophages. [Methods] RAW264.7 cells were cultured and treated with several concentrations of LPZ. LPS was added to the culture medium. The amount of NO and PGE_2 was measured in the RAW264.7 cell cul-

ture supernatant. iNOS and COX-2 protein expression were analysed by Western blot analysis. [Results] LPZ inhibited LPS-induced production of NO in a concentration-dependent manner. In particular, LPZ inhibited NO production to the same extent as the control. PGE_2 levels in the culture supernatant increased, but with LPZ pretreatment, PGE_2 levels also decreased. Expression of iNOS and COX-2 was also inhibited by LPZ at a concentration of 100 μM. [Conclusion] Our study showed not only inhibition of NO and PGE_2 production in RAW 264.7 cells stimulated with LPS, but also suppression of iNOS and COX-2 expression. LPZ may be promising for use in many inflammatory diseases in which activated macrophages play a role.

P2-011

Functional analysis of sLOX-1 in Rheumatoid arthritis

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Conflict of interest: None

[Objectives] Previously, we reported that oxidized-LDL (ox-LDL) causes articular cartilage degradation, and LOX-1 (Lectin-like oxidized LDL receptor 1) is expressed in chondrocytes and fibroblasts. LOX-1 can be cleaved and released as soluble LOX-1 (sLOX-1). Then, we investigate that sLOX-1 are novel targets for the treatment of RA. [Methods] 1) We first examined the effects of sLOX-1 on the expression of MMPs in the presence of the sLOX-1 concentrated medium using RA fibroblast (FLSs) 2) We next examined the ability of sLOX-1 to inhibit the uptake of DiI-labeled ox-LDL in RA FLSs. 3) Mice were assigned to two groups, arthritis group: intraarticular injection of ox-LDL, treatment group: pretreatment of sLOX-1. And the histological change was investigated. [Results] 1) 2) sLOX-1 can block the uptake of ox-LDL and the production of MMPs in human RA FLSs in vitro. 3) Ox-LDL caused synovitis and proteoglycan loss compared with the controls. In contrast, pretreatment with the sLOX-1 prevented these arthritic changes. [Conclusion] These results indicate that sLOX-1 may compete with LOX-1 for the uptake of ox-LDL and neutralize inflammation to reduce joint destruction. Therefore, sLOX-1 may be a potent therapeutic target for RA.

P2-012

Suppression of PP2Ac causes DNA hypermethylation through enhanced pMEK/pERK activity in T cells

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Conflict of interest: Yes

[Objectives] Despite of the evidences of the impaired MEK/ERK pathway in SLE T cells which results in suppression of DNA methyltransferase (DNMTs) expression and induction of gene transcription of methylation-sensitive genes, the involved mechanisms are still unclear. Here we examined whether the catalytic subunit of protein phosphatase 2A (PP2Ac) which is overexpressed in SLE T cells contributes to inhibition of MEK-ERK signaling and DNA methylation. **[Methods]** Peripheral T cells from normal subjects were treated with the selective chemical inhibitor, okadaic acid (OA) or transfected with siPP2Ac to achieve sufficient suppression of the PP2Ac enzymatic activity. Samples were extracted after the stimulation with PMA and ionomycin, and phosphorylated ratio of MEK/ERK, the enzyme activity of DNMTs, the level of global DNA methylation status and the mRNA level of CD70 and CD11a were quantified. **[Results]** Both procedures of PP2A suppression resulted in sustained phosphorylation of MEK/ERK, increased enzymatic activity of DNMT as well as DNA hypermethylation and decreased expression of methylation-sensitive genes subsequently. **[Conclusion]** Increased PP2A in SLE T cells may cause DNA demethylation by promoting dephosphorylation of MEK/ERK pathway and contribute to lupus pathogenesis.

P2-013

Regulation of thrombospondin-1 (TSP-1) production in rheumatoid synovial tissues by transforming growth factor β1 (TGF-β1): Explanation of the appearance of serum immune complex containing TSP-1 in rheumatoid arthritis (RA)

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Conflict of interest: None

[Objectives] We have reported that serum immune complex containing thrombospondin-1 (TSP-1) is a novel biomarker in patients with rheumatoid arthritis (RA). Present study is to investigate the regulation of TSP-1 expression in RA synovial tissues and synovial cells. [Methods] Synovial tissues from patients with RA and osteoarthritis (OA) were obtained at the time of orthopedic surgery. Fibroblast like synovial cells (FLS) were isolated from the RA synovial tissues and used for in vitro experiments. Expression of TSP-1 in the synovial tissues was examined by avidin-biotin complex method. Isolated rheumatoid FLS were cultured in the presence of varying cytokines including transforming growth factor β1 (TGF-β1) and so on for indicated hours. After incubation, expression of TSP-1 was investigated by quantitative RT-PCR and ELISA, respectively. [Results] Expression of TSP-1 was prominent in the RA synovial tissues as compared with OA synovial tissues. Among cytokines examined, TGF-β1 was the most one to stimulate both mRNA expression and protein expression of TSP-1 from cultured rheumatoid FLS. [Conclusion] Overproduction of TSP-1 in RA synovial tissues is supposed to stimulate the synthesis of anti-TSP-1, leadineg to the appearance of serum immune comples containing TSP-1 in patients with RA.

P2-014

Analysis of a transcriptional complex on the core promoter of *SPACIA1* gene, which associated with synovitis

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Conflict of interest: None

[Objectives] Abnormal synovial proliferation is one of the major characteristics of rheumatoid arthritis (RA). However, the molecular mechanisms behind this process are still unclear. We identified a functionally unknown gene, named synoviocyte proliferation-associated in collagen induced arthritis 1 (*SPACIA1*). SPACIA1, when overexpressed, results in increased synovitis and worsened the disease in collagen-induced arthritis, a mouse model of RA. We previously reported a κB binding site-like sequence (κBLS) within the *SPACIA1* core promoter is crucial for the expression of *SPACIA1*. This study was undertaken to elucidate the precise mechanisms of transcriptional regulation via a core element of *SPACIA1* gene promoter. [Methods] To identify and analyze a transcriptional complex on the core promoter of *SPACIA1* gene, we biochemically isolated the complex to be detected by EMSA using the κBLS as probe, and identified the components using shotgun mass spectrometry. [Results] We identified *Pur-α/β* and several DNA binding proteins with lots of nuclear ribonucleoprotein. Other group reported that Pur-α and hnRNP K act together to regulate transcription. We have been analyzing the proteins functionally.

P2-015

The involvement of osteoclast differentiation by CCAAT/enhancer-binding protein be-ta (C/EBPβ)in of rheumatoid arthritis

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Conflict of interest: None

[Objectives] Bone destruction is one of major problems of RA. In this study, we examined whether C/EBPβ drives osteoclast formation using primary synovial fibroblast-like cells (SFs) from RA patients. [Methods](1) Isolated SFs from RA joints were transfected with adenovirus expression vector for C/EBPβ-LAP, -LIP or LacZ control. (2) Peripheral blood mononuclear cells (PBMC) were derived from peripheral blood of healthy donors. Isolated PBMC were cultured in medium containing 50ng/ml of M-CSF for 72hours. SFs transfected with adenovirus for 24hours were added to plate of PBMC and coculture for 72hours. After 3days of coculture, dishes were stained for TRAP. [Results] In cells transfected with adenovirus expression vector for C/EBPβ-LAP and -LIP, The mRNA expression of RANKL were significantly increased. Fluorescent staining showed that RANKL protein was localized in cell cytoplasm of SFs over-expressing C/EBPβ. The number of TRAP-positive multinucleated cells were markedly increased in coculture, especially induced in co-cultures of SFs over-expressing C/EBPβ-LIP and PBMCs. [Conclusion] We demonstrated that C/EBPβ is involved in osteoclast differentiation through the expression of RANKL in RASFs. These findings suggest that C/EBPβ plays crucial role in bone destruction.

P2-016

Hypoxia promotes the latter stage of mouse C2C12 myoblast differentiation and fusion, and suppresses its degradation

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Conflict of interest: None

[Objectives] It has been reported that muscle hypoxia exists in RA patients, suggesting correlation of hypoxia and sarcopenia. The purpose of this study is to examine the role of hypoxia in the latter stage of myogenesis and protein degradation. [Methods] Differentiation of murine myoblast C2C12 was induced under normoxia ($20\%O_2$) for 3 days. Then, cells were separated to normoxia or hypoxia ($5\%O_2$) and cultured for another 7days. [Results] Hypoxia significantly promoted protein expression of myosin heavy chain (MHC) and myogenin ($P<0.01$). In addition, fusion index ($P<0.001$) and the number of myogenin positive nuclei ($P<0.01$) were also increased. With regard to protein degradation, hypoxia suppressed FoxO3a transcriptional activity confirmed by luciferase reporter assay ($P<0.001$), and consequent *atrogin-1* mRNA expression and its protein expression ($P<0.01$). In addition, hypoxia upregulated protein expression of mouse odorant receptor 23 (mOR23) ($P<0.01$), which promotes myoblast fusion in myogeneis. [Conclusion] These results demonstrate that after myocytes initiate differentiation, hypoxia promotes the latter stage of myogenic differentiation and fusion, and downregulates protein degradation. These findings may bring new insights in treating sarcopenia of RA.

P2-017

Sec61 is indispensable for antigen cross-presentation and the development of lupus tissue injuries

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Conflict of interest: None

[Objectives] We found that over-stimulation of $CD8^+$ T cell *via* antigen cross-presentation generated cytotoxic T lymphocyte (CTL) to induce lupus tissue injuries. Here we examine the contribution of Sec61, which is known as a translocon, for antigen cross-presentation and lupus tissue injuries. **[Methods]** BALB/c mice were repeatedly immunized with ovalbumin (OVA) to induce tissue injuries. Dendritic cell (DC) isolated from spleen was cultured with fluorescence-labeled OVA, and endosomal marker EEA1, endoplasmic reticulum (ER) marker calnexin and Sec61 were detected by using immunofluorescent staining. Exotoxin A was co-immunized with OVA to inhibit Sec61. IFNγ-producing $CD8^+$ T cell and proteinuria were examined. **[Results]** OVA was co-localized with EEA1 and Sec61, however, OVA was not co-localized with calnexin. After repeated immunization with OVA, the amount of Sec61 localized in endosome was increased compared with control. Splenic IFNγ-producing $CD8^+$ T cell and preteinuria were increased, and thus lupus nephritis was provoked after repeated immunization with OVA. However, the treatment with exotoxin A, an inhibitor of Sec61, abolished the generation of CTL and development of lupus nephritis. **[Conclusion]** Sec61 is essential for the pathogenesis of lupus tissue injuries.

P2-018

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 secret-

ed mainly by adipocytes. Leptin decreases food intake, increasess 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] Immunological 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.

P2-019

Infection of *Mycoplasma fermentans* facilitates the onset of RA-like arthritis in the knock-in mouse with aberrant cytokine signaling

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Conflict of interest: None

[Objectives] Microorganisms have been thought as a critical environmental factor for the development of autoimmune disease. *Mycoplasma fermentans* (Mf) was reported to exist in the synovial fluid from rheumatoid arthritis (RA). However, causative roles for Mf in the pathophysiology of RA have not been clarified. A knock-in mouse gp130F759 having the gp130Y759F mutant spontaneously develops arthritis like RA at 8 months old (M.O.). Furthermore, over-expression of HTLV-1*pX* in gp130 facilitated the onset and progress of arthritis. In this study we examine the effects of Mf infection in the arthritis of gp130F759. [Methods] C57BL/6 and gp130F759 at 3 M.O. with no symptoms of arthritis were infected with Mf via vein. The clinical scores based on the restriction of joint flexibility (grade 0 ~ 4 /a limb) were determined from 1 month after infection. [Results] At 4 M.O., 5 out of 9 gp130F759 with Mf infection had 1 or higher sum scores of 4 limbs, whereas only 1 out of 8 gp130F759 without Mf infection had the similar score. At 5 M.O., all of gp130F759 with Mf infection showed the sum scores higher than 1. These data indicated that infection of Mf facilitates development of arthritis in gp130F759, being a useful arthritis model clarifying a role for Mf infection as an environmental factor.

P2-020

Differences in effect between IL-6 and TNF inhibitors in arthritis with obesity

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Conflict of interest: None

[Objectives] Although it has reported that RA patients with a high BMI responded less well to TNF inhibitor, the efficacy of IL-6 inhibitor is not fully evaluated obese RA patients. Here, we examined the effects of IL-6 and TNF inhibitors in arthritis with obesity. **[Methods]** To prepare a CIA model, normal (N) and high fat diet-induced obese (Ob) mice (relative body weight: 125%) were immunized intradermally with bovine type II collagen twice on Day 0 and 21. The arthritis score were evaluated by observation of joint swelling. Mice were intraperitoneally treated with 8 mg of anti-mouse IL-6R antibody (MR16-1) twice on Day 0 and 21 or 1 mg of TNFR-Fc three times a week from Day 0. IL-6 and TNF-α mRNA expression in hind limbs of mice immediately before primary immunization was measured by real-time PCR. **[Results]** MR16-1 and TNFR-Fc reduced the arthritis score on the peak in N-CIA at the same level. On the other hand, in Ob-CIA, although both drugs also reduced the arthritis score on the peak, the inhibitory effect of MR16-1 was significantly higher than that of TNFR-Fc. Furthermore, the expression levels of IL-6 correlated more highly with body weights than that of TNF-α. **[Conclusion]** We demonstrated that IL-6 inhibitor is more effective than TNF inhibitor in arthritis with obesity.

P2-021

miR-451 suppresses autoimmune arthritis via downregulating neutrophil chemotaxis

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Conflict of interest: None

[Objectives] The objective of this study was to identify the role of miR-451 in autoimmune arthritis and to examine the compensation of miR-451 could modulate the autoimmune arthritis. [Methods] We used SKG mice as an autoimmune arthritis model by injecting mannan. Double-strand miR-451 mixed with atelocollagen was administered to mice from tail vein. We evaluated neutrophil chemotaxis by air pouch model and under agarose assay. Phosphorylation of p38 mitogen-activated protein kinase (MAPK) was quantified with western blot, ELISA and flow cytometory. Arthritis score for SKG mice were measured in a time-dependent manner. [Results] The concentration of plasma miR-451 from mice with arthritis was significantly lower than that from control mice. miR-451 was expressed high in blood cell and miR-451 was released most abundantly by neutrophil. Chemotaxis of neutrophils from miR-451 overexpressed mice was significantly disturbed. We newly identified two targets of miR-451. miR-451 suppressed the phosphorylation of p38 MAPK via these targets. Arthritis scores were low in SKG mice with treatment of miR-451 compared with control mice. [Conclusion] miR-451 suppressed autoimmune arthritis via suppressing neutrophil chemotaxis and has a therapeutic potential for rheumatoid arthritis.

P2-022

Effect of suppression of IRF5 in the development of collagen-induced arthritis

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Conflict of interest: None

[Objectives] To evaluate the role of IRF5 and the effect of suppressing IRF5 in the development of collagen-induced arthritis (CIA). [Methods] CIA was induced in IRF5-deficient mice, and the severity was evaluated. Wild-type mice were treated with IRF5-specific siRNA during the progression phase of CIA. siRNA was

given by non-specific delivery using atelocollagen or antigen-presenting cell (APC)-specific delivery using schizophyllan. [Results] IRF5-knockout mice showed similar degree of arthritis, but IRF5 heterozygous mice showed reduced severity as compared to wild-type mice. Anti-collagen type II antibody levels were decreased in IRF5-knockout mice. These results suggest that IRF5 has dual effect, suppression and promotion, in the development of CIA. Treatment of mice with siRNA by non-specific delivery induced mild suppression of arthritis, but that by APC-specific delivery induced exacerbation of arthritis. [Conclusion] IRF5 has positive and negative effect in the development of CIA. Suppression of IRF5 in APCs induced exacerbation of arthritis.

P2-023

The influence of individual Th1/Th2 balance on the histological phenotype of lupus nephritis

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Conflict of interest: None

[Objectives] Diffuse proliferative lupus nephritis (DPLN) and membranous lupus nephritis (MLN) are representatives of these histological changes. Several reports suggested that DPLN is developed under Th1 immune responses. On the other hand Th2 immune responses contribute to develop MLN. Here we evaluated SLE model MRL/*lpr* mice being skewed their immune responses from Th1 dominant to Th2 dominant resulted in drastic changes in the pathological features of the glomerulonephritis from DPLN to MLN. [Methods] Histopathological and immunopathologiscal studies were performed in IL-27 R*α* deficient MRL/*lpr* mice, *Schistosoma mansonie* infected MRL/*lpr* mice and WT mice. Th1, Th2, Treg cytokines were measured in each samples. [Results] IL-27 R*α* deficient MRL/*lpr* mice skewed immune response to Th2 dominant compared with WT MRL/*lpr* mice. The kidneys in 24 week-old IL-27 R*a* deficient MRL/*lpr* developed MLN, not DPLN. MRL/*lpr* mice infected orally at the age of 8 weeks with *Schistosoma mansonie* skewed immune response to Th2 dominant compared with uninfected MRL/*lpr* mice. The kidneys in 32 week-old infected MRL/*lpr* developed MLN, not DPLN. [Conclusion] These data strongly support the hypothesis that alterations in the individual Th1/Th2 balance strongly influence the pathogenesis of lupus nephritis.

P2-024

Systemic osteoporosis in a mice model of glucose-6-phosphate isomerase (GPI)-induced arthritis is induced by not only increasing bone resorption but also suppressing bone formation

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Conflict of interest: None

[Objectives] We reported that GPI-induced arthritis induced a systemic bone loss and inhibition of interleukin-6 improved that bone loss. The bone-turnover in primary osteoporosis is reported to be elevated. However, it is not fully understood how arthritis affects the bone metabolism. We investigated bone metabolism in a GPI-induced arthritis model. [Methods] Arthritis was induced by the immunization of GPI (Day 0). Serum and urine were collected on Day 5 and Day 14 (peak of joint swelling). Urinary bone resorption markers (DPD) and serum bone formation markers (P1NP and osteocalcin) were measured by ELISA. [Results] DPD level in immunized mice was significantly elevated 1.26-fold on Day 5 compared with non-immunized mice and was maintained at high level on Day 14. On the other hand, P1NP and osteocalcin levels in immunized mice were significantly declined to 25.6% and 24.8% on Day 5. On Day 14, osteocalcin level was recovered to 83.0% of non-immunized mice, but P1NP was maintained at low level (52.5%). [Conclusion] We demonstrated that GPI-induced arthritis not only increased bone resorption but also suppressed bone formation. This suggested that mechanisms of osteoporosis in RA are different from primary osteoporosis.

P2-025

Pathological examination for the effects of high molecular weight hyaluronic acid and cross-linked hyaluronic acid 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 for experimental OA model. [Materials and Methods] Saline (control), Svenyl® (SVE) or Synvisc® (SYN) are injected to OA rabbit model every each 5th 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, safranin O staining, type II collagen, aggrecan, TUNEL, ki67, BC3 (antibody against fragment by aggrecanase) etc. [Results] In comparison with control group, stromal degeneratin such as type II collagen or aggrecan was inhibited by SVE, SYN, and apoptosis decreased in SVE and SYN. The loss of aggrecan started before type II collagen degeneration. By comparison of SVE and SYN, type II collagen degeneration was inhibited more in SVE than in SYN. In SVE, chondrocytic regeneration was performed. [Conclusion] The protective effect of HA was demonstrated histopathologically.

P2-026

Correlative analysis of handy rheumatoid activity score with 38 (HRAS38) and musculoskeletal ultrasound (MSKUS) for rheumatoid arthritis(RA)

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Conflict of interest: None

[Objectives] To elucidate the reliability between clinical assessment (HRAS38) and MSKUS. [Methods] One hundred and eighty RA patients were enrolled in this study (mean age: 62.8±14.4 years, mean DAS28-CRP: 3.06±1.43, female: 123 cases, male: 57 cases, respectively). Ten joints of the left hand (MCP 1-5 joints and PIP 1-5 joints) were validated both with HRAS38 (score 0-3) and MSKUS semi-quantitative grading. The MSKUS estimation was divided into gray scale (GS) (grade 0-3) and power Doppler examination (PD) (grade 0-3). The agreement between HRAS38 and MSKUS (GS and PD) was calculated using Cohen's Kappa values. [Results] The median Kappa Value for GS examination was 0.221 and for PD examination was 0.268, respectively.

The best results were found for GS in the PIP4 (Kappa =0.505) and for PD in the MCP3 (Kappa=0.420). The fair agreements were found. For the total joints which scored 0 for HRAS38, indicating no swollen joints, positive GS was observed in 35% of joints (387 joints/1107 joints) and PD was observed in 15.9% of joints (205 joints/1289 joints). [Conclusion] MSKUS is more significant in the assessment of RA, with swollen joints which were not revealed according to HRAS38 being revealed as active synovitis by MSKUS.

P2-027

Evaluation of progress and response to drug treatment in tarsal bones of RA

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Conflict of interest: None

[Objectives] To evaluate the progress and response to drug treatment of tarsal bones in RA patients and to compare them to those in toes and hands. [Methods] We investigated the 201 patients of RA (400 feet) in our hospital using X-ray films of hands and foot, which were taken twice at interval of one year. Degree of progress was evaluated in Larsen grade of tarsal bones and toes, and Sharp score of hands and feet. These data were compared between two groups with or without biologic treatment. The levels of disease activity (determined with SDAI) and of anti-CCP antibody were also examined. [Results] Progress in Sharp score of hands was significantly decreased in the biologic treatment group, the remission group, or the negative anti-CCP antibody group. Progress in Sharp score of feet was significantly decreased in the remission group. Progress in Larsen grade of toes was significantly decreased in the biologic treatment group. On the other hand, Larsen grade of tarsal bones progressed regardless of biologic treatment, low disease activity and the negative anti-CCP antibody. [Conclusion] These findings suggest that joint destruction in tarsal bones might progress independently of the response to treatment and the level of anti-CCP antibody.

P2-028

Power Doppler signal is frequently positive among patients with rheumatoid arthritis in clinical remission

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Conflict of interest: None

[Objectives] Ultrasound is useful tool for rheumatoid arthritis (RA). Power Doppler (PD) positive synovia might induce joint destruction. We report the prevalence of active synovia in the clinical remission patients with RA. [Methods] Musculoskeletal ultrasound tests were performed for 89 RA patients (76 females and 13 males) who were in clinical remission (DAS28-CRP<2.6). The patients underwent musculoskeletal ultrasonography at finger PIP, MCP joints, wrist and foot MTP joints (total 34 synovial sites). The GS and power PD signals were scored in each joint using a scale from 0 to 3. The PDUS positive ratio and the factor affected for PD signal in patients in remission were analyzed. [Results] They received conventional DMARD only (n = 42, 47.2%), or biological DMARDs (n = 47, 52.7%). The PDUS grade >1 was positive in 77 patients (86.5%). The PDUS grade >2 was positive in 35 patients (39.3%) and grade >3 was in 5 patients (5.6%). The levels of PDUS score using biological DMARDs were less than patients using only DMARDs. The factors affected total PD score were serum MMP-3 level and total GS score. [Conclusion] In this study, PD signal synovia remains frequently in clinical remission patients. This result indicates that joint destruction may develop even in clinical remission.

P2-029

Comparison of ultrasound findings and physical findings of the joint

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Conflict of interest: None

[Objectives] The use of validated composite measures of disease activity, which include joint assessments, is needed to guide treatment decisions. The primary target for treatment of RA should be a state of clinical remission. And clinical remission is defined as the absence of signs and symptoms of significant inflammatory disease activity. Last year, we showed that must be careful when interpreting the patient's global assessment. Because, patient's global assessment fluctuate for reasons not directly related to the activity of RA, such as anxiety and insomnia. This time, we compared the physical findings and ultrasound findings. [Methods] Performed on the 761 patients by JCR guidelines was evaluated by (0-3) semi-quantitative score for each signal synovial thickening and blood flow on both sides finger, hand, elbow, knee, a total of 26 joints. **[Results]**Concordance rate of physical and ultrasound findings are all PIP: 89.6%, all MCP: 82.7%, hand: 64.9%, elbow: 79.6%, knee: 69.6%. A significant correlation was found each DAS28-CRP, DAS28-ESR, SDAI, CDAI, MMP-3 and synovial thickening total score, total blood flow signal score. **[Conclusion]** We think there is need to make findings as to the US accurate grasp of disease activity of RA.

P2-030

Agreement between physicians, patients and joint ultrasonography to detect joint inflammation of finger joints in rheumatoid arthritis

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Conflict of interest: None

[Objective] Decision of swollen and tender joints are important to diagnose and assess rheumatoid arthritis (RA). This process is strongly influenced by physician's experience or patient's symptoms. Ultrasonography have potential to detect detailed joint information. Aim of this study was to investigate agreement between physicians, patients and joint ultrasonography to detect joint inflammation. [Methods] Fifty three patients with joint pain were enrolled to the study (44 female, 9 male). Patient's symptoms, physician's decision for swollen and tender joints were checked, then ultrasonography (gray scale and power Doppler) was performed. [Results] Thirteen patients were diagnosed as RA. Agreement between physicians, patients and joint ultrasonography were assessed. Counts of tender and swollen joints decided by physicians

were 14% (148/1060) and 7% (74/1060) respectively. As for patient's symptoms, tender and swollen were 25% (265/1060) and 13% (137/1060) respectively. Joints with grade 2 of semi-quantitative score and positive synovial vasucularity were 5% (53/1060) and 7% (74/1060) respectively. [Conclusion] Agreement between physicians, patients and joint ultrasonography showed low level. To detect joint inflammation, comprehensive estimation will be necessary.

P2-031

The musculoskeletal ultrasonography(MSUS) is useful examination during pregnancy and the postpartum in rheumatoid arthritis(RA) patients

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Conflict of interest: None

[Objectives] It is often observed that RA improves during pregnancy and flares postpartum. Practically clinical courses are variety according to patients. X-ray is not available during pregnancy, so we performed MSUS to evaluate RA during pregnancy and the postpartum. [Methods] Six RA patients who got pregnant between November 2011 and August 2012 were recruited at our hospital. Three patients had biologics, two had predonisolone (PSL) and one had no medications before pregnancy. The patients underwent clinical,laboratory and MSUS assessment at baseline and after 3,6,9 months and the postpartum. The Disease Activity Score in 28 joints(DAS28) was recorded at each visit. MSUS examination included intraarticular and periarticular sites in 22 joints of the hands. [Results] One patient had improvement of MSUS findings, but other one had no improvement and needed increased dose of PSL. [Conclusion] MSUS is useful examination for evaluating RA during pregnancy.

P2-032

Change of synovitis in finger joints under achieving low disease activity in rheumatoid arthritis

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Conflict of interest: None

[Objectives] To study change in synovial vascularity based on joint inflammation in rheumatoid arthritis (RA). [Methods] Thirty one patients with RA were initiated with biological agents (ADA, TCZ). All patients achieved clinically low disease activity. We observed abnormal synovial vascularity (SV) of finger joints (MCP and PIP) during 0 to 40th week. [Results] SV of finger joints in 4 patients were negative throughout the study. SV of finger joints in 6 patients decreased and showed negative within 8 weeks (responder joints). SV of finger joints in 9 patients persisted throughout the study (non-responder joints). SV of finger joints in 12 patients showed mixed with responder and non-responder joints. Non-responder joints showed significant joint damage progression. [Conclusion] These results indicated that joint damage progressed despite having clinical improvement. Our data might show further treatment to each of non-responder joint.

P2-033

Power Doppler twinkling artifact of joint ultrasonography observed in two rheumatoid arthritis patients with periarticular calcification induced by intra-articular corticosteroid injection

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Conflict of interest: None

As a rare complication associated with intra-articular corticosteroid injections, periarticular calcification is reported. There were two rheumatoid arthritis patients presented progressive periarticular calcifications treated with repeated triamcinolone acetonide injections. Joint ultrasonography revealed hyperechoic regions in the joint cavity with posterior power Doppler signals. The false-positive Doppler findings without a flow pattern behind calcifications were reported, and they were named as "twinkling artifact". Twinkling artifacts related to gallbladder stones and urinary stones have been reported. In our cases, spectral Doppler sonography was performed to evaluate the nature of PD signals, and an artifactual spectral signal without any definable flow pattern was observed. We concluded that the observed PD signals were power Doppler twinkling artifact. We need careful evaluation of artifact PD signals behind calcification so as not to mistake them for true PD signals and treat excessively. Spectral Doppler sonography is useful to make this distinction.

P2-034

A comparison of the evaluation by FDG-PET and the SJC/ TJC by a doctor in patients with rheumatoid arthritis

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Conflict of interest: None

[Objectives] In FDG-PET, the accumulation is shown in synovial membrane with patients with rheumatoid arthritis (RA) and FDG-PET can determine the grade of synovial inflammation by standardized uptake value (SUV). We evaluated the relationship between the FDG uptake and the evaluations by the doctor. [Methods] 498 joints of 21 RA patients (age 59.9±12.2 years old, disease period 11.1±10.0 year) were included in this study. All cases were treated with Tocilizumab (TCZ). The PET scan was carried out at baseline and 3and 6 months (M) after the medical treatment, then calculating the maximum of SUV of each joints. Simultaneously, the number of tender joint (TJC) and swollen joints (SJC) by a doctor was investigated. The cutoff value of SUV at the time of the existence of TJC or SJC was computed from the ROC curve. [Results] At the time of the 3M and 6M progress, total SUV of the joints was decreased significantly. There was no significant change with TJC. The SJC was also decreased at the time of 3M. The cutoff value of SUV was 1.58. The numbers of the joints which exceed this value were 147. [Conclusion] The SUV was reflected the effect of the treatment. SUV 1.58 became a cutoff value of the existence of the joint view by the doctor.

P2-035

Two cases of rheumatoid arthritis initially developed at Lisfranc joints

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Conflict of interest: None

Case 1: A 35-year-old woman started complaining right foot pain in 2010. She had a diagnosis of complex regional pain syndrome, because her X-ray showed only bone atrophy. In 2012, she was referred to our department because of polyarthralgia. Her X-ray showed narrowing of both Lisfranc joints. Blood test revealed elevation of CRP, RF and anti-CCP antibody (ACPA) levels. Joint ultrasonography (US) showed synovial thickening, bone erosion and positive signal of power doppler (PD). She had a diagnosis of RA and methotrexate (MTX) alleviated her symptoms. **Case 2:** A 49-year-old man started complaining both feet pain in December, 2011. He was referred to our department in April, 2012. Levels of CRP, RF and ACPA were not elevated. His X-ray showed narrowing of both Lisfranc joints, and joint US showed synovial thickening, bone erosion and positive signal of PD. He had a diagnosis of seronegative RA. After administration of MTX, his symptoms alleviated and joint US showed decreased of signal of PD. **Discussion:** Previous reports showed that the rates of initially involved joints in RA were 5.7-23% in ankle joints and 13-21% in metatarsophalangeal joints, but no study described tarsal joints. RA should be considered as a differential diagnosis, when tarsal joint arthritis was diagnosed.

P2-036

The effect of p53 mutant R248Q in RA-derived fibroblast-like synoviocyte against oxidative stress

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Conflict of interest: None

[Objectives] We studied the functional characteristics, especially oxidative-stress responses, of the p53R248Q mutant found in fibroblast-like synoviocytes (FLS) from RA that ectopically express AID (Activation Induced cytidine Deaminase), which is an indispensable gene for somatic hypermutation of immunoglobulin variable region in B lymphocyte. [Methods] By inverted-PCR using a cDNA of wild type p53 as a template, we prepared the p53R248Q mutant. After forced expression of p53R248Q mutant or wild type p53, as a control, in human FLS cell line MH7A, we examined the effects on proliferation, induction of p53-target genes (cell cycle-dependent kinase inhibitor p21, pro-apoptotic genes Bax, Noxa, Puma and p53AIP1) or cellular response to oxidative stress. [Results] The forced expression of p53R248Q did not affect the cell growth, but dramatically suppressed the expression of p53AIP1. Additionally, in the presence of representative genotoxic stress H_2O_2, p53R248Q failed to up-regulate p53AIP1, and showed the reduction of sub-G1 apoptotic cell fraction or annexin-V positive cell fraction in comparison with that of wild type p53. [Conclusion] Whether this anti-apoptotic effect of p53R248Q against oxidative stress is related to the suppression of p53AIP1 is now further investigated.

P2-037

The Sp1 transcription factor is essential for the expression of gliostatin/thymidine phosphorylase in rheumatoid fibroblast-like synoviocytes

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Conflict of interest: None

[Objectives] Gliostatin (GLS) has been reported to be related with the pathology of rheumatoid arthritis (RA). The human GLS gene promoter contains at least seven consensus binding sites for the DNA binding protein Sp1. We previously reported the effects of the Sp1 inhibitor mithramycin (MIT) on the productions of GLS mRNA and protein stimulated with tumour necrosis factor (TNF)-α in RA fibroblast-like synoviocytes (FLSs). Here we examined whether Sp1 is necessary for GLS production in RA from studies of the GLS promoter. [Methods] Intracellular signalling pathway activation was determined by a luciferase assay, a chromatin immunoprecipitation (ChIP) assay and a small interfering RNA (siRNA) transfection. [Results] The luciferase and ChIP assays showed that Sp1 binding sites in the GLS promoter were essential for GLS mRNA expression. MIT decreased GLS promoter activity in FLSs. GLS production was suppressed in FLSs by siRNA against Sp1 transfection. [Conclusion] Pretreatment of MIT and Sp1 silencing resulted in a significant suppression of GLS production in TNF-α-stimulated FLSs. GLS gene expression enhanced by TNF-α was partly mediated through Sp1. As physiological concentrations of MIT can regulate GLS production in RA, MIT is a promising candidate for anti-rheumatic therapy.

P2-038

Expression of ER-beta and VEGFR-1 in synovia from RA patients

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Conflict of interest: None

[Objectives] To assess the association between ER-beta and VEGFR-1 in rheumatic synovitis. [Methods] We collected wrist synivia samples from 41hands. Immunohistochemisty of ER-beta,VEGFR-1 and Ki-67 was performed. We caluculated synovial score on HE stain. [Results] There were significant correlation between ER-beta and synovial score, either ER-beta and Ki67. There were also significant correation between VEGR-1 and synovial score either Ki-67. However there were no correation between ER-beta and VEGFR-1. [Conclusion] Estrogen and VEGF had correlation with inflammatric activity, but it was not clear from this study whether estrogen stimulate rhumatic inflammation via VEGF associate-angiogenesis.

P2-039

Pleural effusion may be affected by adipokines in patients with rheumatoid arthritis

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Conflict of interest: None

[Objectives] The purpose of this study is to clarify the association of adipokines in pathogenesis of pleural effusions in patients with rheumatoid arthritis (RA). [Patients and Methods] Four patients with RA (3F) were studied. A patient with systemic lupus erythematosus (F) and a patient with systemic sclerosis (F) were also included as controls. Concentrations of resistin, leptin, high molecular weight (HMW) adiponectin, and chemerin in pleural effusion and serum (some cases) were determined by respective ELISA.

This study was approved by Ethics Committee of our University Hospital. [Results] Mean±SD concentration of adipokines in the pleural effusion of RA patients were as follows: resistin,15.6±0.4 ng/ml; leptin, 28.7±26.0 ng/ml; HMW adiponectin, 9.5±2.6 μg/ml; and chemerin, 0.53±0.40 ng/ml.Both of resistin and leptin were increased when compared to those in the serum. In contrast, pleural effusion levels of HMW adiponectin and chemerin were decreased when compare with those in the serum. [Conclusion] High concentrations of resistin and leptin in the pleural effusion may play an important role in pathogenesis of pleuritis in patients with RA.

P2-040

TNFα inhibit the expression of circadian clock gene, *Per2*, via D-box in rheumatoid arthritis fibroblast-like 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 *Cry* deficient mice was significantly aggravated experimental arthritis, and TNFα inhibited the mRNA expression of *Per2* in primary cultured RA-FLS. In this study, we examined 1) whether or not TNFα inhibit the expression of *Per2* via D-box motif, and 2) the effect of TNFα on the expression of D-box binding protein, *Dbp*, *Hlf*, *Tef* and *E4BP4*; a transcriptional activator and repressor of *Per2* gene, respectively. [Methods] We constructed the luciferase vector containing wild type and D-box mutated *Per2* promoter, and then transfected RA-FLS with these vectors. After overnight culture, cells were stimulated with TNFα, and promoter activity of *Per2* gene was examined using the luciferase assay. Expression of *Dbp*, *Hlf*, *Tef* and *E4bp4* in TNFα stimulated RA-FLS was determined by qPCR. [Results] TNFα inhibited the transcriptional activity of the wild type *Per2* promoter, but did not inhibit those of the D-box mutated promoter ($P<0.05$). Further, TNFα inhibited mRNA expression of *Dbp*, *Hlf* and *Tef*, whereas enhanced those of *E4bp4* ($P<0.05$). [Conclusion] TNFα modulates the expression of *Per2* gene via Dbp, Hlf, Tef and E4bp4, in RA-FLS.

P2-041

Regulatory and pro-inflammatory properties of CD4+ T-cell subsets defined by CD45RA, CCR7, CD27, and CD28 in patients with rheumatoid arthritis

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Conflict of interest: None

[Objective] CD4+ T cells can be classified as either naïve, central memory (T_{CM}), or effector memory (T_{EM}) cells. To identify the CD4+ 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]** CD4+ T cells isolated from peripheral blood or synovial fluid from RA patients were classified into different subsets by CD45RA, CCR7, CD27, and CD28. The frequency of cytokine-producing cells, and of Foxp3- or RANKL-positive cells was analyzed by FACS. **[Results]** We classified CD4+ T cells into six novel subsets by four cell surface markers. The CD27+CD28+T_{CM} subset comprised a significantly smaller proportion of CD4+ T cells in RA compared to healthy controls, and within this subset, the proportion of Foxp3-positive cells was lower. In contrast, the proportion of IL-17- and TNF-α-producing cells in the CD27+CD28+ T_{EM} subset was significantly increased in RA. The percentage of cytokine-producing cells was higher in the CD27-CD28+T_{CM} and CD27-CD28+T_{EM} subsets of the synovial T cells. **[Conclusion]** The number and/or proportion of inflammatory cytokine- or Foxp3-positive cells of particular CD4+ T cells subsets is significantly changed in RA.

P2-042

Expression of IL-17, IFN-γ and TNF-α in RA synovial tissues and their role in regulation of joint destruction

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Conflict of interest: None

[Objectives] It is thought that Th1 and IFN-γ, TNF-α, and recently Th17 and IL-17 play pivotal roles in RA. The aim of this study was to investigate expression of IL-17, IFN-γ and TNF-α in RA synovial tissues and their role in regulation of joint destruction. [Methods] Synovial tissues from 20 joints in 20 RA patients were used in this study. Real-time PCR was performed using specific primers for IL-17, IFN-γ and TNF-α. Fibroblast-like synoviocytes (FLS) were stimulated with these inflammatory cytokines, and concentration of MMP3 in the culture medium was measured by ELISA. [Results] PCR results showed IL-17 was expressed in half of the patients, while IFN-γ and TNF-α were expressed in most of the patients. Interestingly, in patients with abnormally high levels of IL-17, TNF-α was not expressed. MMP3 production from FLS was not changed by IL-17 alone but increased by costimulation of IL-17 and IFN-γ. Also, it was increased by TNF-α alone but reduced by adding IFN-γ. [Conclusion] Costimulation of IL-17 and IFN-γ increased MMP3 production in FLS, suggesting joint destruction may progress by slight increase in IL-17 and IFN-γ following Th1 activation. Further studies are necessary, but these results suggest a usefulness of IL-17-targetting therapy in regulation of joint destruction.

P2-043

Human synovial mast cells are activated by substance P via MrgX2 and they produce substance P following FcRγ-mediated stimulation

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Conflict of interest: None

[Objectives] Substance P (SP) level in synovial fluids from patients with rheumatoid arthritis (RA) is reportedly higher than that from osteoarthritis (OA) patients. SP is believed to be involved in the pathogenesis of RA. The aims of this study are to identify SP receptor(s) on synovial MCs (syMCs), and to identify SP produc-

ing cells in synovium of RA patients. [Methods] Cultured syMCs were generated by the culture of enzymatically dispersed synovial cells obtained from RA and OA patients in the presence of stem cell factor. MrgX2 expression was analyzed by FACS and immunohistochemistry. MrgX2 expression was reduced using a lentiviral shRNA silencing technique. Mediators were measured by ELISAs. [Results] Histamine was released from cultured syMCs in response to SP, but it was not inhibited by treatment of NK-1R antagonist. Expression of IL-6, IL-8 and osteopontin mRNA was upregulated by SP. MrgX2 expression in syMCs in synovium was confirmed. Diminution of MrgX2 expression in syMCs resulted in downregulation of SP-mediated histamine release and PGD_2 production. Cultured syMCs produced SP following FcRγ-mediated stimulation. [Conclusion] Our findings suggest that the vicious circle triggered by SP autocrine stimulation of syMCs may induce the aggravation of inflammation in RA.

P2-044

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) and that the concentration of DcR3 in RA was significantly higher than in osteoarthritis (OA). Further, by using comprehensive genetic analysis using microarrays, we newly identified TPH1 as one of the genes of which expression in RA-FLS was suppressed by DcR3. In this study, we investigated the expression of TPH1 in RA and OA-FLS stimulated with DcR3. [Methods] After RA or OA-FLS were incubated with DcR3 for 12h, 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. Serotonin expression in RA-FLS was confirmed. [Conclusion] In this study, we first revealed that TPH1 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 and bone remodeling.

P2-045

Detection of a soluble form of folate receptor-beta in rheumatoid arthritis under anti-TNF therapy

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Conflict of interest: None

[Objectives] Anti-TNF therapy suppresses the activity of rheumatoid arthritis (RA) by reducing the number of synovial infiltrating macrophages. Folate receptor-beta (FRβ) is highly expressed in RA synovial infiltrating macrophages but largely absent in monocytes/resident macrophages. Soluble FRβ released from synovial sublining macropahges may affect the total activity of synovial sublining macropahges. The aim was to investigate whether soluble FRβ in serum is a disease activity marker of RA. [Methods] We developed ELISA system for detecting soluble FRβ by using $F(ab')_2$ anti-human FRβ antibodies. We measured the soluble FRβ in sera and synovial fluids from RA patients. Five anti-TNF treated RA patients were also analyzed before and after 4 weeks of treatment. Results were compared to Clinical Disease Activity Index (CDAI) and Simple Disease Activity Index (SDAI). [Results] The values of soluble FRβ in sera were significantly lower as compared with synovial fluids. No significant correlations were shown between soluble FRβ levels and clinical indexes. Moreover, soluble FRβ levels were similar between responder and non-responder during 4 weeks follow up. [Conclusion] Short time anti-TNF therapy did not change soluble FRβ and longer treatments are needs to assess this issue further.

P2-046

Decresed matrix metalloprotease production from rheumatoid synovial cells after adipogenesis

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Conflict of interest: None

[Objectives] The production of interleukin-6 is inhibited in fibroblast-like synovial cell (FLS) after adipogenesis induction, which may lead to the amelioratioin of synovitis in rheumatoid arhtritis (RA). In this study, we examined the effect of adipogenesis on production of Matrix Metalloproteinases (MMPs) in FLS. [Methods] hMSC Differentiation BulletKit, Adipogenic (Lonza) was used to induce adipogenesis of FLS. Total RNA was extracted from FLS with or without adipogenesis to examine the transcript profile. The amount of MMP-1, MMP-2 and MMP-3 in the culture medium were detrmined by ELISA. [Results] The expression levels of MMP-1 and MMP-2 mRNA in FLS after adipogenesis were lower compared to FLS without adipogenesis. The concentrations of MMP1 and MMP-2 in the supernatant of FLS after adipogenesis were lower than that of FLS without adipogenesis. [Conclusion] Our results suggest that the productions of MMP-1 and MMP-2 can be inhibited in FLS by adipogenesis of the cell. The MMP-3 productiuon from FLS was not clearly inhibited by adipogenesis, which is different from our previous report that adipogenesis of FLS by using PPARγ ligand efficiently suppress MMP-3 secression. It is importnat to select an apporopriate method to induce FLS adipogensis in treating RA.

P2-047

Synivial fluid from patients with rheumatoid arthritis enhances superoxide genaration by polymorphonuclear leukocytes

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Conflict of interest: None

Objective. To elucidate a role of polymorphonuclear leukocytes (PMNs) in the joint destruction of rheumatoid arthritis (RA) through superoxide generation. ***Methods***. Superoxide generation

by human peripheral PMNs was measured with a water-soluble formazan dye, 2-(4-iodophenyl)-3-(4-nitrophenyl)-5-(2, 4-disulfophenyl)-2H-tetrazolium, monosodium salt under stimulation of PMNs with *N*-formylmethionyl-leucyl-phenylalanine and cytochalasin B. Characterization of a factor(s) in synovial fluids from RA patients was carried out with gel permeation of high performance liquid chromatography and isoelectric focusing. ***Results***. The formazan dye was applicable for measurement of superoxide in the presence of an intermediate electron transporter, phenazine methosulfate. A chemical factor which augumented superoxide production by PMNs was present in RA synovial fluid. This factor is a basic protein-like nature with an apparent molecular size and an isoelectric point, 70,000 Da and 8.3, respectively. The augumenting activity of the factor was absorbed by newly prepared PMNs. ***Conclusion***. It was suggested that a protein-nature substance in RA synovial fluid augmented superoxide generation by PMNs, which would show one of important pathologic roles in the joint destruction of RA employed by PMNs.

P2-048

Plasma chemerin levels in rheumatoid arthritis are correlated with disease activity rather than obesity

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Conflict of interest: None

[Objectives] To investigate whether plasma chemerin level is elevated in patients with RA and whether its level is correlated with disease activity. [Methods] This study included 71 RA patients and 42 age- and sex- matched healthy controls. We assessed the clinical characteristics and laboratory parameters including BMI, ESR, CRP, and DAS28. Plasma levels of chemerin and TNF-α were measured by ELISA. [Results] Plasma chemerin levels were significantly elevated in patients with RA compared with healthy controls (9.074 ± 13.513 ng/mL vs 0.370 ± 0.219 ng/mL, $p < 0.001$). In RA patients, adjusted plasma chemerin levels according to BMI were significantly higher in the active group (DAS28 ≥ 2.6) than in the inactive group (DAS28 < 2.6) (0.591 ± 0.879 ng/mL/Kg/m^2 vs 0.220 ± 0.154 ng/mL/Kg/m^2, $p = 0.015$). Plasma chemerin levels adjusted to BMI were correlated with DAS28 ($\gamma = 0.340$, $p = 0.004$), but not with plasma TNF-α levels. [Conclusion] Patients with RA showed higher plasma chemerin levels than those of healthy controls. Adjusted plasma chemerin levels according to BMI were well correlated with RA disease activity. These findings suggest that plasma chemerin could play a role in the inflammatory process of RA rather than obesity, and that it may be a useful disease activity marker for RA.

P2-049

Alternation of glycans on glycoproteins in rheumatoid arthritis

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Conflict of interest: None

[Objectives] In rheumatoid arthritis (RA), galactose-deficient immunoglobulin G (IgG) is significantly increased than in the normal and autoantibodies against the galactose-deficient IgG have been detected. However, it is unclear whether the alteration of glycans is a common to multiple proteins or specific for IgG in RA. Here, we make surveillance of glycoproteins with altered glycans in RA. [Methods] Peripheral blood mononuclear cells (PBMCs) were collected from healthy donors and RA patients. Proteins of PBMCs were separated by two-dimensional gel electrophoresis. Then, all proteins and glycoproteins were detected by Sypro Ruby® and ConA, respectively. Glycosylation levels were calculated from the intensities on each spot and compared between the RA and healthy groups. The proteins with altered glycans in the RA group were detected. [Results] In total, 529 protein spots with *N*-glycans were detected. We found that glycosylation levels of 11 protein spots were significantly different between the RA and healthy groups ($p<0.05$). Some of these proteins spots have been identified and autoantibodies against the identified protein have been detected in RA patients. [Conclusion] There is a possibility that unusual glycosylation of these proteins may be involved in the pathogenesis of RA.

P2-050

Risk factors for the prognosis in 167 early RA(ten to twenty years follow up)—rheumatoid factor (RAPA) and large joint destruction (NLJS12)—

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Conflict of interest: None

[Objectives] In patients with early RA the high titer of rheumatoid factor was thought to be a risk factor for the prognosis. And the large joint destruction at early stage was also an important risk factor. So we investigated RAPA and the neck large joint score 12 (NLJS 12) in 167 cases with early RA in relation to the RA activities. [Methods] 167 patients with early RA visited to our hospital within one year from onset in 1985 to 2000. Concerning the titers of RAPA three groups were 51 cases in group A (RAPA negative), 94 in group B (RAPA 40-320-fold) and 22 in group C (RAPA more than 640- fold). Concerning the large joint destruction at five years, three groups were 109 cases in G-1 (NLJ Score 12=12), 24 in G-2 (NLJ Score 12=11) and 34 in group P (NLJ Score 12=less than 10).Methods; RAPA, NLJ Score 12, ESR, CRP, DAS28 and numbers of DMARDs were evaluated. [Results] Regarding CRP in group A, B and C at ten years, the value of CRP in GA was 0.7±0.8, 1.4 in GB and 2.3±2.3mg/dl in GC. In the DAS 28 in group A, B and C at ten years, the value of DAS 28 in GA was 3.4±1.3, 4.1±1.2 in GB and 4.6±1.1 in GC. [Conclusion] The high titer of rheumatoid factor (RAPA) at the first examination and more than two destructed large joints (NLJ12) at five years led to the poor results for prognosis.

P2-051

The background factor of the patient with rheumatoid arthritis which RF has improved by treatment

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Conflict of interest: None

[Objectives] A rheumatoid factor (RF) is few correlation with a

disease activity. We investigate that the change of RF and its factor in patient who have RF positivity at first visit and reach to clinical remission or low disease activity with treatment in our institution. [Methods] IIn 42 cases with RF positivity, 30 cases reached to clinical remission or low disease activity with DAS28CRP4 at the last observation. We define 18 cases which RF had reduced by half or less at the time of the last observation as D group, 12 cases which RF did not result in a reduction by half or increase as N group. [Results] There is no significance with the dose of MTX and Predonisolon and the usage rate of biological agents between D group and N group. From first visit to the last observation, DAS-28CRP of D group has improved from 4.13 to 1.72, and N group has improved from 3.04 to 2.17. RF was 113.1 to 19.6 (55.6% is negativity) in D group and 76.0 to 93.95 in N group. At the time of the last observation, DAS28CRP of D group was significantly lower than that of N group. [Conclusion] It is difficult to predict the improvement of RF from patient's background before treatment. The group which RF has improved is significantly lower its disease activity than the group which RF has not improved.

P2-052

Change of Health Assessment Questionnaire Disability Index is affected by inflammatory process in patients with rheumatoid arthritis

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Conflict of interest: None

[Objectives] To clarify the factors that influence Health Assessment Questionnaire Disability Index (HAQ-DI) in patients with rheumatoid arthritis (RA). [Methods] Five hundred sixty-seven patients with RA (442 F, mean±SD 58.1±14.2 y.o.) who were observed for at least a year were included in this retrospective study. We examined the relationship among changes of HAQ-DI during a year (Δ1HAQ-DI) and other clinical measures. The study protocol was approved by Ethics Committee. [Results] Mean change of HAQ-DI was improved from 0.52 to 0.46 during a year. On the other hand, mean change of DAS28-ESR was also improved from 3.57 to 3.01. There was positive correlation between Δ1HAQ-DI and Δ1DAS ($p < 0.001$). Mean Δ1HAQ-DI/Δ1DAS ratio was 0.10. It was corresponded to the assumption that 1.0 improvement of DAS 28-ESR meant 0.1 improvement of HAQ-DI. Contributing factors to Δ1HAQ-DI were investigated using multivariate analysis. Steinbrocker stage score at baseline, age, and Δ1DAS were positively associated with Δ1HAQ-DI. On the other hand, gender and rheumatoid factor were not significantly associated with Δ1HAQ-DI. [Conclusion] The change of HAQ-DI was strongly affected by inflammatory process in RA, assuming that 1.0 improvement of DAS 28-ESR meant 0.1 improvement of HAQ-DI.

P2-053

Study of Rheumatoid Arthritis in Patients with Knee Arthritis (second report)

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Conflict of interest: None

[Objectives] To clarify whether patients with knee arthritis develop RA. [Methods] This is prospective study in Yamanote do-ri Yagi Hospital, Sapporo, Japan. We enrolled 24 cases with knee arthritis, whose knee joint synovial tissues are chronic hyperplastic synovitis, from April/2009 to April/2012. We investigated whether these are diagnosed with Rheumatoid arthritis after 1 year. [Results] 11 cases were diagnosed with rheumatoid arthritis.These are 1 male and 10 females, a mean age of 70.2 year and each positive rate of rheumatoid factors,the anti-CCP antibody, CRP are 45.5%, 60%, 90.9%. [Conclusion] It is suggested that pathological examination of synovial tissues of knee joints is useful for the diagnosis of Rheumatoid Arthritis with knee arthritis.

P2-054

Study of rapid radiographic progression during biological therapy (2nd report) -Analysis by MRI-

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Conflict of interest: None

[Objective] To identify MRI prognostic factors of rapid radiographic progression (RRP) with joint destruction observed during treatment of any biologics. [Methods] Twenty eight RA patients, who were treated with adalimumab (ADA) and methotrexate (MTX) combination therapy for 1 year, were examined by Sharp-van der Heijde scoring (SHS) and compact MRI for both hands using cMRI score (cMRIS) in low field MRI(0.3T) at baseline and 1 year after treatment (final observation). [Results] Patient demographic data (mean) were as follows: age, 60.1 years; disease duration, 6.7 years; DAS28 –ESR, 6.25; MTX dose, 7.6 mg (89.3%); and BIO naïve, 100%. ⊿SHS and ⊿DAS28 in RRP(SHS/y≧3, n=6) was significantly higher than non RRP (SHS/y<3,n=22,) ($p<0.001$ and $p<0.05$, respectively). In comparison of cMRI findings between RRP and non-RRP RA patients at baseline and final observation, bone oedema in RRP compared with non RA trend to be higher ($p=0.053$) at baseline and was significantly higher($p=0.001$) at final observation. RRP has occurred to the patients not improving bone edema with therapy. In tocilizumub (TCZ), same tendency has been observed. [Conclusion] Bone edema in MRI is prognostic and risk factor for RRP durling biological therapy.

P2-055

A retrospective study of the progression of upper cervical spine lesion with Rheumatoid Arthritis

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Conflict of interest: None

【Purpose】This study investigated retrospectively the risk factor of the progressive instability of upper cervical spinal disorder. 【Material and methods】Thirty rheumatoid arthritis patients (all females, mean age; 68.8 years old, and mean follow-up period; 7.9 years) were assessed for the radiographic instability of the upper cervical spine on X-ray for more than 2-year follow-up. Patients were divided two group: Group I (n=13, progression) and Group II (n=17, non progression) and investigated routine examinations which were CRP, MMP3, ESR, anti-CCP antibody and Larsen grade.【Results】Progressive instability of cercical spine were atlantoaxial subluxation (AAS); 6 cases, vertical subluxation (VS); 7 cases. No significant differences were obsorbed between the two groups with respect to these routine examinations【Conclusion】Routine examinations did not prognose the progression of upper cervical spine. Dynamic radiographic assessment of the cervical spine is necessary to understand respect to the progressive instabil-

ity of upper cervical spinal disorder.

P2-056

Magnetic resonance imaging-proven osteitis at baseline predicts the early rheumatoid arthritis patients who will develop rapid radiographic progression: MRI is beneficial to find the window of opportunity in early RA

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Conflict of interest: None

Objectives: To investigate whether MRI assessment of joint injury, especially osteitis, at baseline predict the development of RRP at 2 years in patients with early RA by Nagasaki Early Arthritis Cohort. Methods: One hundred-eleven early-stage RA patients, DMARDs being introduced within a first year, were consecutively enrolled from Nagasaki Early Arthritis Cohort. All of the subjects had been examined by Gd-DTPA-enhanced MRI and plain radiograph of both wrist and finger joints at the same day every 6 months during 2 years. RRP was defined as yearly progression of Genant-modified Sharp score >3.0 during 2 years. We have examined what variables predict the development of RRP at 2 years by logistic regression analysis (SAS version 9.2). Results: The mean disease duration was 4 months at entry. Twenty patients (18.0%) were classified as RRP at 2 years. Logistic regression analysis has shown that MRI osteitis at baseline is an independent variable to predict the development of RRP at 2 years (Odds ratio = 3.88). Conclusions: Our present data indicate that MRI-proven osteitis at baseline is a predictor toward the development of RRP in patients with early RA. MRI is beneficial to find the window of opportunity in these patients, who are required to be treated early.

P2-057

The new evaluation method of lower extremities function with supportive action for rheumatoid arthritis

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Conflict of interest: None

[Objectives] HAQ is generally used as an evaluation of ADL in a RA patient. Because each question is only four steps answer, it is difficult to understand a detail of disability. Additionally supportive action may change a difficulty against ADL. We make an original questionnaire about supportive action and evaluate its questionnaire. [Methods] 65 cases with RA answered our questionnaire and HAQ and were evaluated by DAS28CRP4. In 65 cases 33 cases who have no difficulty about HAQ were contained in this study. [Results] In 33 cases who answered no difficulty about HAQ, 23 cases (N group) also answered no difficulty about our original questionnaire. 10 cases (D group) complained some difficulty about our original questionnaire. The average of DAS28CRP4 was 1.74 (D group) and 1.99 (N group). There is no significant difference with DAS28CRP4 of both groups (p= 0.32). The average of patient gloval VAS is 16.1 and 28.0, respectively. There is no significance of patient gloval VAS between D and N group. The Boolean remission rate was 30.0% (D group) and 56.5% (N group). [Conclusion] We tried to express a difficulty about ADL which cannot be confirmed by neither DAS nor HAQ. Although the difference was not observed in patient global VAS, the value of VAS affected the Boolean remission rate.

P2-058

The impact of sustained clinical remission on radiological and functional remission in rheumatoid arthritis: KURAMA cohort study

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Conflict of interest: Yes

[Objectives] The sustained maintenance of clinical remission in rheumatoid arthritis may result in radiological and functional remission. We assessed an influence of clinical remission maintain rate on joint damage and functional disability in KURAMA cohort. [Methods] We chose the 200 of consecutive RA patients, both with more than 6 months and with more than three visits during follow-up, in our observational cohort, and assessed swollen joint count, tender joint count, CRP, ESR, patient global health assessment, physician global health assessment, disease activity, health assessment questionnaire, and modified total sharp score. [Results] Patients age 62.3±13.0 years, duration of RA 12.9±11.3 years, stage1+2:3+4=47.0%:53.0%, class1+2:3+4=79.5%:20.5%, Administration of Methotrexate 70.5%, Glucocorticoids 41.5%, Biologics 34.5%, follow-up periods 276.7±73.6 days, number of visits 6.1±1.7 times. Clinical remission maintain rate was 38.9±38.8% for DAS28, 23.7±31.8% for CDAI, and 25.7±33.3% for SDAI. Clinical remission maintain rate was higher with biologics than without. [Conclusion] Our results showed that the maintenance of clinical remission is important to radiological and functional remission.

P2-059

The differenciation between RAPID3 and SDAI in patients with rheumatoid arthritis treated with tocilizumab

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Conflict of interest: None

[Objectives] To compare the assessment of patient index data(RAPID3) and SDAI in patients with rheumatoid arthritis treated by tocilizumab [Methods] We evaluated RAPID3 and SDAI in RA treated by tocilizumab, in baseline, month 1, 3, and 6. [Results] 36 patients were recruited. SDAI and RAPID3 were correlated.($R=0.58$, $p<0.05$) [Conclusion] We need further more study that correlation with Sharp scre.

P2-060

Change of patient global assessment of disease activity by question method

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Conflict of interest: Yes

[Objectives] For good control of RA patients, composite measure of patients disease activity is necessary. In patient global assessment of disease activity (PtGA), existence of individual difference is also suggested, and how to ask is important for suitable evaluation. [Methods] The questionnaires about patient global health, condition of RA, condition of RA joints disease and pain were enforced to 140 RA patients. Count of swollen joints, Tender Joints, CRP and doctor global assessment of disease activity were examined. Anxiety and depression measurement by Hospital Anxiety and Depression Scale (HAD), and the patient's condition-of-life investigation were performed. [Results] In 26 patients only GH-VAS was getting worse 20 mm or more from other VAS scales and the change by the question method was large. Although this patient group did not have the difference in CRP, there were many tender joints and depression mark were intentionally high in HAD scale. [Conclusion] PtGA is under the influence of depression tendency and standardization of how to ask may be necessary to appropriate assessment of RA activity.

P2-061

Maintenance rates of clinical remission for five biologics

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Conflict of interest: None

Objectives: To compare maintenance rates of clinical remission for five biologics in clinical practice.Methods: Patients with RA started the following biologics at our hospital through October 2011: infliximab (IFX, n=54), etanercept (ETN, 40), tocilizumab (TCZ, 40), adalimumab (ADA, 20) and abatacept (ABT, 26). The maintenance rates of clinical remission over time were compared for patients who achieved clinical remission, evaluated by DAS28-ESR and SDAI.Results: Clinical remission by DAS28-ESR was achieved by 28 (51.9%) patients on IFX, 15 (37.5%) on ETN, 34 (85%) on TCZ, six (30%) on ADA and six (23.1%) on ABT. Over time, the maintenance rate of clinical remission was highest for TCZ, followed by IFX, ADA, ETN and ABT. The maintenance rate was significantly higher for TCZ than for ETN or ABT. Clinical remission by SDAI was achieved by 10 (18.5%) patients on IFX, six (15%) on ETN, 15 (37.5%) on TCZ, four (20%) on ADA and four (15.4%) on ABT. Over time, the maintenance rate of clinical remission by SDAI was highest for TCZ, followed by IFX, ADA, ETN and ABT. The maintenance rate was significantly higher for TCZ than for ETN.Conclusion:These findings can inform the choice of optimal biologic from the available options.

P2-062

Evaluation of the American College of Rheumatology (ACR)/ European League Against Rheumatism (EULAR) (2011) remission definition for rheumatoid arthritis (RA) with treatment of DMARD ~especially take notice of patient global assessment (PtGA)~

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Conflict of interest: None

Purpose: To evaluate the new ACR/EULAR remission definition for patients with RA treated by DMARD in medical examination. Method: There is no history of biologic treatment and there is a treatment history for one year or more. The cross-sectional method estimated retrospectively for 121 RA patients. (It is possible to evaluate DAS28, SDAI, Boolean definition, x-ray change by mTSS in about one year, and functional evaluation (HAQ-DI).) Result: The remission rate of DAS28, SDAI and Boolean definition were 72%, 49.6% and 34.7%. The rate of PtGA≦1 was only 33.9% in component of Boolean definition, but other components were fulfilled more than about 90%. Moreover, the rate of no radiographic progression was 81%. The remission rate of DAS28 and SDAI were as low as 61.7% and 36.7% respectively in 77% of no radiographic progression in PtGA>1, but HAQ-DI was 0.4 and a low value. Moreover, the rate of radiographic progression of PtGA≦1 was 14%, and the remission rate of DAS28 and SDAI were as high as 100% and 66.7% respectively, and it required cautions. Conclusion: New remission definition required combination with imaging evaluation and functional evaluation to treat patients with RA in daily medical examination.

P2-063

Evaluation of radiographs and function of rheumatoid arthritis patients in near remission by Boolean index (swollen joint, tender joint ≦ 1)

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Conflict of interest: None

[Objectives] The treatment goal of rheumatoid arthritis (RA) has been clinical remission. It is difficult to decide whether to strengthen therapy by adding or changing drugs for RA patients in near remission by Boolean index (swollen joint, tender joint ≦ 1). The aim of the present study was to evaluate radiographs and function of RA patients in near remission. [Methods] Forty eight RA patients (12 males and 36 females) who are in near remission by the Boolean index (swollen joint, tender joint □ 1) were examined. Patients were classified by region of swollen and/or tender joints or not. We evaluated radiographic change by scoring erosion and joint space, and the functional disability difference by using HAQDI and DASH scores between groups. [Results] In radiographic scores, only the no swollen/tender joint group scores improved, while the hand joint group score deteriorated significantly faster compared with other groups. Some patients in the hand joint and elbow joint groups were not in functional remission by HAQDI. The DASH scores of hand joint and elbow joint groups were higher significantly compared with other groups. [Conclusion] We expect RA patients in near remission who have swollen and/or tender hand or elbow joints might improve by additional treatment.

P2-064

Assessment of T2T on clinical effectiveness

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Conflict of interest: None

Objectives We have investigated the clinical effectiveness of Treat-to-Target (T2T) in evaluating disease activity of rheumatoid arthritis (RA). Methods Since August 2010, we have been treating

RA according to T2T recommendations. 298 patients have been treated for more than 6 months. These patients were divided into groups. According to treating duration in our office, groups were classified to until 3 months (3M), 3 to 6 months (6M), 6 to 12 months (12M), more than 12 months (O12M). These groups' average SDAI and distribution of SDAI evaluation were compared statistically. For patients who had begun treatment before August 2010 (old), their SDAI were compared statistically. Results Average SDAI decreases significantly in order of 3M, 6M, 12M, and O12M, respectively ($P<0.01$). Distribution of SDAI evaluation also demonstrated significantly as remission and LDA proportion increases while MDA and HDA proportion decreases, as the same order respectively. Old demonstrated that as time passed, SDAI decreases significantly ($p<0.01$). Conclusions From these results, disease activity control with T2T recommendations have contributed on clinical results improvement. It is beneficial to share medical information and clinical target between patient and physician.

P2-065

Ten cases with rheumatic arthritis (RA) who exhibited pancytopenia during methotrexate (MTX) treatment

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Conflict of interest: None

【Objectives】To clarify clinical characteristics of cases with RA who developed pancytopenia during MTX treatment.【Methods】In this single hospital retrospective survey, we identified 10 cases with RA on MTX treatment who admitted to our hospital due to pancytopenia, from September 2010 through October 2012.【Results】The mean age of the patients (F/M: 8/2) was 78.5 years, and 8 cases were over 75 y.o. Seven cases had an eGFR level <30 ml/min/1.73m2. The mean dose of MTX was 6 mg/week, and duration of MTX treatment ranged from 15 days to 7 years. Six cases were concomitantly treated with prednisolone, with an average dose of 5.75 mg/day. We obtained the information on the blood testing within 8 weeks before the admission from eight patients, of which seven (88%) received the testing. Eight cases discharged with MTX cessation or it's dose-reduction, but one needed a chronic hemodialysis due to infection-induced renal failure, and one died of perforation of her digestive tract, which we did not consider related with MTX or pancytopenia.【Conclusion】We found RA patients who developed pancytopenia during MTX were mostly over 75 years and had renal dysfunction. It is important to pay more caution on the MTX treatment for RA, especially in elderly patients with low eGFR.

P2-066

Efficacy of low-dose tacrolimus therapy in patients with rheumatoid arthritis

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Conflict of interest: None

[Objectives] To assess efficacy of low-dose tacrolimus (TAC) in patients with rheumatoid arthritis (RA). [Methods] Thirty patients (M:10, F:20), who were treated of low-dose TAC (0.5-1mg/day, mean dose was 0.6mg/day), were analyzed prospectively. [Results] Twenty six patients treated by MTX and mean dose was 8.8mg/week. Twenty six were treated by predonisolone and mean dose was 4.1mg/day. Two patients were used biologics. One patient was treated by infliximab, other one was treated by etanercept. Result: Twenty six of 30 patients were evaluated after 48 weeks and 4 patients dropped out. DAS28 (CRP) score was significantly decreased 3.96 to 3.25 and 9 patients having Low disease activity. But twelve patients were not attained more than moderate response. Mean dose of steroid was decreased statistically 4.1±2.9mg/day to 3.40±2.81mg/day and dose of MTX was not significantly increased. No serious adverse events were observed during 48 weeks. [Conclusion] Low-dose TAC therapy was considered statistical effective for RA patients, but 46% of patients were not attained good or moderate response.

P2-067

Efficacy of mizoribine pulse therapy in patients with rheumatoid arthritis who show an insufficient response to golimumab

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Conflict of interest: None

[Objectives] We evaluated the efficacy of mizoribine (MZR) pulse therapy by using ultrasonography (US) in patients with rheumatoid arthritis (RA) who show an insufficient response to golimumab (GOL). [Methods] Eight patients with RA including 7 patients treated previously with other biologics agents were started with the therapy of 100 mg GOL every 4 weeks. At week 16 of treatment, the patients who did not achieve SDAI remission began MZR pulse therapy. MZR was given at a dosage of 450 mg/week (150 mg x 3 per week, 12 hour intervals) for 16 weeks. At weeks 0, 16 and 32 of treatment, US examination was performed at bilateral MCP, PIP, IP, and wrist joints. Pulse Doppler (PD) signal was recorded in each joint using semi-quantitative score (0 to 3). The sum of these scores obtained from each joint was used as PDUS score. [Results] At weeks 0 and 16 of GOL treatment, mean PDUS score was 26 (range 10-46) and 18 (0-45), respectively. Six patients were treated with MZR pulse therapy, and three patients of them have been evaluated at week 32. The mean PDUS score of these 3 patients with MZR pulse therapy was 14 (9-20) and 7.3 (4-14) at weeks 16 and 32, respectively. [Conclusion] MZR pulse therapy is effective in terms of PDUS for patients showing an insufficient response to GOL.

P2-068

A case of patient with RA in elderly that combination with mizoribine and tacrolimus was useful

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Social Insurance Kyoto Hospital

Conflict of interest: None

[Case] 86-year-old woman of rheumatoid arthritis (RA) had been medical treatment by MTX4mg/week+PSL5mg. Because of intractable stomatitis, palpitations, cough,dyspnea appeared from August 2010, introduction was admitted to our hospital at September. Stomatitis and bronchiolitis showed at chest CT, forced to stop MTX and increase PSL to15mg. Then her symptoms were improved. However her joint pain has been gradually increased, so we began 1mg of tacrolimus (TAC) in October. Then we reduced to 0.5mg because trough level was high by renal dysfunction. Since improvement of articular findings was still poor,we thought that treatment with TAC alone was difficult and added 150mg of mizoribine (MZB)(every other day). Her joint symptoms improved,we reduce PSL to 8mg and she was discharged in December. The course can be observed on our outpatient basis reducing PSL to 5mg without serious infections. [The clinical significance] Use of MTX in patients with RA in elderly at risk of

infection, in many cases we forced to stop it. In patients with renal dysfunction in elderly, combination of small amount of mizoribine and tacrolimus performs clinical efficacy equivalent to MTX. It is suggested to obtain potentially better continuity by reducing the risk of infection.

P2-069

Efficacy and safety of methotrexate usage over 8mg/week for rheumatoid arthritis patients

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Conflict of interest: None

[Objectives] To evaluate the efficacy and safety of methotrexate (MTX) usage over 8mg/week for rheumatoid arthritis (RA) patients. [Methods] We examined 91 RA patients who had increased MTX dose from 8mg/week or less dose to over 8mg/week after February 2011 at Osaka Rosai Hospital. Patient characteristics, adherence, efficacy and safety were examined. [Results] Fourteen male and 77 female patients were included. The mean age was 56.1 years and mean disease duration was 9.4 years. Maximum MTX dose was 10 mg in 42, 12 mg in 35, 14 mg in 10, 16 mg in 4 patients. Adherence of increased MTX was 88.2% in 24 weeks and 77.7% in 52 weeks (Kaplan Meier method). Biologic agents were added to 10 patients for insufficient efficacy. Nineteen patients decreased MTX to 8 mg/week or less, 12 patients for adverse events, 5 patients for remission, 2 patients for other reason. DAS28ESR improved significantly from 4.02 (0week), to 3.16 (24 weeks), and to 3.05 (52 weeks) ($p<0.001$). Fifty six patients were good or moderate response, and 35 patients were no response in EULAR response criteria. Using logistic regression analysis, baseline DAS28ESR($P=0.012$), and number of tender joint($P=0.018$) were significantly correlated with EULAR response. [Conclusion] MTX over 8 mg/week usage was effective and safe.

P2-070

The current situation of the RA treatment with MTX therapy in our department

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Conflict of interest: None

[Objectives] Though methotrexate (MTX) plays a important role in the treatment of rheumatoid arthritis (RA), we in Japan had have to use it under 8mg/week for a long time. From February 2011, we became to be able to increase it up to 16mg/week and its effectiveness is expected.To clarify and analyze the current situation, we studied the RA treatment with MTX in our department [Methods] 221 RA patients in our department were studied. All of them were newly started the MTX therapy or changed the applied dose of MTX after February 2011.Their profiles such as the background, the dose of MTX and adverse events were investigated. [Results] The mean age of patients at the enrollment the study was 60.5±13.5 years old and the average dose of MTX was 8.35±2.87mg/week. Although 89 patients (38.9%) were administered over 8mg/week of MTX, half of them were treated with under 10mg/week. The common adverse events were nausea. The elevation of liver enzymes tended to interfere with the dose escalation of MTX. [Conclusion] There was little change in the dose of MTX despite of the permission for escalation. One of the reasons might be an influence of a local characteristic as aging. Further investigation about effectiveness of the treatment should be needed especially in combination therapy with biologics.

P2-071

Efficacy and safety of increasing dose of MTX from 8mg/week to 10mg/week or more in RA

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Nippon Medical Shool

Conflict of interest: None

[Objectives] We investigated the efficacy and the safety of 10mg/W or more of MTX increased from 8mg/W. [Methods] According to medical records, 35 RA patients were treated with 10mg/W or more of MTX and followed up for over 6 months. Disease activity, response and adverse effects were evaluated. [Results] At 6 months, DAS28-ESR was improved from 3.55 to 2.85, MMP-3 and RF values were decreased from167.2 to131.3, and from 189.3 to 61.9, respectively. 17% of the patients reached good response, and 40% of patients reached moderate response evaluated by EULAR response criteria. 3 patients showed liver dysfunction and were recovered by decreasing doses of MTX. Among 11 patients without response, 4 patients were treated with 12mg/W of MTX, one patient was changed to biologics, and 5 patients maintained their MTX dose. 66.7% of patients with increasing dose up to 12mg/W reached good response. MTX dose was increased from 8mg/W directly to 12mg/W in 3 patients and 2 of them reached good response. [Conclusion] MTX might be increased up to 12mg/W rapidly or directly in patients who did not respond to 8mg/week of MTX, if their conditions permit.

P2-072

Examination of the rheumatoid arthritis patients who have remitted with DMARDs

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Conflict of interest: None

[Objectives] It examines what kind of case have remitted with antirheumatic drugs in rheumatoid arthritis patients. [Methods] One hundred and one patients was examined. Nine patiens have remitted and maintain drug free remisson. Twenty-four of 97 patients continuing antirheumatic drug treatment have remitted. Seventy-three of 97 patients continuing antirheumatic drug treatment have not remitted. Steroid administration history, sex and the remission rates were examined. [Results] Thirteen of 30 male patients had remitted. Twelve of 76 female patients had remitted. Twelve of 65 patients with steroid administration history had remitted. Twenty-one of 41 patients without steroid administration history had remitted. The remission rate is 61% in male patients without steroid administration history. The remission rate is 29% in male patients with steroid administration history. The remission rate is 46% in female patients without steroid administration history. The remission rate is 15% in female patients without steroid administration history. [Conclusion] In male patients without steroid administration history, the remission rate is high. In female patients with steroid administration history, the remission rate is not high, and It is predicted that biologics is probably needed.

P2-073

Study of rheumatoid arthritis patients treated with methotrexate more than 10mg/week achieved normal revel of C-reactive protein

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Conflict of interest: None

[Object] the purpose of this study was to evaluate the association between synovitis and dose up of methotrexate (MTX) more than 10mg/w in rheumatoid arthritis (RA) patients. [Method] We studied 11 RA patients treated with MTX who achieved a serum C-reactive protein (CRP) concentration less than 0.25 mg/dl, and they had swollen joints. they were mean of age was 61.7±11.3 (37-80) years old, female/male 6/5,mean of duration years was 6.5±4.9(1-16) years. Mean of MTX was 11.6±1.2mg/week (median 12mg/week). We measured number of swollen joint and tender joint, CRP, DAS28CRP, CDAI, SDAI at the time of dose up over 10mg/week and the last investigation. And imaging of hands using standardized scoring techniques (grade0-3) with Power Doppler ultrasonography (PD-US) was performed at last investigation. [result] Number of swollen joint and tender joint, CRP, DAS28CRP, CDAI, SDAI, were not significant difference statistically. Despite they achieved normal revel of CRP, 7 patients continued to evidence of active inflammation, as shown by PD-US. [Conclusion] We concluded that RA patients, they achieved normal revel of C-reactive protein and had swollen joints, trended to remain swollen joints in spite of dose up of methotrexate.

P2-074

The superior response in early rheumatoid arthritis concomitant treatment induction of Low dose tacrolimus addition to conventional MTX monotherapy

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Conflict of interest: None

Objective: An early intervention with methotrexate (MTX) to rheumatoid arthritis is essential, followed the close monitor with DAS28, considering the addition of other disease modifying drugs (DMARDs) to prevent deterioration of joint. Recently, the effectiveness in additional induction of low dose tacrolimus(LD-Tac) to MTX is reported in Japan. Method: RA patients, duration less than 1-year, 24 patients are assorted to with MTX or concomitant of MTX and tacrolimus in low dose, 3mg/day. Every 3-month, additional DMARDS or biologics is considered if DAS28ESR over 3.2. Every 3-month for 1year, comparison of DAS28ESR in MTX monotherapy and concomitant induction of MTX plus LD-Tac are recorded. The secondary end point is the induction of another DMARDs. Result: The initial DAS28ESR were 4.15 in MTX monotherapy and 5.16 in concomitant treatment. In 3-month evaluation, DSA28ESR went down to 3.10 in MTX, and 2.08 in concomitant. The haif of MTX group, and all cases in concomitant fulfilled DAS28ESR<3.2. In 6-month period, 30% of MTX group survived the monotherapy but no further failure in the concmitant, average CRP 0.13mg/dl, DAS28ESR went down to 2.06, the remisson status in every case. Conclusion: The concomitant induction of LD-Tac to MTX resulted in excellent responses in early RA.

P2-075

Low-dose Methotrexate-induced Neurotoxicity

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Conflict of interest: None

[Objectives] Acute, subacute and chronic neurotoxicity have been observed after the administration of high-dose and/or intrathecal methotrexate (MTX) but rare in low-dose weekly oral MTX. [Methods] We report a patient with rheumatoid arthritis (RA) who developed chronic progressive neurological abnormality mimicking spinocerebellar degeneration while being treated with low-dose MTX. We also summarized the reported cases of MTX-induced neurotoxicity. [Results] Seven patients, 5 with RA and 2 with psoriatic arthritis, had been reported. Brain MRI of the reported 6 cases showed leukoencephalopathy. However, the MRI of this patient only showed slight cerebellar atrophy. [Conclusion] Low dose MTX rarely causes severe neurological abnormality. Prompt diagnosis and discontinuation may alter the outcome.

P2-076

Results of one-year treatment by methotrexate at dosages more than 10mg per week in patients with rheumatoid arthritis - Evaluation of efficacy, inhibition of the joint damage and safety -

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Conflict of interest: None

[Objectives] 70 patients administered methotrexate (MTX) at dosages more than 10mg per week under more than one year treatment were investigated for efficacy, inhibition of the joint damage and safety. [Methods] The subjects consisted of 15 males and 55 females with an average age of 56.2 years and a mean duration of disease for 86 months. Complications were observed in 36 cases. The efficacy was evaluated by the DAS28-ESR, biomarkers and modified Total Sharp Score (mTSS). [Results] Of 70 patients, 53 cases continued to be administrated MTX at dosages over 10mg per week for one year, 17 cases discontinued by side effects(8 cases), lack of efficacy(7 cases), no visit during the treatment(2 cases). MTX dosage was increased from 8 mg/w to 11.8 mg/w, and the DAS28-ESR was decreased from 4.36 to 3.58, significantly ($p<0.0001$). Evaluation of inhibition of the joint damage in 38 cases for whom X-ray analysis was feasible revealed the significantly improved of mTSS/y from 9.15 at baseline to 1.85 at one year ($p<0.0001$).The adverse reactions were found in 38 cases including respiratory infections in 7 cases, nausea in 5 cases, liver dysfunction in 4 cases, etc. [Conclusion] Efficacy,safety and the inhibitory effect of the joint damage were confirmed in the use of increased amount of MTX.

P2-077

Very early arterial stiffness improvement as cardio ankle vaslular index predicts disease activity in treatment with vitamin D in patients with infiximab treated rheumatoid arthritis

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Conflict of interest: None

[Objectives] Vitamin D difieciency is related to response with infliximab (IFX) in patients with rheumatoid arthritis (RA). However Japan goverment is not covered with estimation of vitamin D. In this study we evaluated that any factor predict the effect of vitamin D in IFX treated RA. [Methods] We evaluated 24 IFX treated RA were prescribed vitamin D. We evaluated that any factor(CRP, ESR, SJC, TJC, CAVI) in 2 weeks could predict outcome in 12 weeks. [Results] CAVI improvement in 2 weeks could predict infliximab response in later. [Conclusion] Vitamin D dificiency might

be related to artreial stiffness.

P2-078

The efficacy and retention rate of biologics in our hospital; 2013 edition

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Conflict of interest: None

[Objectives] To examine the efficacy and retention rate of biologics in our hospital. [Methods] 370 patients who started to treat biologics between May, 2001 and August, 2012, were included in this study. The average age was 55.3. The average follow-up period was about 2.3-year. They were subdivided as follows; Infliximab (IFX); 56, Etanercept (ETN); 56, ETN+Methotrexate (MTX); 123, Tocilizumab (TCZ); 77, Adalimumab (ADA); 40, and Abatacept (ABA); 15, 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 4.41 in IFX, 4.23 in ETN, 4.20 in ETN+MTX, 4.77 in TCZ, 3.42 in ADA, and 3.59 in ABA group, respectively. Then 6 months after, each value was 2.83, 2.75, 2.41, 2.46, 2.47 and 2.17. The retention rate 1 year after was 72.8% in IFX, 81.0 % in ETN, 85.4% in ETN+MTX, 85.3% in TCZ, 58.0% in ADA and 92.3% in ABA group, respectively. The retention rate 2 years was 60.6, 76.3, 79.3, 78.2 and 42.8, respectively (exclude ABA). [Conclusion] These findings suggest that each group showed almost the same efficacy in DAS28(3)-CRP. ETN+MTX and TCZ group showed highest retention rate in 1 year and in 2 years.

P2-079

Efficacy of Golimumab (GLM) on Rheumatoid Arthritis (RA) Patients in multi-center by The Fukuoka RA Biologics Registry (FRAB Registry)

Eisuke Shono
The Fukuoka RA Biologics Registry

Conflict of interest: Yes

[Objectives] We evaluated the efficacy of GLM on RA patients in general practice. [Methods] From 170 RA patients of GLM administration at The Fukuoka RA Biologics Registry during September 2011 to October 2012, 58 patients (mean age was 59.8 years, mean disease duration was 12.4 years) who could be evaluated on 24 weeks after GLM administration were evaluated at this time. Naïve patients were 22, and switching patients from other biologics were 36, and 27 patients were second biologics, 7 patients were third and 2 patients were fourth. About the starting dose of GLM, 50mg was 51,100mg was 7 patients respectively. All patients were evaluated by DAS28-CRP and SDAI. [Results] The Mean DAS28-CRP was decreased from 4.03 at initiation of GLM to 2.28 at 24 weeks, and the mean SDAI was decreased from 20.97 to 6.32. 60.3% (35 of 58 patients) were achieved clinical remission (DAS28<2.3), in naïve patients were 68.2% (15 of 22 patients) in switching patients were 55.6% (20 of 36 patients). In 100mg dose group, 42.9% (3 of 7) patients were achieved clinical remission. [Conclusion] GLM expects an effect to the not only biologics naïve patients, but also switching patients from other biologics. Also 100mg dose of GLM became a valid alternative of biologics.

P2-080

Clinical features and course of 12 rheumatoid arthritis patients with clinical remission after cessation of biologics in clinical practice

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Conflict of interest: Yes

[Objectives] To evaluate the clinical features and course of rheumatoid arthritis patients with clinical remission after cessation of biologics. [Methods] [Results] [Conclusion] This study suggested that the clinical features of patients that achieve continued after cessation of biologics were as followed: 1) anti-TNF antibody therapy, 2) Bio-naïve, 3) short duration between the disease onset and the initiation of biologics, 4) more than 1 yr of biologics, 5) more than 8mg/w of MTX during biologics therapy, 6) discontinuation or low dose steroid at the cessation of biologics.

P2-081

The Effect and the Safety of Golimumab in Patients with Rheumatoid Arthritis

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Conflict of interest: None

[Objectives] To assess the efficacy and safety of GOLIMUMAB (GLM) in patients with RA. [Methods] We followed a total of 33 RA patients with GLM in multicenter study (FIT-RA). DAS28 (ESR), DAS28 (CRP), SDAI, CDAI were evaluated at base line (0), 1, 3, and 6 months (M) after GLM treatment started. [Results] At the data of the base line, the mean age was 64 y.o., the mean disease duration was 17years, stage4 was 13patients (40%), class3 was 13patients (40%), the history of biologics was 26patients (79%). Three patients (9%) withdrew due to efficacy reasons and one patient (3%) withdrew due to moving to another hospital. The mean DAS28 (ESR) was 4.22, 3.45, 3.11, 2.95, the mean DAS28 (CRP) was 3.58, 2.87, 2.42, 2.48, the mean SDAI was 17.9, 11.7, 8.3, 8.5, and the mean CDAI was 18.5, 12.5, 9.3, 9.6, at 0M, 1M, 3M and 6M, respectively. At any point, all disease activity indexes decreased more than these indexes at base line. With regard to the good response in clinical improvements in the DAS28 using the EULAR criteria, DAS28 (ESR) was 46%, 42%, 47%, and DAS28 (CRP) was 45%, 43%, 53% at 1M, 3M and 6M, respectively. [Conclusion] Many patients with GLM had long disease duration and were old, and GLM were used as used as second or later line biologics., but GLM was well-tolerated and effective.

P2-082

Efficacy of clinical improvement and change of ultrasound sonography about Golimumab in real practice

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Conflict of interest: None

[Objectives] Golimumab (GLM) is a forth anti-TNF inhibitor and highly clinical efficacy and safety were reported. Although it has been used before 1 year, there are no clinical results about GLM in clinical practice. We investigated efficacy of GLM in clinical practice by using evaluation of disease activity and ultrasound sonography (US). [Methods] We evaluated DAS28-ESR, SDAI, and mHAQ about 17 cases (female 13 and male 4 cases) followed over 3 months. We compared 7 cases that was examined US at bilateral fingers and wrist in pre GLM and after 24 weeks. Gray scale (GS) and power doppler (PD) was scaling 4 grade and calculated each. [Results] Average age was 62 years, disease duration was 8.4 years, and DAS28 was 4.99. Follow up duration was 0.7 years, and naïve were 7 and switch were 10 cases. DAS28 was decrease 4.06 after 4 weeks and 3.54 after 1 year, and efficacy was maintained. SDAI and mHAQ also were improved significantly. There was significantly difference about clinical results between naïve and switch. About US, GS was improved from 22.3 points to 15.1 and PD was from 11 points to 5 (P=0.015, 0.004, respectively). [Conclusion] Although follow up period was short, clinical efficacy was good in naïve and switch. About US, synovitis was decrease after 24 weeks started GLM.

P2-083

Treatment-specific changes in circulating adipocytokines: a comparison between biological treatment for rheumatoid arthritis

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Conflict of interest: None

[Purpose] Adipose tissue can secrete soluble mediators and involvement of adipose tissue in pathology of rheumatoid arthritis (RA) has been recently paid attention. We here investigated the association of adiponectin and biomarkers of fat metabolism with response of biologics. [Subjects] Forty cases treated by biologics were investigated. We comparatively studied Responders (DAS28response >0.6; n=20) and Non-responders (DAS28response<=0.6; n=20). [Results] The serum levels of T-cho, HDL, LDL, Lesistin and Leptin were higher and that of Adiponectin was lower in the Responders than in the Non-responders, however, no significant difference was observed in two groups. The serum levels of MDA, and OHdG8 were higher in the Responders than in the Non-responders. [Conclusion] The results show that lipid metabolism is involved in pathology of RA and indicate that MDA and OHdG8 can be a predictor for the effects of biologics in RA.

P2-084

Outcome of Novel Anti-TNF Inhibitor Golimumab for Rheumatoid Arthritis in Our Facilities

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Conflict of interest: None

[Objectives] Golimumab (GLM) is 4th anti-TNF inhibitor approved in Japan on July 2011, which is administered once every four weeks in spite of subcutaneous injection. In this study, we investigate the characteristics of this biologics and its therapeutic results for 56 cases of Rheumatoid arthritis (RA) with GLM. [Methods] We examined the background, safety and efficacy of 34 RA with GLM in our hospital and related facilities at 52 weeks. [Results] Thirty-four cases (11 male, 45 female) are entitled. Their background is as follows. Mean age: 9.37 years old, disease duration: 8.68 years, CRP: 1.12mg/dL, ESR: 49.3mm/hr, DAS28-CRP: 4.25, DAS28-ESR: 5.13. Of these, 22 patients are biologic agents naive, and 34 patients have history of using biologics. Two patients were changed to other biologics because GLM comes to invalid. Disease activity was decreased in relatively early at 12 weeks in many cases. Patients who used at least three biologics tend to relapse after achievement of temporal efficacy. [Conclusion] Because of various biologic agents have been released, we hope to establish RA treatment taking advantage of the characteristics of each biologics including GLM for tighter control of disease activity. We show study of 34 RA cases with GLM, including currently induced cases.

P2-085

Onset of effect and Efficacy of Golimumab on Biologics Naïve Patients

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Conflict of interest: None

[Objectives] To evaluate the onset of effect and efficacy after Golimumab (GLM) introduction on RA patients. [Methods] Background of 19 biologics naïve RA patients who introduce GLM were as follows; mean age 58.5 years, sex ratio (male/female) 5:14, disease duration 9.7 years, mean DAS28-CRP 3.84, mean SDAI 15.91 at before GLM administration. All patients were administrated MTX, mean dosage were 9.1mg/weeks. 8 patients were administrated PSL, the mean dosage were 1.6mg/day. All patients were started 50mg of GLM, and evaluated by DAS28-CRP and SDAI at 2 and 24 weeks. [Results] DAS28-CRP and SDAI were rapidly improved to 2.5 and 6.86 respectively at 2 weeks after GLM initiation. And, they were 2.01 and 3.39 respectively at 24 weeks to the 8 patients who were evaluable at 24 weeks. All of 8 patients achieved clinical remission by DAS28-CRP<2.3, and 5 patients (63%) achieved by SDAI<3.3. No patients increased to 100mg of GLM. Adverse events were observed at 2 patients, pharyngitis and liver function abnormality respectively, however, they were non-serious. [Conclusion] Introduction of GLM demonstrated rapid onset of effect at 2weeks and high efficacy at 24 weeks. In order to evaluate the long-term efficacy and joint damage prevention effect, further study would be necessary in future.

P2-086

Golimumab therapy in patients with rheumatoid arthritis - 24 week results

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Conflict of interest: None

[Objectives]: To describe the effects of golimumab therapy in patients with rheumatoid arthritis (RA). [Methods]: Data were collected retrospectively from thirty-two RA patients treated with golimumab in a multicentre in Yamaguchi prefecture. Average age was 63.7 years old and mean disease duration was 7.9 years. MTX was used in 78%,with average dosage of 8.3mg. 47% of the patients used biologic DMARDs previously. DAS28-CRP score, SDAI and CDAI at treatment onset were 3.9, 22.2 and 20.4, respectively. [Results]: Median DAS28 declined to 1.9 at week [Results]24. Clinical remission was seen in 64% of the patients. Patients treated with golimumab plus MTX showed better clinical response than those with golimumab alone. Prior use of biologic DMARDs had no influence on clinical response. Patients with disease duration of less than one year was 19%, and had a good response. Three patients discontinued golimumab therapy because of unsatisfactory response. Adverse events were seen in 5 cases, including one case of tuberculosis. [Conclusion]: Golimumab therapy can effectively control disease activity in RA patients refractory to antitumor necrosis factor biologics.

P2-087

Efficacy and safety of methotrexate at dosages over 8mg/week in patients with rheumatoid arthritis administered biological drugs

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Conflict of interest: None

【Objective】To investigate the efficacy and safety of MTX at dosages over 8mg/week in patients with rheumatoid arthritis treated with biological agents【Methods】40 RA patients (9 male, 31 female), who are administered biological drugs and MTX at dosages over 8mg/week in our department, were included in this study. We assessed the efficacy of MTX using DAS28-CRP at initiation of dose escalation and at 3 and 6months after dose escalation. Adverse events were also assessed.【Results】Mean age of 54 Years old(14-77Years old).. Mean RA duration is 11 years(1 -27years).15 patients, 12 patients, 6 patients, 5 patients, 2 patients are treated with Infliximab, Etarnercept, Adalimumab, Tocilizumab, Abatacept respectively. MTX at dosages over 8mg/week is continued for 6 months in 35 patients (88%). In 6 months continuation group, mean DAS28-CRP were significantly decreased. We compare Infliximab+Adalimumab group with Etarnercept group. DAS28-CRP is each 3.41 and 3.51 at 0 month, respectively. There is no statistical difference. At 3 month DAS28-CRP is each 2.27 and 2.85 (P=0.03) respectively. However at 6 month DAS28-CRP is each 2.31 and 2.33 (no statistical difference)【Conclusion】It is effective to administer over 8mg/week MTX to the RA patients administered biological drugs

P2-088

The investigation of patients treated with Etanercept (ETN) in Akita cohort

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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). [Methods] 1663 patients were registered with AORA in 2012. Of these, 202 patients were treated with ETN who comprised the subjects of this study. [Results] The patient characteristics were as follows:33 males and 169 females, the mean age was 62 years and the mean disease duration was 171 months. ETN had been administrated with a mean duration of 28 months. One hundred and forty-nine patients had been prescribed methotrexate (MTX) with a mean dose of 6.7 mg, and 115 patients had been prescribed a steroid (PSL) with a mean dose of 3.8 mg. The mean DAS28ESR(4) was 3.31 in 178 patents. One hundred and fifty-one patients could continue ETN during the investigation with a mean duration of 32 months. MTX was prescribed in 119 patients with a mean dose of 6.4 mg, and PSL was prescribed in 81 patients with a mean dose of 3.6 mg. The mean DAS28ESR(4) was 3.20 in 133 patients. Fifty-one patients could not continue ETN during the investigation with a mean duration of 16 months. MTX was prescribed in 34 patients with a mean dose 8.2 mg, and PSL was prescribed in 34 patients with a mean dose of 4.2 mg. The mean DAS28ESR(4) was 3.61 in 45 patients.

P2-089

Use of Golimumab in Our Department

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Conflict of interest: None

Objective: To investigate the efficacy and safety of golimumab (GLM) in rheumatoid arthritis (RA) patients treated in our department. **Methods:** The efficacy of GLM at week 24 of treatment was investigated in 9 RA patients (1 man and 8 women). **Results:** Mean age was 45.0±14.4 years, and mean duration of illness was 10.3±8.7 years. One patient had previously used 5 biological agents, 1 had used 4 such agents, 1 had used 3 such agents, 3 had used 1 such agent, and 3 were treatment naïve. Six of the patients concomitantly used methotrexate. Mean dose was 10 mg/week at the start of GLM treatment and 13.5 mg/week at the evaluation point. Baseline Disease Activity Score 28 based on erythrocyte sedimentation rate (DAS28-ESR) was 4.22±1.20. Four of the patients took a GLM dose of 100 mg at the evaluation point. At the evaluation point, 2 of the patients had a good response, 4 had a moderate response, and 3 had no response according to the EULAR response criteria. No patients experienced adverse drug reactions. **Discussion and Conclusion:** GLM is a safe and effective biologics.

P2-090

Clinical experience with golimumab in patients with rheumatoid arthritis

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Conflict of interest: None

【Objective】To evaluate the efficacy and safety of the 6th approved TNFα-inhibitor, golimumab (GLM).【Patients】GLM was administered to 25 RA patients from Sep. 2011 to Oct. 2012, and 12 were examined for more than 24 weeks after initiation, including 4 men and 8 women, with mean age and disease duration of

67.4 and 13.6 yr, respectively. 75% were concomitantly administered MTX (mean dose: 5.2 mg/week), 2 were bio-naïve, and 10 switched from other biologics.【Methods】All patients were examined 0, 4, and 24 weeks after initiation of GLM. The endpoints were DAS28-CRP, SDAI, and MMP-3.【Results】The mean DAS28-CRP, SDAI, and MMP-3 scores of 4.03, 20.24, and 214.8, respectively, at baseline decreased to 3.51, 14.51, and 183.5 at 4 wk, and 2.74, 9.23, and 144.6 at 24 wk after initiation, confirming rapid onset and sustained efficacy. Although our patients were older than those in other trials in Japan, the administration continuation rate was high, at 24 wk (91.7%), and only 1 suffered adverse events.【Discussion】GLM is effective in bio-naïve and bio-switched patients. Because of less frequent dosing, the possibility of dose intensification with DMARD, and best use of 50- and 100-mg doses for disease activity control, GLM will be considered the first choice for treating RA.

P2-091

Evaluation of the clinical use of infliximab (IFX) for the treatment of rheumatoid arthritis (RA)

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Conflict of interest: None

[Objectives] To investigate the efficacy of IFX for RA [Methods] Using the Kaplan-Meier method, we evaluated the continuation rate of 55 patients who started IFX as a primary biologic post October, 2003 (patients treated<2 weeks<6 years 7months). Endpoint: Discontinuation due to adverse effects (AEs), insufficient efficacy, or social situation. Types and onset of AEs leading to discontinuation were evaluated, along with patients sustaining remission after discontinuation due to their social situation. [Results] 10 discontinued due to AEs, 15 due to inefficacy and 14 due to social situations. Treatment continuation rates were 84%, 71% and 40% after 36 months, and 79%, 61% and 32% after 60 months. Most AEs leading to discontinuation occurred in 1st 3 years. Among discontinuing patients due to social situations, 6 were for financial reasons, all of whom sustained remission with no flare-ups (remission<2 years<8.5years). Their disease duration was 4 months to 12 years; 4 at Stage I and 2 at Stage IV. All had poor-prognosis factors, testing positive for anti-CCP antibody and RF. [Conclusion] Patients sustaining remission showed marked response by DAS28 and MMP-3 by the third infusion of IFX. Baseline serum TNF-α level at initiation may be a factor to induce bio-free remission.

P2-092

Clinical result of Golimumab

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Conflict of interest: None

[Objectives] Golimumab (GLM) is the newest human anti-TNF antibody available in Japan. We treated 7 RA patients with GLM since February, 2012, and this is the report on those cases. [Methods] 7 patients (1 man, 6 women) with the mean age of 66 years (56-83 years) and the mean disease duration of 17.7 years (3-30 years) received the treatment. 5 patients switched from other treatments (ADA:4, IFX:1), and 2 patients were biologically naïve. ADA patients switched to reduce the number of administration, and the IFX patient was experiencing adverse events. 6 patients combined MTX. We clinically evaluated the above patients using DAS28-CRP and SDAI. We also compared the switched and the biologically naïve patients. [Results] We observed maintained or improved clinical evaluation with fewer administrations (2-5 times) and observed no difference between the switched and the monotherapy patients. Pneumonia was observed in 1 patient after the second administration. [Conclusion] It is assumed that many switchings will be observed since it is a new treatment. Although we did not recognize significant difference, it was administered fewer times and gave us the impression of being effective on both switched and naïve cases. Further study of more GLM-treated patients is necessary.

P2-093

Clinical results of Golimmab therapy in rheumatoid arthritis

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Conflict of interest: None

Objectives We retrospectively evaluated GLM-treated patients. **Methods, targets** The retrospective study 5 patients of Rheumatoid Arthritis (1 men, 4 women; mean age 60.8) treated with GLM since Sep 2012. 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, switchover from other biologics: 2. Clinical results are evaluated by DAS28(CRP). **Results** DAS28 before prescribing are as below. 50mg does group: High disease activity (75%), Middle (25%). 100mg does group: Middle disease activity (100%). At the final assessment, one case of naive group (25%) has improved to low score, or remission of RA, while no case from switched group (0%) There were one case that were increased to 100 mg within 24 weeks because of insufficient efficacy, while starting by 50 mg of dosage. **Discussion** GLM showed effectiveness equal to other anti-TNF, regardless of naive or switched cases. More examinations, including additional case, are necessary for verification of the start dose and decision for increase to 100mg. GLM is subcutaneous administration drug subscribed by every 4-week, and decrease visits and staying time in hospital. I believe that it contributes to improve compliance of patients.

P2-094

The examination of remission and adherence rate in the Rheumatoid arthritis treatment with biological agents. A single center study

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Conflict of interest: Yes

[Objectives] To examine the efficacy and safety with biological agents (Bio) in Rheumatoid arthritis (RA) patients. [Methods] We examined the outpatient number of RA, Bio users, clinical remission (C-DAI), and Biotherapy adherence by overveiwing of clinical record respectively since April 2011 to October 2012. According to these data, we analyzed efficacy and safety among 6 kinds of Bio. [Results] The number of RA was 326 (70 males and 256 females) and Bio user was 54, so that rate of Bio user was 16.6%. Each Bio user was 17 Eternercept (ETN), 14 Tocilizumab (TCZ), 9 Abatacept (ABT), 7 Infliximab (IFX), 4 Golimumab (GRI), and 3 Adalimumab (ADA). The remission and adherence rate was ETN 53/71%, TCZ 79/79%, ABT 67/89%, IFX 43/57%, GRI 75/100% and ADA 33/33%, respectively. The discontinuation by serious adverb events occurred 5 cases, including 2 serious infusion reaction (IFX), 1 pneumonia (ETN), 1 phlegmon (TCZ), 1 leucopenia (TCZ). [Conclusion] The therapy of TCZ, ABT, GRI was good

enough both remission and adherence rate. However, the number of GRI therapy seemed to be small. ETN therapy was the cheapest because weekly half dose of ETN was enough to maintain remission status with Japanese RA patients.

P2-095

Analyzing the positioning of the subcutaneous injection (SC) golimumab (GLM) in our clinic

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Conflict of interest: None

Introduction: We have hypothesized to classify the SC GLM, the sixth biologic agent used for RA, as the third-line SC biologic in our clinic, following adalimumab and etanercept. Objective: To analyze the positioning of GLM as the third-line SC biologic, based on its efficacy up to week 52. Method: Evaluating the clinical course of the first 52 weeks of 12 RA patients receiving GLM treatment by DAS28-CRP. Average age: 66.1, biologic naive patients: 1, biologic-switching patients: 11 (2^{nd} bio: 6, 3^{rd} bio: 5, 4^{th} bio: 1). Results: At week 12-24, significant improvement was seen in DAS28-CRP, with no reports of adverse events. Factors of patients showing marked improvement were the concomitant use of MTX, disease duration< 3 years, age <60 years, and bio-switching<twice. Conclusion: Although GLM showed significant improvement at weeks 12-24, it was not seen as rapidly as in other SCs. However, GLM has been proved to be effective on biologic-switching patients, and with no dropouts due to AEs and its high level of safety, has confirmed its position as the third-line SC biologic. Moreover, its higher level of efficacy used as a 2^{nd} biologic suggests that it may be necessary to evaluate the efficacy of GLM classified at an earlier position, including the use on biologic naive patients.

P2-096

Efficacy and Safety of Etanercept in MTX Non-Indicated Cases

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Gifu Red Cross Hospital

Conflict of interest: None

[Objectives] Efficacy and safety of etanercept (ETN) were evaluated in patients w/ rheumatoid arthritis (RA) unable to receive methotrexate (MTX) due to complications etc. (MTX non-indicated cases). [Methods] MTX non-indicated cases treated with ETN were analyzed retrospectively. [Results] Among 29 patients on ETN, 8 were subject to analysis. Reasons for MTX non-indication was history of adverse events (AEs) in 4 cases, complications in 2 cases and others in 2 cases. Initial ETN dose was 50 mg/week. Two cases were concomitantly treated with SASP + PSL, 3 cases with PSL and 3 cases with no concomitant drug. DAS28CRP improved from 4.65 (before treatment) to 3.64 (after 12-week treatment), accompanied by rapid improvement in other each component. No severe AE developed, and only mild events of herpes zoster, hepatic dysfunction, etc. were noted. [Conclusion] ETN treatment on MTX non-indicated cases improved their clinical results, w/out any problematic AE. In MTX non-indicated cases, general condition is often poor and is important to conduct periodical monitoring and to detect changes in the condition w/out delay. ETN that does not require concomitant MTX use and has short half-life in blood, is promising as an alternative for treating MTX non-indicated RA patients.

P2-097

Case report of 3 RA patients who gained bio-free remissions treated with infliximab

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Conflict of interest: None

〔Objectives〕I aim the bio-free remissions and choose infliximab (IFX) for the poor control of the RA conditions despite of MTX medications. 3 RA cases who gained bio-free remissions despite of late type of RA were reported. 〔Methods〕13 cases were treated with IFX. Stage4 were 10 cases, Stage 3 were 2 cases, Stage2 was 1case. Class IV were 2cases, Class III was 1case, Class II were 7cases, Class I were 3cases. 6 cases had joint operations. 〔Results〕Case1. 18-years female. Stage1, Class I. She was getting worse from the JIA. In spite of MTX8mg, the synovitis continued. IFX was started. Case2.34-yearsfemale. Stage3, Class II. RA came out after the childbirth. From the first aiming the bio-free remission IFX was started. Case 3. 68-years female. Stage4, Class II. The deformity of the hand was admitted. DAS28 ESR at the start of IFX were 2.83, 4.04, 4.03 respectively. DAS28 ESR at the stopping of IFX were 2.55, 1.27, 2.33. And now 1.68 (after 5months), 1.80 (after 2 years), 2.45 (after 2months). All had no getting worse points in the X-ray views after the staring IFX. RA are not obstacles to their livings. 〔Conclusion〕By aiming for the bio-free remission from the start of treatments, 3cases of all 13cases gained bio-free remissions witth IFX regardless of not early stages of RA conditions.

P2-098

Validation of algorithms using genome-wide SNP analysis for prediction of remission (R) or low disease activity (L) for infliximab (IFX) or etanercept (ETN)-treated RA patients using multiple medical cohorts

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Conflict of interest: None

[Objectives]Achievement of R or L in IFX and ETN treatment is currently one of the most important matters in RA treatment. However, there is no method for prediction of R or L. In this study, we validated the third cohort sample by using the first and second cohort algorithms. **[Methods]**The first cohort included 187 RA patients, the second, 206 patients, and the third, 145 patients, for a total of 538 patients from eleven hospitals in different regions of Japan. R and L was determined by DAS28(CRP) within 24-30 weeks after the initiation of treatment with the biologics. We selected 10 SNPs associated with IFX or ETN-R or L which were common in both analyses of the first and second cohort ($p < 0.05$). We scored the relationship between each SNP and responsiveness, the estimated total score of 10 SNPs, and then examined relationships between R (L) and non-R (non-L), and the total score in the third cohort. **[Results]**Although only 18-44% of the patients

achieved R or L with IFX and ETN, the SNP algorithms can predict R or L with 76.7-88.9% accuracy in the third cohort samples. **[Conclusion]**These highly accurate algorithms using SNP analysis may be useful in the prediction of remission or low disease activity before treatment with IFX or ETN.

P2-099

Double remission criteria achieved better infliximab effect to RA patients

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Conflict of interest: None

[Objectives] [Methods] We adopted double remission criteria when we use infliximab to treat RA patients. 'Double' means strictly low CRP (lower than 0.1 mg/ml) and DAS28 criteria. At first Infliximab was administered 3mg/kg body weight as standard to each patient. At 10 weeks which is 4weeks after third IFX administration, when patient's data did not satisfy both criteria, we changed IFX dose to 6mg /kg at the fourth IFX infusion. Further at 22weeks which is fifth infusion time, double criterion was used and 10mg/kg was administered if necessary. [Results] We experienced 21 RA patients with IFX treatment 12 patients could achieve continuous remission. After keeping remission at least 1 year, IFX was stopped in 6patients. Out of these 6patients, 4cases continued remission more than 1 year. Further, 2 of them were drug-free for more than 1 extra year. [Conclusion] IFX is one of the best anti-TNF agents because of its strong anti-inflammatory effect to RA. But weakening of the effect often attacked us after several months from the start of the treatment, and it was the most difficult problem to be solved. This strict 'double remission criteria' may provide more efficient introduction of IFX and less discontinuation, both of which are necessary to better control of RA.

P2-100

Experience of Golimumab Treatment for Rheumatoid Arthritis Patients in my Clinic

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Conflict of interest: None

Objectives: We investigated the efficacy of Golimumab (GLM), as a first biologics on biologics-naïve rheumatoid arthritis (RA) patients comparing with other anti-TNF drugs in my clinic. **Methods:** 5 biologics-naïve patients of 17 patients treated with GLM (50mg) in my clinic were evaluated on swollen joint count, tender joint count, C-reactive protein (CRP), patient's global assessment, DAS28-ESR, SDAI and Boolean remission during more than 24 weeks. The efficacy of GLM was compared with other anti-TNF drugs (infliximab (IFX) 18 and adalimumab (ADA) 6) using current our clinic data. **Result:** In characteristics of patients, the mean age and disease duration of patients were 57.7±11.2 and 8.42±8.0 years. MTX (7.5±0.8mg) and PSL (3mg) were treated in 4 or 1 patients.The continuation rates of GLM, IFX and ADA were 100, 89 and 83% at 24 weeks individually. There were no serious adverse events by GLM treatment. GLM treatment improved swollen joint count, tender joint count, CRP, patient's global assessment, DAS28-ESR, SDAI in 24 weeks as well as IFX and ADA. The remission rates of DAS28-ESR, SDAI and Boolean at week 24 were 80%. **Conclusions:** These data suggested that the efficacy of GLM was induced rapidly, and maintained during 24 weeks. Finally, GLM may be first anti-TNF drugs for RA therapy.

P2-101

Consideration of the effectiveness of adalimumab for rheumatoid arthritis

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Conflict of interest: None

[Objectives] At this time, the effectiveness of administration of adalimumab (ADA) is considered, and its effect is reported. [Methods] Subjects were 22 patients (4 men and 18 women) who were receiving ADA (naive: 16, switch: 6). Mean age at the time of ADA introduction was 64.6 years. Whether a treatment effect could be achieved by ADA and the relationship with MTX dose in both continued and discontinued administration of ADA (no effect, adverse effects) were considered. [Results] 15 cases (68.2%) showed a treatment effect by ADA and 7 cases (31.8%) showed no effect. There were 11 cases of continued administration of ADA (naive: 10, switch: 1), and 11 cases of non-continued administration (no effect: 7, adverse effect: 4). Among bio-naive cases, in cases of low combination dose of MTX at ADA introduction, treatment effect could be gained by increasing the dose. In cases of a high combination dose of MTX at the early stage, even if the dose is reduced afterwards, a continuous effect can be expected In switched cases, full effect was not observed even at a combination dose of MTX of 8 mg. [Conclusion]. ADA is considered to be a drug which can be easily used in naive cases.

P2-102

Adalimumab (ADA) introduction in an Early RA patient attains Drug Free, Case which carried out pregnancy and childbirth

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Conflict of interest: None

[purpose] Effect of MTX low dose (6 mg or less) was evaluated on a early RA patient with biologicals [Methods] Case in which the MTX low-dose (6 mg) administrated patient was treated with ADA40mg to early RA of this department consultation.DAS-CRP, DAS28-ESR, SDAI, and CDAI were used for the effect monitoring. [Results] During the disease of a development-of-symptoms early stage, for six months, remission was attained from the 4th week, 52 or more weeks were maintained to the MTX (6 mg or less) use patient, and Drug Free was attained by introducing ADA to patient from the 86th (DAS28-CRP0.96, DAS28-ESR1.8, SDAI 0, CDAI 0) week.It was able to fulfill the pregnancy and the delivery which was the hope of the patients. High validity and tolerability have shown by introducing MTX low-dose +ADA40mg in an early stage to the development-of-symptoms. [Conclusion] MTX and the domestic only biological preparation which can be started to use from the time of said are ADA. We would like to examine the usefulness of ADA which can carry out a medical treatment start earlier on at the same period as MTX to the patient who needs medical treatment more powerful than the time of the first medical examination.

P2-103

The mode of effectiveness of etanercept treatment in patients with rheumatoid arthritis

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Conflict of interest: None

[Objectives] To analyse the mode of effectiveness of etanercept (ETN) treatment in patients with rheumatoid arthritis. [Methods] Inclusion criteria were (1) the duration of ETN treatment was over one year and (2) clinical data was fully available. Exclusion criteria was ETN was stopped less than one year due to adverse events. 89 patients were divided into two groups, GO group(47cases) (ETN was continued over one year and low disease activity or remission in DAS28-CRP was achieved at one year) and NGO group (42cases) (not GO group). [Results] Mean age in GO group was significantly lower than that in NGO group (54.8 yo vs. 61.4 yo) and the rate of concomitant MTX in GO group was higher than that in NGO group (80.9% vs 61.9%). There was a significant difference in baseline DAS28-CRP between groups (GO group; 4.58, NGO group 5.74).delta-DAS28-CRP from 0w to 1y was 2.47 in GO group and 1.54 in NGO group ($p<0.001$). The only delta-parameter that was different between groups was delta-VAS from 0w to 1y. [Conclusion] Age and concomitant MTX were related to effectiveness of ETN. Baseline disease activity should be lower before ETN treatment and this suggested that MTX treatment before ETN treatment was key point. ETN showed stable and constant effectiveness in both GO group and NGO group.

P2-104

Consideration of the persistence rate of infliximab in rheumatoid arthritis

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Conflict of interest: None

[Objectives] We examined the curative effect and its continuity of infliximab (IFX) for the rheumatoid arthritis (RA) patients. **[Methods]** It was aimed at 97 RA patients who were treated with IFX in our department from 2003 to 2012. The average age was 56.8 years old, and the mean duration was 10.3 years. We examined the dosage continuation rate of IFX using the Kaplan-Meier method. Moreover, stratified examination by a patient background was also performed. **[Results]** The average IFX given dose was 173 mg at the first time, and 232 mg at the last observation. IFX duration was an average of 2.8 years, and the longest was 9.0 years. IFX persistence rates in all patients were 75% in the first year, 64% in the second year, and 35% in the fifth year, and those in the 53 patients evaluated by DAS28-CRP were 89% in first, 82% in second, and 69% in fifth. In stratified examination, the conditions for obtaining a high persistence rate are that a patient was female, that it was less than 65 years old, that its serum CRP value was less than 1.0 mg/dL at ten weeks after an IFX medication start, or that it was evaluated with composite measure. **[Conclusion]** In the IFX therapy for RA, it was suggested that an improvement of a ten-week serum CRP value lead to the improvement of a persistence rate.

P2-105

Study on the efficacy of Adalimumab at this institution: group comparison based on pateints' background

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Conflict of interest: None

[Objectives] To compare clinical, functional, and structural effectiveness of Adalimumab (ADA) between patients with various backgrounds. [Methods] 67 RA patients being treated with ADA in our hospital between September 2008 and November 2010 were evaluated. We sequentially evaluated their DAS28, CDAI, mHAQ up to 104 weeks. We comparatively evaluated patients by different combinations of medication, stages, disease activity at the beginning of the disease, treatment history of biologicals, and duration of the disease. We also underwent X-ray image assessment (TSS) on the 52nd and 104th weeks. [Results] In different combinations of medication, a significant improvement was found among the groups with MTX or with TAC. The comparison between Naïve and Switch groups,significant improvement was found in Naïve group. [Conclusion] As a result of group comparison, there were differences in clinical, functional, and/or structural evaluations; however, effectiveness was recognized in combination groups with MTX or TAC, low stages, and high disease activity. ADA showed higher effectiveness with the combination usages of MTX or TAC, in a shorter duration of the disease, and in a high disease activity. However, it is said that ADA is effective for the progress cases and/or with Switch cases.

P2-106

Changes in the patient's baseline characteristics of biologics in the first year after their launch

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Conflict of interest: None

[Objectives] It is plausible that biologics has been introduced in milder RA patients, thus we investigate the changes in the patient's baseline characteristics of biologics in the first year after their launch. [Methods] RA patients who started infliximab (IFX, n=49), etanercept (ETN, n=50), tocilizumab (TCZ, n=62), adalimumab (ADA, n=52), abatacept (ABT, n=40) and golimumab (GLM, n=77) in our institute in the first year after their launch. [Results] Baseline characteristics of patients who started IFX/ETN/TCZ/ADA/ABT/GLM include age (median): 50/49.5/60/52/55.5/52years-old, duration (median) 6/8/8/8.5/10/9.5years, %methotrexate (MTX) 100/59.5/69.5/78.3/86.8/88.2, dose of MTX (average) 7.6/8.4/9.0/8.4/8.5/9.5mg/week, %prednisolone 87.5/85.4/78.0/58.7/65.0/47.4, dose of prednisolone (average) 6.7/7.0/6.0/5.8/5.8/4.9mg/day and 0/31/50.9/47.8/67.5/49.3% had history of prior use of biologics. In each biologics, DAS28 (median) improved from 5.8/5.4/5.2/4.7/4.6/4.5 to 4.4/3.8/2.4/3.5/3.6/3.1at 6 months, and retention rate at 6 months was 89.8/85.7/88.1/84.6/75/89.6%. [Conclusion] Baseline characteristics of biologics in the first year after their launch have been changed over the years.

P2-107

Outcomes of golimumab in patients with RA on the Tsurumai Biologics Communication Registry

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Conflict of interest: None

[Objectives] To investigate the efficacy and use of golimumab (GLM) in RA patients. [Methods] GLM was administered to 39 patients, who were then examined 24 weeks after the first administration. [Results] At 24 weeks, the drug survival rate (%) of cases administered 50 (n = 32) and 100 (n = 7) mg GLM was 65.6 and 85.7, respectively. The 50-mg cases were initially categorized into 3 groups depending on the time of first GLM administration and then examined. The drug survival rate (%), baseline data of the MTX concomitant rate (%), and mean dosage of MTX (mg/week) of the early, middle, and late groups were 40.0, 81.8, and 72.7; 30.0, 81.8, and 100; and 6.0, 7.0, and 9.6, respectively. Next, we categorized the 50-mg cases into 2 groups depending on the presence or absence of MTX. The drug survival rate (%), baseline data of disease duration (year), bio-naïve rate (%), and DAS28-ESR of MTX (−) (n = 9) and MTX (+) (n = 23) were 55.5 and 69.6; 19.9 and 11.4; 11.1 and 69.6; and 5.70 and 4.64, respectively. [Conclusion] Although use of 100 mg GLM is permitted in Japan, we mostly used 50 mg GLM. Concomitant MTX, moderate or less disease activity, and bio-naïve patients at baseline were necessary for obtaining an endpoint of 24 weeks in patients receiving 50-mg GLM.

P2-108

Analysis of the MTX dose-related efficacy and safety in the concomitant therapy of adalimumab

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Conflict of interest: None

[Objectives] Analysis of the methotrexate (MTX) dose-related efficacy and safety in the concomitant therapy of adalimumab (ADA) and MTX in our hospital. [Methods] We analyzed 47 patients who were given ADA as the 1st-biologcs more than 12 months ago about their efficacy and safety, dividing into 3 groups: MTX 8mg/w<(n=11), MTX 8mg/w≧(n=22) and MTX 0mg(n=14) combining at the time of ADA introduction. We additionally examined the association between efficacy and MTX dose as body weight and body mass index (BMI). [Results] DAS28-ESR and SDAI significantly improved at 3 months after the ADA injection in the patients receiving MTX. In them receiving MTX8mg/w<, we have observed the same tendency at 12 months. ⊿DAS28-ESR(0-12 months) and ⊿SDAI(0-12 months) were significantly largely decreased in the patients given MTX8mg/w<(-2.8, -19.3) compared to them given MTX8mg/w≧(-1.6, -10.9) and MTX-0mg(-0.5, -4.7). The dose of concomitant corticosteroid was also largely tapered in the group given MTX8mg/w<. The more MTX dose as BMI(mg/(kg/m^2)/w), ⊿DAS28-ESR(0-12 months) and ⊿SDAI(0-12 months) were more decreased significantly. [Conclusion] ADA was more effective when given concomitantly with MTX8mg/w<. It's preferable to start of ADA administration after using MTX8mg/w<.

P2-109

A study of estimation of effectiveness factors in RA patients with Adalimumab treatment for 24 weeks

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Conflict of interest: None

[Objectives] The purpose of this study is clarify the active predictive factor of the 24th week of the Adalimumab treatment. [Methods] We examined whether in RA patient with Adalimumab treatment for 24 weeks, each factor measured in 4 or 12 weeks would serve as a predictive factor of the validity of 24 weeks after. [Results] Correlation that the evaluation for 12 weeks of each factor was stronger was accepted. It was CRP(Correlation coefficient0.515, P=0.001), ESR(Correlation coefficient0.420, P=0.019), and DAS28(3) CRP(Correlation coefficient0.515, P=0.0015) that accepted DAS28(3) CRP after a start for 24 weeks, and strong correlation in four weeks. [Conclusion] It was shown that CRP of four weeks of ADA treatment, ESR, and DAS28(3) CRP serve as a predictive factor of the effect of 24 weeks after.

P2-110

Comparative clinical efficacy of anti-TNF-α inhibitors for 24 weeks in patients with RA

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Conflict of interest: None

【Objective】 We analyzed the comparative clinical efficacy of anti-TNF inhibitors for 24 weeks in patients with RA.【Method】 We compared DAS-CRP and clinical course of disease activity between 3 groups of patients in RA administered anti- TNF inhibitor (IFX, ETN, ADA) for 24 weeks.【Results】 There was no difference on the background between each group. The ratio of combined with MTX was highest in IFN group (100%) and lowest in ETN group (75.6%). The dose of combined MTX was highest in ADA group as 7.27 mg/W. DAS was significantly improved at 4 weeks in all of groups, especially ADA, that improved also at 24 weeks, improved more significantly.【Discussion】 We analyzed the reason why ADA improved DAS most significantly as below, Recently our consciousness and the importance of MTX itself have been changed, Increased dose of IFN has not been accepted yet, The dose of combined MTX was relatively higher in ADA group. The HARMONEY test showed the reason why ADA combined with enough dose of MTX was achieved additional efficacy was the decreased clearance of ADA.【Conclusion】 We consider that anti-TNF inhibitors, especially antibodies, improved efficacy of treatment for the patients with RA significantly with combined therapy of MTX at enough dose.

P2-111

Drug survival rate of Adalimumab compare within the annual transition- Based on Tsurumai Biologics Communication Registry (TBCR) -

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Conflict of interest: None

[Objectives] It has been reported that how maximize Adalimumab (ADA) efficacy under the daily practice, and further improvement has been shown after higher MTX dose was approved on February 2011. We evaluated the status of ADA drug survival rate under annual transition retrieved by Tsurumai Biologics Communications registry (TBCR). [Methods] 353 patients who were registered in TBCR were subjected for our analysis. Patients were subdivided into the three groups (Group1; Jun. 2008 – Aug. 2009, Group2; Sep. 2009 – Jan. 2011, Group3; Feb. 2011-), and Kaplan-Meier analysis was used to estimate drug survival rates and the difference in retention curves was examined by means of a log-rank test. [Results] 139 patients (Group1), 153 patients (Group2) and 61 patients (Group 3) were on drug disease durations were 13.4y, 11.7y, 8.6y subsequently. DAS28CRP were 3.86, 3.44, 3.66 and naïve patients were included 62.6%, 63.4%, 85.3% in each group. Drug survival rate based on the discontinuation because of the lack of efficacy was significantly higher in Group 3 compared to the other two groups. There is no difference among three groups in AE rate. [Conclusion] Recent changes in the daily practice have shown that ADA usage with higher MTX shows better efficacy and drug survival rate.

P2-112

Impact of body weight on the efficacy of Golimumab and the response to dose escalation in patients with rheumatoid arthritis

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Conflict of interest: None

Objective: The purpose of this study is to evaluate the impact of body weight (BW) on the efficacy of Golimumab (GLM) and to analyze the response to dose escalation. Patients and methods: Fifteen rheumatoid arthritis patients (pts) treated with GLM were enrolled in this study. The average age and disease duration were 58.0 years and 14.7 years, respectively. These pts were divided into two groups by their BW: group A (A) (n=10), BW<60 kg, and group B (B) (n=5), BW≧60 kg. We evaluated the retention rate, disease activity 12 weeks (wks) after the initiation of GLM and the efficacy of dose escalation. Results: The retention rate was 93.3% (A: 100%, B: 80%). The average DAS28-CRP at the baseline and 12 wks were 3.60 and 2.62 in A, and 4.46 and 4.80 in B, respectively. The pts achieving more than a moderate response according to EULAR criteria were 80% in A, and 40% in B. 40% in A achieved remission. Three of four pts in B had their dose of GLM increased to 100 mg. The average DAS28-CRP 12 wks after the dose escalation decreased from 4.92 to 3.11. Discussions: Although GLM tended to be less effective in heavy pts, the dose escalation ameliorated the disease activity in them. Although we analyzed only a small number of pts, BW may be one factor influencing the efficacy of GLM.

P2-113

Analysis of rheumatoid arthritis treated with usual dosage and interval of infliximab

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Conflict of interest: Yes

[Objective] To evaluate the rheumatoid arthritis patients who had been treated well by infliximab with ordinary dosage and interval; 3mg/kg and 8 weeks interval. [Methods] We treated 150 RA cases with infliximab. Among these cases, there were 29 cases that had been treated well more than two years in the treatment of ordinary dosage and interval of infliximab. [Results] Patients consisted of 24 women and 5 men. At the initiation of infliximab, RF positive rate was 79.3% and anti-CCP antigen positive rate was 75.9%. Steroid usage rate was 24.1%. Seven cases were infliximab free due to the good response to the therapy. [Conclusion] Less usage of steroid and shortage of disease duration were the factors for well response with usual dosage and interval of infliximab.

P2-114

Clinical efficacy of Simponi (golimumab) in 36 patients with rheumatoid arthritis(RA)

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Conflict of interest: None

Golimumab under the brand name Simponi is a human monoclonal antibody targeting tumor necrosis factor alpha (TNF), and approved as a forth TNF inhibitor in Japan. [Objectives] To assess the efficacy and easiness of administration of golimumab at the outpatients clinic in RA patients. [Methods] Patients with flared RA, not depending on the dosage of methotrexate (MTX) and another TNF inhibitors selected the biologics referring to the booklets all six products. We analyzed the background, clinical course and inflammatory condition of patients had selected Simponi. [Results] 36 patietns including 11 naive cases and 25 cases swiched from other biologics are performed a once monthly subcutaneous injection. The reasons they made a choice recieving Simponi were one month interval, less pain, asking nurse to inject it. Among the 11 naive cases, the average dose of methotrexate was 5mg per week and the average of oral prednisolone was only 2.4mg /day. The clinical symptomes and values improved soon after the injection, but 6 not naive cases changed from Simponi to others because of insufficient effects. [Conclusion] Golimumab effectively reduces the symptoms of RA and is generally well quickly tolerated in patients with relapsed RA even after tightly controlled by TNF inhibitors.

P2-115

Necessity of steroids for the administration of biologics in RA patients with low DHEA(S) levels

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Conflict of interest: None

[Objectives] To retrospectively compare the use of steroids and

continuation of biologic agents (without discontinuation) between RA patients receiving biologic agents, with normal blood dehydroepiandrosterone sulfate (DHEA-S) levels, and those with low DHEA-S levels. [Methods] The DHEA-S level was measured using the CLEIA method at SRL®. The low-DHEA-S group was established in accordance with the normal reference range provided by SRL®. The subjects were 53 patients with RA. The normal DHEA-S group (mean: 103±81.4μg/dl) consisted of 36 patients. The low-DHEA-S group (mean: 6.9±5.5μg/dl) consisted of 17. [Results] Before the start of bio therapy, steroids had been administered to 15 (42%) of 36 patients in the normal DHEA-S group. After bio administration, steroid therapy was discontinued in 3. In the low-DHEA-S group, steroids had been used in 15 (88%) of 17 patients before the start of bio therapy. After bio administration, there was no patient in whom steroid therapy was discontinued. Bio therapy was continued in 32 (89%) of 36 patients in the normal DHEA-S group. In the low-DHEA-S group, the percentage was significantly lower (47%, 8/17). [Conclusion] In RA patients with low DHEA-S levels, steroid therapy is necessary, but the continuation of biologics is not indicated.

P2-116

Examination of the MTX dose at the time of the adalimumab injection treatment start

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Conflict of interest: None

[Objectives] We examined which lowered the disease activity effectively in groups more than 10 mg at the time of the introduction or below 8 mg in the ADA introduction case in our institute. [Methods] Seven 8 mg group, average age 61 y.o., mean disease period is 5.5 ys.. The 10 mg group is nine cases, 54 y.o., 7.8 ys.. The evaluation reached at a rate of change of DAS28-ESR and SDAI. [Results] A rate of change at the time of the introduction was very high, 0.366 (8mg group), 0.443 (10mg group) in DAS28-ESR, 0.448 (8mg group), 0.550 (10mg group) in SDAI. 10 mg group tended to be high rate without the statistical examination. [Conclusion] In a TNF inhibitor installation guide line, we do it when I consider ADA use in the case with the poor-prognosis factor with high disease activity to overcome with less than six months in a disease period with MTX. It is a well-known fact that ADA+MTX is higher in the joint destruction suppressant effect than MTX alone. There was the one where ADA introduced MTX more than 10 mg into after administration in the tendency that the disease activity rate of decline was high by the result in our institute, otherwise if time to ADA introduction is long, the joint destruction is more likely to go and should think for adaptation to circumstances by a case.

P2-117

Safety assessment of abatacept in rheumatoid arthritis – Report from TBCR on patients after Week 52 –

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Conflict of interest: None

[Objectives] Regarding the safety of abatacept (ABT) in Japan, many reports show that serious adverse events (AEs) tend to occur less frequently compared with conventional biological products. However, few reports on safety after Week 24 exist, so we assessed safety after Week 52. [Methods] Among 282 RA patients receiving ABT who were registered in the TBC Registry (TBCR) of the Nagoya University, this study focused on withdrawals due to AEs and assessed risk factors in 156 patients for whom follow-up observation was possible for 52 weeks or more. [Results] The 52-week adherence was 76.3%, and administration was withdrawn because of lack of efficacy (16.0%), AEs (4.5%). AEs leading to withdrawal were mainly interstitial lung disease, malignant lymphoma. Withdrawal due to AEs occurred on average after 72.1 days, and only one patient withdrew after Week 24. All withdrawals due to AEs were in patients on concomitant MTX, including many switched patients. [Conclusion] A lower proportion withdrew from ABT due to AEs than for lack of efficacy, similar to the previous reports. The withdrawals due to AEs tended to take place early in the administration period and infrequently after Week 24, suggesting that ABT is a biological agent that is safe when administered continuously.

P2-118

Assessment of efficacy and safety of abatacept in the elderly

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Conflict of interest: None

[Objectives] Abatacept (ABT) is regarded as a biological agent that is relatively safe to administer to elderly patients with rheumatoid arthritis (RA). We assessed the efficacy and safety in elderly patients aged ≥65 years at Week 52. [Methods] Of 282 RA patients receiving ABT who were registered in the Tsurumai Biologics Communication Registry (TBCR) of the Nagoya University, 156 patients in whom administration and observation were possible for 52 weeks or more were assigned to the elderly (E) group (≥65 years, n=68) and non-elderly (N) group (n=88) to assess drug adherence and adverse events. [Results] DAS28CRP(4) decreased from 4.3 and 4.6 at the start of administration to 3.2 and 3.4 at Week 52 in the E and N groups, respectively, but there was no inter-group difference. Drug adherence in the E, and N groups was 82.4% and 70.5%, respectively, thus the E group had the higher adherence. Withdrawal due to adverse events, which occurred in 7 of 156 patients, included 2 in the E group (malignant lymphoma, interstitial lung disease) indicating no trend towards higher incidence. [Conclusion] In the elderly, drug adherence tended to be higher with lower withdrawal due to adverse events. This study suggests that ABT is a useful biological agent in the elderly.

P2-119

Two cases of ulcerative colitis during abatacept therapy in patients with rheumatoid arthritis

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Conflict of interest: None

[Case1] A 24-year-old woman was diagnosed with rheumatoid arthritis (RA) in Mar 2010 and was treated with methotrexate (MTX). Abatacept (ABT) was initiated 3 months later. In Jun 2012, she developed diarrhea and bloody stool and discontinued ABT and MTX. By colonoscopy, a diagnosis of ulcerative colitis (UC) was made and oral mesalamine was started. The intestinal symptoms were improved in a month and MTX was restarted. In

Oct 2012, a recurrence of UC symptoms along with arthritis was observed. She was planned to use Infliximab. [Case2] A 21-year-old woman was diagnosed with RA in Jul 2011 and was treated with MTX. ABT was started next month. In Mar 2012, she developed diarrhea and bloody stool. ABT and MTX were discontinued, 5 months later. By colonoscopy, a diagnosis of UC was made and oral mesalamine was started. However, no satisfactory response was observed. Therefore, a combination therapy with prednisolone and granulocytapheresis was administered. The intestinal symptoms were rapidly improved. In contrast, arthritis was relapsed and MTX was restarted. [Conclusion] Although coexistence of RA and UC is rare, a complication of UC should be taken into consideration, when diarrhea and bloody stool were observed in patients with RA during ABT therapy.

P2-120

Case report: melena due to bleeding colonic diverticulum during abatacept treatment

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Conflict of interest: None

[Objectives] Perforation of the digestive tract is one of the most important adverse events of biological DMARD treatment. No perforation reported in Japanese rheumatoid arthritis patient treated with abatacept before, therefore abatacept was recognized comparatively safer biological DMARD. [Case] 63-y.o.-Japanese female, 9 years disease duration, Stage III, Class III. She previously suffered perforation of the digestive tract during tocilizumab treatment. [Clinical course] She treated with 750mg of abatacept each for ten times, then the disease activity significantly improved. DAS28-ESR decreased from 5.87 to 4.01. She showed massive melena 9 days after last administration of abatacept and hospitalized for further examination. [Results] Colon fiber scope examnation showed no active bleeding, but many diverticula in assending and transverse colon. Therefore we diagnosed bleeding colonic diverticulum. [Conclusion] Since perforation possibly occurs secondary to bleeding colonic diverticulum abatacept is no longer safer biological DMARD. Perforation of the digestive tract is an important adverse event of all of biological DMARDs

P2-121

The case of critical pneumocystis pneumonia during abatacept medication

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Conflict of interest: None

A case is 75 years-old woman.The symptoms of RA were shown at April 2011.Since it was CDAI 30 and a high disease activity in MTX10 mg/W and PSL5mg, combined administration of the abatacept was carried out from November, 23.Although remission was attained in May, 24 and it was able to maintain after that, it falls with an appetite loss and SpO2 86% at October1. The ground glass opacity on chest X-ray and the mosaic which spreads in all the lung in CT was accepted. The positivity of pneumocystis jirovecii was checked from expectoration PCR and βD glucan rise, and diagnosis was pneumocystis pneumonia. It gradually decreased from PSL60mg after that between 9 doses of ST, and three days of 1000mg methylprednisolones.Nausea after a medical treatment start changes into pentamidine from an ST. Although βD glucan decreased, fibrosis of a pneumonia part reinforces and reduction of slight mediastinal pneumothorax and a lung appears. Furthermore, the secondary infection of a cytomegalovirus and the pseudomonas aeruginosa is caused on October 29, and it is under medical treatment still now. Although the safety of abatacept to infection is high, there is a danger of causing critical pneumonia like this case. It was a case made to have a new appreciation of the risk of applying immune suppression.

P2-122

Comparison of the first biological treatment responses between abatacept and infliximab in patients with rheumatoid arthritis

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Conflict of interest: None

[Objectives] To compare treatment responses between abatacept (ABT) and infliximab (IFX) in which the first biologic treatment was initiated. [Methods] We evaluated 19 patients with RA who had received firstly abatacept (A group) (mean age: 62.6, male/female: 3/16, disease duration: 63.0 months, stage I: 10, II: 3,III:4, IV: 2, class1:3, 2: 16) compared with 91 RA patients who newly treated with IFX (I group). All subjects were full-filled with ACR/EULAR new criteria (2010) or 1987 ACR classification for RA and examined by ACR core set, DAS 28(ESR,), modified HAQ, and MMP-3 monthly [Results] 1. There was no difference of clinical responses between A and B groups. 2. A group was older aged and slightly lower value of DAS28 compared to I group. 3. A group was slightly higher disease activity score (DAS28) than I group during post-treated 12 month. There was the same clinical response treated after 24 weeks between A group and I group. [Conclusion] Our data indicate that there were no clinical relevant differences between ABT and IFX which was firstly treated in patients with RA.

P2-123

Evaluation of efficacy of abatacept (ABT) in RA patients

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Conflict of interest: None

Evaluation of efficacy of abatacept (ABT) in RA patients 12 patients with RA(mean age,62.8 years;mean disease duration,11.1 years;mean DAS28-ESR/CRP, 3.89/3.23; 9 patients were bio-naïve and 3 were switched from TNF blocker;8 were treated in combination with MTX and 4 received ABT alone) received ABT from December 2010 to July 2011.Efficacy was assessed based on prior use of biological products and combination with MTX. Before administration,mean DAS28-CRP was 3.16 in bio-naïve patients and 3.40 in those switched from TNF blocker but improved significantly to 2.49 and 2.30 at Week24.Mean DAS28-CRP at Week 52 was 2.37 in bio-naïve patients and 2.47 in those switched from TNF blocker.Mean DAS28-CRP was 2.57 and 2.33 in patients with and without MTX coadministration. At Week 52,4 patients(44.4%) were in remission and 3 patients(33.3%) had low disease activity. Adverse reactions comprised headache/itching,eruption,and pleural effusion in one patient each. In contrast to previous biological products,ABT showed stable clinical outcomes regardless of whether patients were bio-naïve,switched or administered MTX. However,caution is required because we have also experienced difficulty in administration of ABT for one year in patients ≥70years where MTX is not used.

P2-124

The efficacy of abatacept in a patient with refractory rheumatoid vasculitis complicated with bilateral leg ulcers

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Conflict of interest: None

Administration of abatacept (ABT) successfully improved bilateral leg ulcers complicated with refractory rheumatoid vasculitis (RV). We report this case with some discussion in terms of the treatment with refractory RV. Case: A 54-year-old man. Current history: He developed RA since 1997 and had been treated with several DMARDs. Since disease activity was not controlled, he was administered tocilizumab (TCZ) as a case in clinical trial in 2002. After the first initiation of TCZ, pain and edema in bilateral legs deteriorated. He was diagnosed as RV by skin biopsy from his leg. He discontinued TCZ immediately and was treated with oral steroid, leflunomide and cyclosporin A, but these were insufficient. Then, he was administered etanercept (ETN) in 2008. Since edema got worse, ETN discontinued after 3 months of first initiation. After that, ulcers of bilateral legs developed. He was treated with immunosuppressants such as azathioprine, steroid pulse therapy, and intravenous cyclophosphamide. Because multiple ulcers in bilateral legs gradually got worse, he was hospitalized in April 2012 and administered with ABT. After the first initiation of ABT, his clinical symptoms such as pain and edema obviously improved. And multiple leg ulcers also improved with continuous use of ABT.

P2-125

Four cases of rheumatoid arthritis complicated with systemic lupus erythematosus treated with abatacept

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Conflict of interest: Yes

[Background] TNF inhibitors occasionally develop lupus-like syndrome as a result of the therapy, but it has not been reported abatacept (ABT) induces such reactions. ABT is also expected to be effective to SLE by inhibition of T cell activation. [Objectives] To assess efficacy and safety of ABT in RA overlapped with SLE in our department. [Patients & Methods] 4 patients(1 male), Average age; 58.0±14.7 years old, Average disease duration; 6.8±3.8 (RA) and 11.3±10.6 (SLE) years, Steinbrocker stage; I(1), II(1), IV(2). All cases were class 2. Disease activity (SDAI and CDAI); high (1), moderate (1), low (2). Prednisolone (PSL) and methotrexate were administered to all cases. The disease activity of RA was measured by DAS28, SDAI and CDAI. That of SLE was evaluated with SLEDAI and BILAG index. [Results] Two patients achieved a clinical remission by DAS28-CRP(4), SDAI and CDAI. Although anti-dsDNA antibody titer was not changed in all cases, hypocomplementemia was improved in 2 patients. SLEDAI and BILAG score decreased in all cases. Adverse events were not observed in the observational period. PSL dose was reduced in 3 patients. [Conclusion] ABT could be administered safely in RA overlapped with SLE. Thus, it is thought that ABT might be the first biologics in DMARDs-resistant RA with SLE.

P2-126

Therapeutic effects of abatacept in patients with rheumatoid arthritis complicated with autoimmune diseases

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Conflict of interest: None

[Objective] To investigate therapeutic effects of abatacept (ABT) in patients with rheumatoid arthritis (RA) complicated with autoimmune diseases. [Patients and Methods] We evaluated clinical course of 11 RA patients in our hospitals treated with ABT retrospectively. The autoimmune diseases complicated with RA observed were: Sjögren's syndrome in 7 patients, systemic lupus erythematosus (SLE) in 2, and myasthenia gravis in 3 patients. [Results] The mean simplified disease activity index (SDAI) of the eleven patients before the start of ABT was 21.72. Ten of the eleven patients had continued administration of ABT without adverse effects. Improvement of disease activity of RA was found: the mean SDAI of the ten patients after 24 weeks administration of ABT was 11.83. No exacerbations of complicating autoimmune diseases were observed during follow-up period. In addition, a decline in the titer of anti-double-stranded DNA antibodies was found in a patient with SLE. [Conclusion] ABT might be useful for both RA and complicating autoimmune diseases.

P2-127

The effect on changing to abatacept from the other biologics for the patients with rheumatoid arthritis(RA) complicated with systemic lupus erythematosus(SLE)

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Conflict of interest: None

[Objectives] Abatacept is known as a agent inhibits the costimulation of T cells. And a clincal trial is studying abatacept treatment in lupus nephritis. This study examined the effect on abatacept for the RA patients complicated with SLE. [Methods] Abatacept(500mg/4w) was administered to 4 RA patients (male:1, female:3, age:23-69) 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 immune-serological test data 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 the other 2 patients. As indicators of the activity of RA, normalization of serum CRP was observed in 1 patient. Improvement of MMP-3 was observed in the other 1 patient, No worse case was found for these 4 kinds of tests during the abatacept therapy. Improvement of joint symptoms was observed in 2 patients and no deteriorations was found in the other 2. No side effect was observed in the patients undergoing abatacept therapy. [Conclusion] Abatacept seemed to be a useful agent for RA patients complicated with SLE

P2-128

KL-6 decreased after using Abatacept(ABT) to two patients who has RA and polymyositis with interstitial pneumonia

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Conflict of interest: None

We used Abatacept in two patients who has RA and polymyositis with interstitial pneumonia (IP). After administration of ABT, their KL-6 was decreased. Case1: 52 years old man. He was given diagnosis of IP on June 2011. After then he felt polyarthralgia and elevation of ACPA, he was lead to the diagnosis of RA. He had drug eruption by SASP, so he used Mizoribine. In October His CPK elevated and he had loss of muscle strength, and he was given diagnosis of polymyositis and Steroid pulse therapy was done, after then PSL1mg/kg was administered. During the reduction of PSL dose, his RA was flared. In February 2012 ABT was administered, after then KL-6 decreased from 1550 to 406. RA became remission. Case2: 62years old woman. She had RA and polymyositis and scleroderma with IP. She used MTX4mg/Week, tacrolimus 2mg/day, PSL10mg/day, but her RA was very active, so she began to use etanercept (ETN)25mg/week on June 2011. After then RA was improved but KL-6 elevated to 1830 without worsening computed tomography image. We stopped to use ETN and changed to ABT, after then KL-6 decreased to 1020. We think ABT is related to worsening of IP, but two patients who are noted above revealed decreasing KL-6. We cannot find report about this, so we will report this two cases.

P2-129

The prospective analysis of serum oxidative stress and serum pentosidine in RA patients treated with tocilizumab

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Conflict of interest: None

[Objectives] To analyze how tocilizumab (TCZ) affects the oxidative stress in RA patients. [Methods] Ten RA patients administered with TCZ were selected. Of 10, 8 were bio-naive, and average doses of methotrexate and methylprednisolone were 4.3mg/week and 3.8 mg/day. Age was 53 year old, and disease duration was 9.2 years. Disease activity score (DAS) 28(4)-ESR, serum pentosidine (PGE), d-ROM, and MMP-3 were examined just before TCZ treatment, 3, 6, and 12 months after TCZ. Time course of each parameter and the correlation between DAS28 and the others were statistically analyzed. [Results] DAS28(4)-ESR was 4.61 before TCZ, and significantly decreased to 1.96 after 3 months of TCZ treatment. The d-ROM value was 406 U.CARR, and significantly decreased to 236 after 3 months, and preserved until 12 months. No significant decrease was detected in serum PGE. MMP-3 data showed significant decrease after 3 months (97 ng/ml) compared to before TCZ treatment (212 ng/ml) and then preserved until 12 months. DAS28(4)-ESR was significantly correlated with d-ROM value ($r=0.56$, $p<0.01$). [Conclusion] Tocilizumab prominently decreases DAS28(4)-ESR and d-ROM in RA patients by 3 months and these decreases were preserved until 12 months, suggesting that d-ROM is a useful marker of RA disease activity.

P2-130

The evaluation of the onset time of TCZ therapy for RA patients using FDG-PET/CT

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Conflict of interest: None

[Objectives] While tocilizumab (TCZ) is known to decrease the C-reactive protein (CRP) in the early phase of its administration, the evaluation of the clinical efficacies by TCZ seems to be difficult. In this study, FDG-PET/CT was employed for the evaluation of TCZ against rheumatoid arthritis (RA) at both 3 and 6 months after the administrations of TCZ, and to investigate the relationships between FDG uptake and clinical symptoms. [Methods] A total of 20 patients with RA have undergone TCZ therapies; 5 males, and 15 female with an age of 61.5 ± 12.0, and with a disease duration of 15.3 ± 13.2 years. The maximum standardized uptake value (SUVmax) was calculated. And, both the temporal changes in the total SUV and those of clinical symptoms were examined. [Results] The total SUVs were significantly decreased at both 3 and 6 months after TCZ administrations compared to those before administrations ($p=0.001$ and $p=0.01$). No significant differences were achieved between those of 3 and 6 months. Furthermore, at these two points, other clinical parameters except TJC, RF and ACPA were also shown to be significantly decreased ($p< 0.05$). [Conclusion] The present study indicated that TCZ have clinically beneficial effects on RA patients as early as 3 months after its administrations.

P2-131

The Usefulness of Measuring Bone and Cartilage Metabolism Markers in the Utilization of Tocilizumab (2)

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Conflict of interest: Yes

[Objectives] TCZ was administered to RA patients and clinical assessment and Spearman rank-correlation coefficient (ρ) of bone and cartilage markers were examined. [Methods] Markers were examined in 20 RA who received TCZ at Kinki University in 2010-12. Average age 57, stage I5/II5/III1/IV9, class I4/II14/III2/IV0, disease duration of 8.8 years, MTX 6.5mg/W, PSL 4 mg. 13 RA had history of biological agent use, and they were evaluated before administration and after 12, 24 and 52 weeks. [Results] DAS28 at 52 weeks was significantly decreased from 5.1 to 1.9. Under TCZ treatment, the ⊿value of markers at 52 weeks showed significant correlation for ⊿MMP-3 with ⊿CRP: ρ=0.6108 and swollen joint count (52W): ρ=0.5571; ⊿IL-6 with OC (24W): ρ=0.6762, NTX (24W): ρ=0.6985, CTX-2 (24W): ρ=0.5 and OC (52W): ρ=0.8088; ⊿OC with body weight (pre): ρ=-0.496 and CTX-2 (52W): ρ=-0.4662; ⊿NTX with SJC(24W): ρ=0.5016; ⊿OPG with ⊿CRP: ρ=0.4485; DKK-1 with body weight (pre): ρ=0.-5043, OC (52W): ρ=0.5805, ESR (24W): ρ=-0.6194 and CRP (24W): ρ=-0.484; ⊿CTX-2 with swollen joint count (52W): ρ=0.6751, tender joint count (52W): ρ=0.609 and DAS28-ESR (52W): ρ=0.5206; and ⊿OC/NTX with DKK-1 (52W): ρ=0.697. [Conclusion] TCZ suppresses RA disease activity and promotes bone formation.

P2-132

Analysis for background and comports for RA patients categorized DAS remission and low disease activity (LDA) by Clinical Disease Activity Index(CDAI) treated with tocilizumab(TCZ)

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Conflict of interest: None

[Objectives] Clinical Disease Activity Index (CDAI) remission is strict compared to DAS28ESR. But low disease activity of CDAI is wider than LDA of DAS28ESR. We are going to analysis background and comports for RA patients categorized DAS remission and low LDA by CDAI treated with tocilizumab (TCZ) and then we are going to make sure what is the consolidation points. [Methods] 55 DAS remission cases treated with TCZ from Tsurumai Biologics Communication Registry were entered. Tender joint count (TCJ), Swollen joint count (SJC), operation history, joint trouble different from the 28 joints were also checked. [Results] 55cases were categorized CDAI remission 15, CDAI-LDA 33, CDAI-MDA 7cases. 26 cases from CDAI-LDA and 2 from CDAI-MAD was located in TJC+SJC≤2 group. 10 from the 28 cases had Operation history. 8 cases had trouble on joints different from the 28 joints. [Conclusion] We must care for operation history and other joint trouble different from the28cases. Figure TJC SJC is so high figure, we must intensify the treatment.

P2-133

Early efficacy of tocilizumab in rheumatoid arthritis patients

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Conflict of interest: Yes

[Purpose] The objective is to evaluate the early effect of tocilizumab (TCZ) in moderate to severe active rheumatoid arthritis (RA) patients. [Method] One hundred and one patients treated with TCZ were registered in this retrospective study. We assess the changes of the clinical evaluation index (DAS28-CRP, DAS28-ESR, SDAI, and CDAI at baseline and 4weeks). [Result] Most patients were female (83%),mean age was 58.6y,mean disease duration was 8.3y,mean rate of previous biologics (Bio) use was 49.5%.The amount of change in DAS28-CRP was -2.3 ± 1.2, DAS28-ESR was -2.8 ± 1.2, SDAI was -27.6 ± 15.0, CDAI was -26.1 ± 14.7.The rate of change in DAS28-CRP was -38.5 ± 16.5%, DAS28-ESR was -41.3 ± 15.5%, SDAI was -53.7 ± 20.7%, CDAI was -52.8 ± 21.2%. In the change of all index, the Bio-naive patients was significantly better than the group of the Bio-switch patients. [Conclusion] These data presented the early clinical efficacy of TCZ. In addition, the result that the Bio-naïve patients were better response suggested the importance of the early and aggressive treatment for achieving the good efficacy of TCZ.

P2-134

A 52-week prospective study of the effect of tocilizumab (TCZ) as a first biologic on QOL -SAQRA study-

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Conflict of interest: None

Objective: To evaluate QOL after 52 weeks of TCZ treatment in patients with RA. **Methods:** Sixteen biologic-naive RA patients had been treated with TCZ along with the QOL (SF-36) study completed, we prospectively investigated efficacy using DAS28-ESR, HAQ and SF-36 (LOCF analysis). **Patient characteristics:** Mean age, 64.3 y; sex (M/F), 1/15; mean disease duration, 4.2 y; and 14 patients were taking MTX (mean dose, 10.4 mg/w). Results: The following measures improved significantly: DAS28-ESR, 5.0 to 1.6 (remission rate, 85%); TJC, 6.6 to 0.6; SJC, 3.3 to 0.1; ESR, 39.6 to 7.5; patient global VAS, 52.6 to 15.0; HAQ, 0.89 to 0.29 (remission rate, 89%). The SF-36 scores showed improving tendencies: physical health score, 26.3 to 41.0; mental health score, 52.6 to 55.7. The continuation rate at Week 52 was 88% (one discontinuation for AEs and one for lack of efficacy). **Conclusions:** The SF-36 physical and mental health scores improved, but not significantly so. However, high efficacy and remission rates were obtained for not only DAS28-ESR, but also for HAQ. Excellent clinical and functional remission can be achieved with TCZ as a first biologic.

P2-135

Effects of baseline C-reactive protein and matrix metalloproteinase-3 levels on 1-year tocilizumab treatment outcomes

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Conflict of interest: None

[Objectives] To examine associations between clinical results of 1-year tocilizumab (TCZ) treatment and baseline CRP and MMP-3 levels. [Methods] This study included 65 patients whose CDAI after 1-year TCZ treatment was assessed at our hospital. They were stratified into low (L), medium (M), and high (H) groups by baseline CRP and MMP-3 levels. [Results] The analysis by CRP showed that L, M, and H groups had mean baseline CRP levels of 0.6, 2.3, and 5.4 mg/dL, and mean baseline CDAI of 22.0, 23.5, and 34.1, respectively. The baseline CDAI was significantly higher for the H group than others. However, no significant between-group differences were noted in mean CDAI at 1 year (L 12.0, M 10.8, H 14.4). When stratified by baseline MMP-3, L, M, and H groups had mean baseline MMP-3 levels of 103.0, 209.7, and 551.5 ng/mL and mean baseline CDAI of 23.0, 28.0, and 29.2, respectively. The baseline CDAI were significantly higher for the H group than the L group, whereas CDAI at 1 year demonstrated no significant differences between groups (L 11.3, M 12.8, H 13.1). [Conclusion] Patients showed remarkable decrease in CDAI after 1-year TCZ therapy, regardless of baseline CRP and MMP-3 levels. This study suggests that TCZ is effective for patients with elevated levels of these markers.

P2-136

Clinical interventions for achieving Boolean remission in patients with rheumatoid arthritis undergoing tocilizumab (TCZ) treatment

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Conflict of interest: None

[Objectives] To identify clinical approaches for achieving Boolean remission in patients with RA receiving tocilizumab (TCZ). [Methods] 12 RA patients receiving TCZ for 8 or more weeks were retrospectively analyzed for remission in DAS28-ESR and Boolean criteria, and also the components of disease activity. [Results] After 24 weeks, a difference was noted in remission rate between DAS28-ESR and Boolean criteria (80% and 40%). The proportions of TJC, SJC, CRP, and Pt-VAS scores ≤ 1 were 80, 90, 90 and 40%. These data suggest that Pt-VAS is the limiting factor for meeting Boolean remission, and Pt-VAS was strongly correlated with MMP-3 ($r = 0.9$, $P < 0.01$). Additionally, Pt-VAS was also correlated with HAQ. Actually, 2 patients who underwent synovectomy while receiving TCZ showed that Pt-VAS scores were reduced to ≤ 1 by normalization of seum MMP-3 levels, postoperatively. [Conclusion] Although TCZ is shown to powerfully reduce disease activity in DAS28-ESR, Pt-VAS ≤ 1 is the key criterion for patients receiving TCZ to fulfill the Boolean remission. Improvement in Pt-VAS correlated with decrease in serum MMP-3 level. We believe that surgical interventions including arthroscopic synovectomy are appropriate for patients receiving TCZ to achieve optimal clinical outcome.

P2-137

Significance of Combining Tocilizumab and Methotrexate in Patients with Early Stage Rheumatoid Arthritis

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Conflict of interest: Yes

[Objectives] To examine the efficacy of combining tocilizumab (TCZ) and methotrexate (MTX) in patients with early stage rheumatoid arthritis as a multicenter observational study in Yamaguchi prefecture. [Subjects and Methods] Subjects were 9 patients who could be observed for at least 24 weeks among 20 patients who were enrolled. Patient demographics: Mean age 47.4 years, mean disease duration 12.3 months, DAS28-ESR 5.2±1.2, CDAI 24.7±9.3, MTX 8.4±1.7mg/week, history of TNF inhibitors 77.9%, ACPA 58.9U/mL, IL-6 22.4pg/mL, MMP-3 280.9ng/mL, and m-HAQ 0.74. Efficacy was evaluated using DAS28-ESR, CDAI and m-HAQ. [Results] After 24 weeks, DAS28-ESR 1.5±1.2, CDAI 3.0±3.1 and m-HAQ 0.14 were significantly improved. ACPA, IL-6 and RF did not show significant change, and did not correlate with treatment response (⊿DAS, ⊿CDAI). However, MMP-3 significantly improved after 12 weeks and correlated with treatment response. Adverse events were 4 events in 3 patients, all non-serious. [Conclusion] TCZ+MTX treatment in RA patients about 1 year after onset showed efficacy equaling or surpassing other drugs, and the change in MMP-3 after 12 weeks may be able to predict the effects.

P2-138

Study for Treatment Adherence of RA with Tocilizumab comparing initial phase of going on the market, next phase, and last phase

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Conflict of interest: None

[Objectives] First object is study for adherence of RA with tocilizumab (TCZ) comparing initial from going on the market to one year after initiation, next from one to two year, and last from two to three year after initiation. Next object is to make sure accumulation of experience with TCZ affects on adherence. [Methods] 290 RA cases treated with TCZ from Registry are divided into 3 groups. Initial contains 109 cases from May 2008 to April 2009,Bio-Naïve 37%, MTX user 38%, average DAS28ESR(4) 5.7 before initiation. Next contains 92 from May 2009 to April 2010,Bio-Naïve 29%, MTX user 49%, DAS 5.7. Last contains 89 from May 2010 to April 2011, Bio-Naïve 27%, MTX user 64%, DAS28 5.4. After 12 months, we check treatment adherence and average DAS28 from each, also check reason for cessation of treatment. [Results] The treatment adherence after 12months is 71% from initial group, 82% from next, 90% from last. The treatment adherence from last group, 90%, is significantly high (P=0.003). Average DAS28 is 2.9 from initial, 3.1 from next, 2.8 from last. [Conclusion] Initial phase of TCZ, we are not familiar with effectiveness and adverse event. Year by year, Adherence goes up, 71, 82and90%. Nowadays, we knows how to deal with TCZ, we conclude 'Adherence 90%' is real potential of TCZ.

P2-139

Interval extension of Tocilizumab in patients with rheumatoid arthritis

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Conflict of interest: None

[Objectives] To evaluate the effect of interval extension of Tocilizumab (TCZ) for Rheumatoid Arthritis (RA). [Methods] We analyzed 71 RA patients treated with TCZ in our hospital, whose treatment was decided by each doctor. [Results] Dosing interval was 4 weeks for 53 patients (75%; non-extended group, NE-group), while that for 18 patients was over 5 weeks (extended group, E-group), in detail, 5 weeks for 8 patients (11%), 6 weeks for 9 patients (13%), and 10 weeks for one. When TCZ was started, no significant difference was found in their background (age, sex, disease duration/activity, medication) between 2 groups. In E-group, all patients had CRP ≦0.1 mg/dL and 9 patients had

achieved CDAI remission at the first extension. CDAI improvement of E-group at the first extension was significantly better than that of NE-group at the end of study. Functional class, CDAI remission rate, and corticosteroidal requirement were significantly improved in E-group than in NE-group throughout the study. No significant difference was found about infection or discontinuance of TCZ. [Conclusion] TCZ responder could achieve or keep remission despite interval extension.

P2-140

Bio-Switch for the patients with RA who discontinued Tocilizumab

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Conflict of interest: Yes

Objectives This study aimed to examine the results of bio-switch in RA patients who discontinued tocilizumab (TCZ), based on prospectively registered data (Fukuoka RA Biologics treatment group, FRAB registry). **Methods** Twenty-four RA patients who discontinued TCZ and then received other biologics were examined with a minimum follow-up of 6 months. The patients (average age 56.4 years; average disease duration 14.1 years) were divided into two groups; the Ineffective group who discontinued TCZ due to lack of efficacy (N=16) and the Other group who discontinued TCZ by other reasons such as adverse event (N=8). Biologics for the switch included ABT (10), GLM (10), ETN (4) and their combination. **Results** DAS28 at baseline and the final observation was 4.3 and 4.6, respectively. Bio-switch was effective in the Other group (3.7 to 2.4), however, it was not in Ineffective group (4.6 to 4.7). There was no case with Low disease activity (EULAR) in the Ineffective group. No difference of efficacy was noted among the biologics. **Conclusions** Bio-switch for the patients with the TCZ inefficiency was not effective regardless of the biologics.

P2-141

Investigation of availability of Tocilizumab(TCZ) for Rheumatoid arthritis(RA) patients -the differences in treatment efficacy between Bio naïve and pre-administration-

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Conflict of interest: None

[Objectives] We investigated differences in treatment efficacy between naïve to biological agents (Bio-naïve) and those who had preceding with other biological agents: antibody preparation administration group (pre-IFX/ADA), and receptor antagonist administration group (pre-ETN). [Methods] Subjects were 56 RA patients for whom TCZ was initiated, including 15 in the bio-naïve, 18 in the pre-IFX/ADA, and 23 in the pre-ETN group. [Results] Average doses of MTX at the start of TCZ were 3.6mg in Bio-naïve,5.9mg in pre-IFX/ADA and 3.1mg in pre-ETN($p=0.03$,pre-IFX/ADA vs pre-ETN).No intergroup differences in absolute values of DAS28 were observed. However, the improvement rate of DAS28CRP and MMP-3 were significantly higher in the pre-IFX/ADA than pre-ETN ($p<0.01$, $p<0.01$). No significant differences were observed between the bio-naïve and pre-administration group. [Conclusion] No significant differences in treatment efficacy were observed between the bio-naïve and pre-administration group. Among the pre-administration groups, pre-IFX/ADA responded more favorably to TCZ than pre-ETN.

P2-142

Comparison of Patients with Rheumatoid Arthritis who Showed both DAS28 (ESR) and CDAI Remission after 24 Weeks of Tocilizumab (TCZ) and Infliximab (IFX) Therapy

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Conflict of interest: None

[Objectives] We previously reported that ACPA is a related factor in patients with both DAS and SDAI remission by TCZ therapy. We increased the number of patients and conducted comparison with the TNF inhibitor IFX. [Methods] Subjects were patients who met DAS28 remission criteria 24 weeks after initiation of IFX or TCZ therapy. Patients who attained DAS remission only and who attained both DAS and CDAI remission were compared. Age, sex, disease duration, disease stage, ACPA, RF, MMP-3, DAS, CDAI, mHAQ, PSL and MTX dose at start of treatment were compared. [Results] After 24 weeks there were 11 patients of DAS remission in the IFX group and 41 in the TCZ group. Among these were 9 and 28 patients of DAS/CDAI remission (DAS/CDAI remission rate: 81.8% vs. 68.3%). In multivariate analysis, ACPA, disease duration and mHAQ at the start of administration were extracted as factors for DAS/CDAI remission ($p=0.009$, $p=0.003$, $p=0.002$, respectively). In examination of the effects of the drug, these three factors were extracted in the TCZ group, while none of them were extracted in the IFX group. [Conclusion] ACPA-positive RA can have immunopathological mechanisms which differ from negative RA, and TCZ can be first choice for patients with high ACPA, short disease duration and low mHAQ.

P2-143

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 and Method] Some rheumatoid arthritis (RA) patients have progressive bone lesions despite being persistently negative for C-reactive protein (CRP), an inflammatory reaction marker. Cumulative percentages are approximately 10% at 6 months and 30% at 24 months. 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 with RA and progressive bone lesions despite persistently negative CRP. Tocilizumab efficacy and their clinical courses were evaluated. [Results] Pre-treatment serum IL-6 levels were undetectable, 10 pg/mL, and 17 pg/mL in one patient each. DAS28-ESR and CDAI results at 12 weeks after tocilizumab treatment showed a tendency for marked improvement in all three patients. Two followed up for 24 weeks had no further bone lesion progression. [Discussion] As tocilizumab was marked-

ly effective, IL-6 was assumed to play an important role in RA pathophysiology, even in patients with persistently negative CRP. [Conclusion] CRP negativity does not always suggest mild RA. RA patients negative for CRP require comprehensive evaluation including periodic radiography.

P2-144

A study of the persistency ratio of tocilizumab for the second biologic in patients with rheumatoid arthritis

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Conflict of interest: None

[Objectives and Methods] In this study, we analysed the persistency ratio in 64 patients with rheumatoid arthritis with inadequate response to anti-TNF therapy for first biologic from July 2008 to September 2011 in our hospital. 25 patients were treated with tocilizumab (an anti-IL-6 receptor antibody) and 39 patients treated with infliximab, etenercept and adalimumab (anti-TNF drugs) for second biologics. [Results] The persistency ratio for 2 years was 79.8% on the group with anti-IL-6 versus 50.0% on the group with anti-TNF. In addition, the persistency ratio for 2 years in patients with inadequate response to anti-TNF therapy for first biologic as secondary failure was 90.0% on the group with anti-IL-6 versus 25.0% on the group with anti-TNF. [Conclusion] After inadequate response to anti-TNF, particularly after secondary failure, the persistency ratio in patients treated with anti-IL-6 was higher than anti-TNF.

P2-145

Clinical significance of the MTX combination in tocilizumab treatment in rheumatoid arthritis

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Conflict of interest: None

[Objectives] In TCZ treatment, we analyze the influence of the combination of MTX and the reduction in dose or the stop of MTX called anchor drug of RA. [Methods] The clinical results were observed in 50 patients with RA who TCZ was administrated over 3 months. Average age was 59 years, mean disease duration was 15 years and 74% of the patients had the history of biologics. Using in combination of MTX at the time of TCZ medication start was 37 cases, and was 7 mg in average dose. [Results] The chronological course (3→6→12→24 months) of remission rate (DAS28-ESR<2.6) was 58→72→75→75% in TCZ combination with MTX, and 31→50→80→60% in TCZ without MTX. The remission rate was no significant difference between two groups. In 22 cases who the improvement continued among 37 cases of MTX combination treatment, MTX was discontinued and the dose was reduced, and 19 cases were in remission and 2 in low disease activity. Although it was in insufficient improvement,3 cases which stopped MTX and reduced the dose because of adverse effects, were dissatisfied results. ([Conclusion] The remission rate was also high in TCZ monotherapy as compared with MTX combination therapy. In TCZ treatment, it is thought that a combination of MTX and a maintenance of the MTX dose are not indispensable.

P2-146

Evaluating the efficacy of tocilizumab (TCZ) in elderly RA patients with musculoskeletal ultrasonography (MSUS)

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Conflict of interest: None

[Objective] To evaluate the efficacy of tocilizumab (TCZ) in elderly RA patients with MSUS. **[Methods]** We examined 19 RA patients in TCZ therapy, 10 patients were 65 years or older (elderly group, 74.0±5.4 yo) and 9 were younger than 65 years (younger group, 53.6±7.1 yo). DAS28-ESR(4), mHAQ and MSUS findings (wrist, knee and finger joints) were compared before TCZ therapy and after 6 months. We chose the RA patients who had history of prior biologics use. **[Results]** After 6 months of TCZ therapy, DAS28-ESR(4) was improved from 5.61±1.46 to 2.55±0.71 (elderly group), from 4.91±1.50 to 1.99±1.19 (younger group) respectively ($P<0.01$). The score of mHAQ was improved from 1.47±0.70 to 1.36±0.84 (elderly group), from 0.93±0.81 to 0.74±0.90 (younger group) respectively (not significant respectively). 30% of elderly patients and 33% of younger patients had one or more joints with PDS grade 3 before TCZ treatment. After 6 month, 20% in elderly and 11% in younger still had one or more joints with PDS grade 3. 30% in elderly and 11% in younger got remarkable MSUS improvement in PDS (ex. grade 3 to 1, 2 to 0) at least one joint (not significant respectively). **[Conclusion]** As a second line biologics, TCZ may be effective for elderly RA patients as well as younger RA patients from the viewpoint of MSUS.

P2-147

Prediction of infectious adverse event in rheumatoid arthritis patient treated with tofacitinib

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Conflict of interest: None

[Objectives] Tofacitinib, a Janus kinase (JAK) inhibitor, has demonstrated high clinical efficacy with increased infectious adverse events resembling biologics on rheumatoid arthritis (RA). Therefore, elucidating the mode of action and factors predicting infectious events is crucial to increase not only benefit but also safety of tofacitinib. [Methods] Twenty-eight RA patients (23 women, mean age; 55 years, mean disease duration 75 months) participating the phase II and III clinical trials in our department were enrolled. [Results] Twenty-four patients out of 28 completed 104 weeks treatment. Forty-five infectious adverse events (Grade 2; 21, Grade 3; 2) were observed. There was no change in the total lymphocyte counts nor lymphocyte subset profiles. Although $CD4^+$ T cell proliferation *in vitro* was significantly reduced ($p<0.01$), it did not correlated with incidence of the infections. The number of $CD8^+$ T cells at baseline ($\leqq 211/\mu l$) was extracted as a predictive factor affecting incidence of infections (odds ratio 9, sensitivity 75 %, specificity 75 %). [Conclusion] The mode of action of tofacitinib on RA through suppression of lymphocyte was shown. Our results also suggest that patients with lower $CD8^+$ T cell counts should be considered to possess a higher risk of infections.

P2-148

The combined effects of iguratimod with anti-TNFα antibody on experimental arthritis models in mice

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Conflict of interest: None

[Objectives] Using two arthritis models in DBA/1J mice, the combined effects of a new DMARD iguratimod (IGU) with anti-TNFα antibody (αTNF) were examined. [Methods] Collagen-induced arthritis (CIA) was induced by immunization with type II collagen twice on day 0 and 21. From day 25, IGU was given *p.o.* once daily and αTNF was injected *i.p.* twice a week to day 34. GPI-induced arthritis (GIA) was induced by immunization with recombinant GPI on day 0 and the treatments were started on day 5. IGU was given *p.o.* daily and αTNF was injected *i.v.* every other day to day 14. Efficacy was evaluated by arthritis score, X-ray examination and serum biochemical analysis. [Results] In CIA, IGU significantly inhibited the arthritis and articular destruction by combination with αTNF and its effect was stronger than those of each alone. The decline of serum COMP and MMP-3 levels on day 35 was significantly enhanced by combination with IGU. In GIA, IGU and αTNF lowered the arthritis scores and the combination of both treatments showed a significant effect compared with IGU alone. IGU and αTNF had no effect on serum anti-GPI titers on day 14 [Conclusion] In mouse models, combination of IGU and αTNF was in an additive manner, suggesting that such therapy would bring a good response in clinical use.

P2-149

The efficacy of tyrosine kinase inhibitor Imatinib Mesylate for Rheumatoid arthritis

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Conflict of interest: None

A 66-year-old man developed Rheumatoid arthritis (RA) in 1992 had not been in good condition of disease, though various DMARDs and the immuno adsorption plasmapheresis were tried. The use of infliximab (IFX) was started in 2000, and his condition had become better. Since 2006 his disease activity had shown a little over 3.0 in DAS28(CRP) with IFX 200mg/8weeks+ methotrexate (MTX) 8mg/week+prednisolone (PSL) 3mg/day. In June 2011, segmental resection of small intestine was performed in emergency for jejunum gastrointestinal stromal tumor (GIST) and perforation-related peritonitis. Therefore the use of IFX and MTX discontinued, so his condition had become worse and DAS28 (CRP) showed 5.51 with PSL 8mg~10mg/day. Imatinib Mesylate 400mg/day was started for peritoneal metastasis of GIST since September 2011. After that, his condition had got better, and PSL could be reduced to 4mg~7mg/day. Restart of MTX in addition since May 2012 has made his condition of disease more better, and his disease activity shows a little over 3.0 in DAS28(CRP) with Imatinib Mesylate 400mg/day+MTX 6mg/week+PSL 3mg/day now. It is suggested that tyrosine kinase inhibitor Imatinib Mesylate is effective for RA.

P2-150

Effect of iguratimod, a new DMARD, and other synthetic DMARDs on osteoclast differentiation

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Conflict of interest: None

[Objectives] The effect of iguratimod (IGU) on *in vitro* osteoclast differetiation was investigated in comparison with those of other synthetic DMARDs. In addition, the combined effect of IGU and methotrexate (MTX) was examined. [Methods] Osteoclast differentiation was assessed using TRACP activity and MTS assay in RANKL-stimulated RAW 264.7 cells. Quantitative analysis of combined effect was performed by a calculated combination index (CI), where CI < 1, = 1, and > 1 denote synergism, additive effect, and antagonism, respectively. [Results] IGU significantly inhibited the increase of TRACP activity in a dose dependent manner. MTX reduced not only TRACP activity, but also cell proliferation. Salazosulfapyridine and tofacitinib did not show any clear effects. In contrast, prednisolone enhanced the TRACP activity. Additive effect was seen for the combination of IGU and MTX as represented by a CI = 1. [Conclusion] These results suggest that IGU inhibits the osteoclast differentiation with a different mechanism to other DMARDs and that IGU will bring a good clinical effect on rheumatoid bone destruction in combination with MTX.

P2-151

Early predictive factors of good clinical outcomes in rheumatoid arthritis patients treated with tofacitinib

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Conflict of interest: Yes

[Objectives] Tofacitinib, a Janus kinase (JAK) inhibitor, has demonstrated clinical efficacy in rheumatoid arthritis (RA). We herein investigated potential predictive factors of response to tofacitinib. [Methods] Twenty-eight patients (23 women) with RA in clinical trials of tofacitinib were enrolled. Clinical features and $CD4^+$ T cell proliferation was evaluated by CFSE dilution. [Results] Twenty-four patients completed 104-weeks treatment. Tofacitinib improved SDAI (36.4 to 5.8), HAQ-DI(1.4 to 0.6), yearly progression of mTSS (14.0 to 1.4), and 60 % of patients were prevented from radiographic progression (ΔmTSS $\leqq$ 0.5) at week 104. Predictive factors for good outcome were: $\Delta SDAI_{[0\text{-}2W]}$ for SDAI remission at week 52 and 104 (p=0.04, 0.04), SDAI $\leq$ 26.0 at week 2 for preventing radiographic progression at week 52 (p=0.03), $\Delta HAQ\text{-}DI_{[0\text{-}2W]} < -0.25$ for HAQ remission (< 0.25) at week 52 (p=0.01). Proliferation of $CD4^+$ T cells was significantly reduced at week 52 and was also a significant predictive factor for improvement in SDAI from baseline to week 52 (p=0.04). [Conclusion] Long-term good clinical outcomes by tofacitinib can be predicted by assessing the $CD4^+$ T cell response *in vitro* at baseline as well as SDAI and HAQ-DI at week 2.

P2-152

Pain relieving effect of TRAMCET® on rheumatoid arthritis. A prospective study of small number of cases

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Conflict of interest: Yes

[Objective] Since many evaluation measures of RA disease activity include pain, its relief is important. We studied therapeutic effect of TRAMCET on pain in RA. [Methods] Patients with 30≧ mm pain on Visual Analogue Scale (VAS) in spite of standard treatment for RA were recruited. Six female patients (mean age, 65.2yrs; mean duration, 11yrs) were included, and TRAMCET was prescribed for 16wks. NSAID, MTX, steroid and biologics were prescribed in 5, 5, 2, 2 patients, respectively. One patient had concomitant cervical spondylosis and another had lumbar canal stenosis (LCS). [Results] Three patients exhibited significant decrease of VAS and MHAQ at the last observation, whereas other three did not show any change from pretreatment period. In the patient with LCS, pain was so strong that she stopped taking TRAMCET and underwent surgery. In the rest 5 patients, disease activity evaluated by DAS28-CRP(4) was high in 2 and moderate in 3 before TRAMCET treatment, but was high in 1, moderate in 2 and low in 2 at the last observation. Adverse effects recognized at early stage were nausea, somnolence and constipation in 3, 4 and 4 patients, respectively, but was only somnolence at the last observation. [Conclusion] TRAMCET could be considered as a useful treatment option for pain relief in RA.

P2-153

Effects of irbesartan on IMT in the patients of connective tissue disease or rheumatoid arthritis with hypertension.(4th report)

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Conflict of interest: None

[Objectives/Methods] Oral steroids often cause secondary hypertension and progress atherosclerosis for connective tissue disease and rheumatoid arthritis. On the last conference, we reported that irbesartan100mg/day could suppress the progression of arteriosclerosis (no IMT increase of 105patients for 52weeks). We continued to follow them and examine the efficacy and safety next 2years. [Results] As a result, we found that irbesartan was effective and safe for 3-years. [Conclusion] In conclusion, irbesartan is useful for secondary hypertension of connective tissue disease and rheumatoid arthritis.

P2-154

Evaluation of the usefulness of golimumab in patients with rheumatoid arthritis in our Department

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Conflict of interest: None

【Objectives】To investigate the usefulness of golimumab (GOL) in patients with RA【Patients and Methods】Twelve patients, all were females. Mean age of patients was 61 years old and the mean disease duration was 10 years. The disease activity was measured by DAS28-CRP. The responsiveness to GOL was evaluated by EULAR response criteria.【Results】Seven patients (58.3%) were able to continue GOL therapy for 12 weeks. DAS28-CRP was significantly reduced from 4.93 to 4.03 by 12-week GOL therapy (P=0.047). EULAR response was as follows: good response; 1, moderate reponse; 2, no response; 4. HAQ-DI was decreased from 1.39 to 1.11 (not significant). Six out of 7 patients (86%) used concomitant MTX and 57% was biologics naïve.【Conclusion】GOL may have a good adherence capacity even in the patients with previous biologics.

P2-155

Accuracy of the second toe metatarsal as a landmark for extramedullary tibial alignment in total knee arthroplasty for rheumatoid arthritis knee

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Conflict of interest: None

[Objectives] The objective of this study was to investigate accuracy of the second toe metatarsal (MT2) as a landmark for proximal tibial cut in total knee arthroplasty (TKA) for rheumatoid arthritis (RA) knee using CT based 3D imaging software. [Methods] Twenty rheumatoid arthritis knees and thirty osteoarthritis (OA) knees were investigated in this study. We used CT-based preoperative TKA planning software to determine the tibial mechanical axis (MA) and perform measurements of the accuracy of the MT2. We performed two following simulations using a virtual extramedullary cutting guide which had 8cm long between proximal fixation spike and rod.1; AP axis of the guide was Akagi line and rod was pointed toward the base of the MT2 bone, 2; AP axis of the guide was MT2 axis and was pointed toward the MT2 bone. [Results] Simulation1;The mean difference between MA and rod of the guide was 0.1º±2.6º of varus(range 3.3º of valgus to 8.1º of varus) in RA and 0.8º±1.0º of valgus(range 4.0º of valgus to 2.4º of varus) in OA. Simulation 2;The mean difference between MA and the rod was 0.5º±1.4º of varus (range 3.3º of valgus to 3.3º of varus) in RA and 0.7º±0.9º of varus (range 1.8º of valgus to 2.8º of varus) in OA. [Conclusion] MT2 bone was not a reliable landmark in TKA for RA knee.

P2-156

Long term result of Kinemax Total Knee Arthroplasty for the Rheumatoid Arthritis Patients

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Conflict of interest: None

[Objectives] We investigated long-term results of Kinemax type TKA for the RA patient. [Methods] We performd Kinemax type TKA on 123 knees (14 men, 109 women; an average of intraoperative age was 63 years old) from 1993 to 2001 for the RA patient. The examples which we can follow up to date were 33 knees

(an average of intraoperative age was 58.9 years old; the average of follow-up period was 15 years 4 months; 6 Kinemax type, 26 Kinemax plus type, 30 CR type, 3 PS type). We investigated these examples on clinical or X-ray. [Results] We coud not followed up of 90 knees, and their average of intraoperetive age was 65.1 years old. The complications ware one infection, two supracondylar fracture of Femur, and two revisions (polyarticular RA case, performed 17 years after primary TKA). In X-ray, that can be followed up of 33 knees, no clear zone was seen in Femur, 7 clear zones were seen in zone 1 of AP view within 1mm in Tibia, but there was no loosening. Final average of Japan Orthopaedic Association (JOA) score was 74 points, and average extension was -1 degree, flexion was 109 degrees. [Conclusion] Long-term results of TKA by Kinemax CR type for the RA patient are satisfied for clinially and in X-ray.

P2-157

Comparison of the pathological findings of the synovial tissue obtained during the total knee arthroplasty and the clinical findings. A prospective study

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Conflict of interest: None

[Objectives] The purpose of this study was to identify the prevalence of RA which was newly diagnosed following the total knee arthroplasty (TKA). [Methods] One hundred and thirty two patients were operated of TKA under the diagnosis of osteoarthritis (OA). The synovial tissue was obtained during the surgery and regular HE staining was performed. The pathological findings were classified based on Rooney's criteria. Those were divided as 3 groups; non-specific inflammation, possible RA, and probable RA. On clinical findings, the prevalence of new onset of RA, amount of rheumatoid factor (RF), and the patellar resurfacing rate were analyzed. [Results] One patient from possible RA group developed RA 8 months following the surgery. Three of 43 patients from possible RA group complained anterior knee pain, and all of them did not have patellar resurfacing. The average RF of them was 24IU/ml, however, the average RF in the non-specific inflammation group was 3.9IU/ml. [Conclusion] The prevalence of newly diagnosed of RA was 0.76% in the patients who were operated of TKA under the diagnosis of OA. RF and the pathological findings of synovial tissue may be a predictor of the anterior knee pain if patellar resurfacing was not performed in TKA.

P2-158

Functional outcome of total knee arthroplasty in elderly patients with rheumatoid arthritis

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Conflict of interest: None

(Purpose) We compared functional outcome of total knee arthroplasty for over and under the age of 70 in patients with rheumatoid arthritis. (Materials and Methods) Twenty-four patients (38 knees) after total knee arthroplasty were evaluated at more than three years after surgery. In the over 70 years old group (A group), there were 4 men and 8 women with an average age at surgery was 77 years (range, 72-83). On the other hand, in the under 70 years old group (B group), there were 3 men and 9 women with an average age at surgery was 61 years (range, 52-68). We investigated functional outcome according to JOA RA knee surgery score at admission, discharge, three years after surgery and compared with group A and B. (Results) The average score was 45 points preoperatively, 61 points at discharge, 63 at the survey in group A and 48 points preoperatively, 66 points at discharge, 81 points at the study in group B. It was a significant difference between the two groups on the score at the time of the survey. These score was significantly reduced in four patients of group A. (Conclusion) Functional outcome of total knee arthroplasty in rheumatoid patients over 70 years with was poor. The surgical indication is considered carefully and early surgery is recommended.

P2-159

Atraumatic periprosthetic fracture after total knee replacement in patients with rheumatoid arthritis

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Conflict of interest: None

[Objectives] We studied 3cases of atraumatic periprosthetic fracture after total knee replacement in patients with rheumatoid arthritis. [Methods] All 3 patients had disease duration of longer than 20 years and were over 60 years old. The value of C reactive protein was over 2 in all cases before the operations. [Results] Case 1 and 2 were treated consevativel with external bracing. However both of them resulted in malalignment of the lower extremities. Revision TKR was performed on case 3. The fractures in all 3 cases seem to be due to poor bone quality. [Conclusion] Preoperative evaluation of bone strength or quality is important whe performing TKR in cases of RA with poor disease control. When poor bone quality is suspected, implants should be selected carefully. The disease control of RA is imortat even after the joint damage is obvious in order to keep good bone quality, whichi is necessary for the success of joint replacement surgery.

P2-160

A clinical study of revision total knee arthroplasty after minimum invasive total knee arthroplasty

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Conflict of interest: None

[Objectives] We investigated the cases who had had an aseptic loosening after minimum invasive total knee arthroplasty (MIS-TKA). [Methods] From April 2004 to October 2010, 340 consecutive MIS-TKA were performed for the patients of osteoarthritis. Six knees who had had an aseptic loosening were evaluated. [Results] Six Knees were revised. The mean duration from initial MIS-TKA to revision-TKA was 37 months (range, 13 to 72 months). The average age of the patients at the time of revision-TKA was sixty-nine years (range, sixty-five to seventy-eight years). All cases were an aseptic loosening of the tibial comportment. In 5 cases, the loosening was caused by the cementing failure. The average JOA scores were 81 points at the time of the latest follow-up. The average knee flexion was 118°at the latest follow-up evaluation. [Conclusion] We consider that the cementing technique was most important for preventing of the aseptic loosening of tibial comportment.

P2-161

A case of streptococcal toxic shock syndrome occurred after revision total knee arthroplasty and treated by above knee amputation

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Conflict of interest: None

Streptococcal toxic shock syndrome (STSS) has a fulminant course and is associated with high mortality rate. We report a case of STSS occurred after revision total knee arthroplasty and could be saved life by above knee amputation. A 57-year-old female developed rheumatoid arthritis 20 years ago and was underwent bilateral total knee arthroplasty several years after onset. She was underwent right revision total knee arthroplasty last year due to metallosis. She caught a chill and presented to our emergency room five months after surgery and she was diagnosed with the flu. After getting home, she felt severe pain in her right knee and returned to hospital by ambulance. She was in a state of shock and was admitted in an intensive care unit. Her general status got worse despite multimodality therapy. She developed redness and blister rapidly in her right lower leg, so we decided to amputation as a life-saving surgery. Her general status improved after operation, and she was discharged from the hospital 6-months after amputation. STSS is famous for necrotizing fasciitis but it is comparatively rare associating with suppurative arthritis. STSS often have a serious course, so it is important to decide to operation without delay even if after joint arthroplasty.

P2-162

Leg alignment of rheumatoid patients before and after total knee arthroplasty

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Conflict of interest: None

[Objectives&Methods] We evaluate 50 knee joints in 30 RA patients and 100 knee joist in 71 OA patients before and after total knee arthroplasty. [Results] Mean femorotibial angle (FTA) before and after TKA were, respectively, 178 degree and 173 degrees in RA patient and 188 degrees and 175 degrees in OA patients. The mechanical axis of the leg passed 28% on the joint surface before TKA and 50% after TKA in RA patients, and -3% before TKA and 50% after TKA in OA patient. [Conclusion] Leg alignment of RA patients was more valugs than that of OA patients and improved after TKA.

P2-163

Mid-term clinical results of flexion enhanced posterior cruciate-retaining total knee arthroplasty (CR-TKA) : Comparison between rheumatoid and osteoarthritic knees

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Conflict of interest: None

[Objectives] To investigate the mid-term clinical results and the range of motion of rheumatoid knees implanted with a flexion enhanced posterior cruciate-retaining total knee arthroplasty (CR-TKA) [Methods] The clinical results were assessed for of 21 knees implanted with CR-TKAs. Patients (mean age at surgery of 68 years) included 3 males (4knees) and 13 females (17knees), and the mean follow-up period was 73 months. For comparison, the results of osteoarthritis knees (24 knees) were also investigated. [Results] At latest follow-up, mean JOA score increased from 44.2 to 80.1. Preoperative maximum flexion and extension angles were, on average, 111° and -8.8 ° (RA), 121° and -11 ° (OA), respectively. In contrast, at 1 year post-ope period, the angles were, 122° and 0.6 ° (RA), 119° and -2.2 ° (OA), respectively, At latest follow-up, the angles were, 121° and 1.3 ° (RA), 116° and -1.2 ° (OA), respectively. The mean FTA improved from 181° to 175°. Postoperatively, the recurvatum knee was confirmed in one 2 knees, and the revision surgery was performed in another knee due to aseptic loosening of the tibial component. No deep infection was confirmed. [Conclusion] Longer follow-up is necessary to evaluate for potential advantage and disadvantage of CR-TKA in rheumatoid patients.

P2-164

VTE incidence and clinical findings in OA and RA patients using enoxaparin following TKA

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Conflict of interest: None

[Objectives] To evaluate VTE incidence and clinical findings in OA and RA using enoxaparin following TKA. [Methods] In 624 cases performed in our institution between August, 2008 and November, 2011, we selected the patients only with OA and RA and receiving an enoxaparin 2000 IU twice a day. As a result, we evaluated 267 cases (443 knees) with OA (176 cases for simultaneous bilateral TKA and 91 cases for lateral TKA) and 27 cases (34 knees) with RA (7 cases for simultaneous bilateral TKA and 20 cases for lateral TKA). [Results] The DVT incidence was 14 cases (8.5%) with OA and one case (14.3%) with RA in simultaneous bilateral TKA, and 3 cases (3.5%) with OA and none case with RA in lateral TKA, so that they did not indicate a significant difference. The PE incidence did not have a significant difference comparing OA and RA, either. The lower limbs swelling measured at a patella and calf height comparing with preoperative circumference, and significantly showed more swelling for OA than RA. ($p=0.007$, $=0.042$) The subcutaneous hematoma incidence was observed in OA higher than in RA (65.8%vs40.7% $p=0.009$). [Conclusion] The significant difference did not indicate for VTE incidence in OA and RA patients.

P2-165

The incidence of abnormality of renal and liver function test and the bleeding as adverse effect of Edoxaban in patients undergoing total knee arthroplasty

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Conflict of interest: None

[Objectives] Patients undergoing TKA are at high risk of VTE, prophylaxis for VTE has been of great concern. We investigated the incidence of abnormality of renal and liver function test and bleeding events as adverse effect of Edoxaban for the prevention of VTE. [Methods] 14 patients were received one of two doses (15, 30 mg) of edoxaban orally once daily for 14 days after primary TKA. The patient that with renal impairment, low body weight, a daily dose of 15 mg were received.Treatment was started 36-39 hours after surgery. Mechanical thromboprophylaxis, including venous foot pump was permitted.The incidence of VTE, abnormality

of renal and liver function test, and bleeding events were investigated. [Results] Symptomatic DVT was detected in no patients, and there were no DVT-related deaths or symptomatic PE.The incidence of bleeding events was 0 %. Serum AST (IU/L) was not increased from baseline (26.7±11.6) at 14 days (22.7±5.68), ALT (IU/L) was not increased from baseline (22.5±18.3) at 14 days (17.9±10.0), CCr (mL/min.) was not increased from baseline (66.4±29.7) at 14 days (80.4±30.3). [Conclusion] Edoxaban result in no significant changes in renal and liver function test.The results suggest that edoxaban can be regarded as one of the choice to prevent VTE after TKA.

P2-166

Effect of total knee arthroplasty with capsulosynovectomy on disease activity in patients with rheumatoid arthritis

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Conflict of interest: None

[Objectives] We evaluated effect of total knee arthroplasty (TKA) with capsulosynovectomy on disease activity in patients with rheumatoid arthritis (RA). [Methods] Fifty RA patients with severe joint destruction underwent TKA with capsulosynovectomy. The patients included 43 females and 7 males, with a mean age of 66 years at the time of surgery. Preoperative and postoperative RA disease activity was measured using the Disease Activity Score 28 (DAS28). Clinical results were assessed using the Knee Society rating score (KSS) and function score. [Results] DAS28 was significantly decreased from 4.5+/-1.0 preoperatively to 3.1+/-0.8 postoperatively ($P < 0.05$). The mean KSS was significantly improved from preoperative 43.9 points to postoperative 93.5, and the mean function score was significantly improved from 38.0 points to postoperative 70.8 ($P < 0.05$). [Conclusion] This study suggested that TKA with capsulosynovectomy has a secondary systemic effect on disease activity in patients with RA.

P2-167

Clinical results of posterior cruciate ligament-retaining total knee arthroplasty in patients with rheumatoid arthritis

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Conflict of interest: None

【Objective】In cases of RA, there have still been arguing about primary TKA using the posterior cruciate ligament-retaining (CR)-type prosthesis. In this study, consecutive series of patients with CR-type TKA performed between 2001 and 2011 were analyzed. 【Methods】Fourty CR-type TKAs in 28 RA patients were studied prospectively. All surgical procedures were performed with two prosthesis, The Foundation Total Knee System and FNK. The assessment was based on JOA score and radiological analysis, which was evaluated for loosening, radiolucent line, and subsidence according to the Knee Society Roentgenographic Evaluation.【Results】The mean follow-up was 7.8 years (5 to 11). Late infection occurred in 2 patients and supracondylar fracture of the femur occurred in 2 patients. The mean postoperative flexion angle was 115.0, and JOA score improved from 44.5 to 89.4 points at final follow-up visit. The radiolucent lines were identified at zone 1 and 4 of femoral component and zone 1 and 2 of tibial component (AP view). There were no cases of revision surgery.【Conclusion】These results indicate that CR-type TKA has not caused any problems in RA patients during our follow-up period. Although further follow-up studies are required, this type TKA might be one of effective surgery.

P2-168

Stress fracture of the tibia following the total knee arthroplasty

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Conflict of interest: None

[Objectives] In the treatment of degenerative knee arthritis, total knee arthroplasty (TKA), is a common performed surgery. It is popular that stress fracture of proximal femur and pubis is occurred as the complication of TKA, althought stress fracture of proximal tibia is very rare. We experienced the case of the stress fracture of proximal tibia following the TKA, which was a contralateral side of the TKA, without any apparent trauma or cause. [Case] A 51-year –old woman had undergone left TKA for rheumatoid arthritis. At 3 months postoperatively, pain developed in the proximal medial aspect of tibia during walking. Physical examination showed tenderness of proximal medial aspect of tibia and varus deformity. Right knee radiographs showed no abnormal signs. After 4 months postoperatively, she had difficulty walking. Plain radiographs showed the obvious stress fracture line in proximal tibia in right knee. Treatment of rest and immobilization for 4 weeks was remarkably successed. She had no complain of the knee. [Conclusion] The causes of this rare complication may include increased level of activity after TKA, general osteoporosis and varus deformity of the knee. These results demonstrate that it is important to aware of the risk of this rare complication after TKA.

P2-169

The effect of tocilizumab for rheumatoid arthritis patients requiring surgical treatment

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Conflict of interest: None

[Objectives] The aim of this study was to investigate the effect of tocilizumab (TCZ) for rheumatoid arthritis (RA) patients requiring surgical treatment. [Methods] Of the RA patients registered in the Tsurumai Biologics Communication Registry, 12 patients underwent surgical treatment while treated with TCZ. All patients were female, and age and disease duration at initiation of TCZ were 59.3 years old and 12.7 years, respectively. The changes in DAS-ESR and remission rate were investigated, and postoperative retention rate of TCZ was estimated by the Kaplan-Meier method. [Results] DAS28-ESR was 6.2, 3.6, 3.2 and 3.2, and remission rate was 0%, 16.7%, 33.3% and 41.6% at each time point of initiation of TCZ, surgery, and 6 months and 12months after surgery. In one case that disease activity was not reduced by TCZ prior to surgery, the disease activity remained high after surgery. Postoperative retention rate of TCZ was 92.3%. [Conclusion] TCZ can modify RA disease activity after surgery by controlling disease activity prior to surgery. Therefore TCZ can be used continuously even after surgery, and it may be useful for RA patients requiring surgery.

P2-170

Surgical treatment for hand deformity in RA patients with biologic agents

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Conflict of interest: None

Clinical results of reconstruction for hand deformity performed in rheumatoid patients treated with Biologic agents were evaluated. Thirty eight surgeries were performed on 22 RA patients(15 woman),with mean age 58.5 years old, treated with biologic agents (etanercept 13, infliximab 5,tocilizumab 4) The methods of surgeries were thumb 11cases (CM 3 joints, MP 13 joints, IP 4 joints), finger 20cases(MP 84 joints, PIP 12 joints). Silicon implants were used in 101 joints (thumb MP 13, finger MP 80, PIP 8). Flare-up of the disease was not found in all patients.Infection was observed in 2joints of 1case, but wound was healed by removing implants. Most patients were satisfied with appearance and functioning of fingers after surgery. Reconstruction of finger joint seems to be useful procedure for finger deformity in rheumatoid patients with biologic agents.

P2-171

The pathology of distructed hip and knee joint of RA patients treating with biologic agents

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Conflict of interest: None

[Objectives] We assessed the status of hip and knee joint, which underwent total arthroplasty treating with biologic agents for rhumatoid arthritis (RA), radiogaraphically, macro and microscopically. [Methods] We studied 36 RA patients (age 58;28-78, RA duration 14 years;4-34) who underwent total knee arthroplasty (TKA) and 15 RA patients (age 51;25-67, RA duration 11.9 years;2-38) who underwent total hip arthroplasty (THA) between September 2004 and September 2012 [Results] All patients received biologic agents including infliximab, etanercept, tocilizumab, adalimumab, abatacept and others. We observed the active synovitis and inflammatory destruction of the both hip and knee joints with non-responder against biologic agents. Compared with non-responder group, proliferateive osteoarthritic (OA) change, osteosclerosis and osteophyte formation, in all hip and knee joints with good responders. [Conclusion] RA patients well controlled with biologic agents underwent TKA or THA, joint distraction could be caused by not inflammatory sinovium but proliferative OA chage pathologically.

P2-172

Early repairs of the damaged rheumatoid ankle articular cartilage founded after forefoot surgery. -A case report-

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Conflict of interest: None

We report a case of a 62-year-old woman with a 12-year history of rheumatoid arthritis. At the age of 57 she complained of right ankle pain. Radiographs showed Larsen grade III damage. She had no deterioration of the ADL until the age of 61 when she developed progressive pain and gait disturbance. Radiographs showed progressive joint destruction of ankle joint and subtalar joint with Larsen grade IV as well as advanced forefoot deformity. Resection arthroplasties of the forefoot was performed in order to correct the malalignment. Postoperative radiographs at 4 months showed repairs of ankle joint destruction, reappearance of the cortical plate and increased joint space. Her ankle pain disappeared and she was able to walk outdoors.She was treated with MTX and infliximab, however it was switched from infliximab to golimumab due to effect attenuation. [Discussion] Although various biological agents have been reported to prevent of joint destruction, some cases have incomplete responses. In our patient forefoot surgery was able to reduce the mechanical stress of the ankle joint and resulted in an enhanced pharmacological efficacy. [Conclusion] We showed that the efficacy of biological agents could be enhanced by correction of malalignment, and reduction of mechanical stress.

P2-173

Open-ended questionnaire and health assessment questionnaire for functional impairment derived from hand deformities in rheumatoid arthritis

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Conflict of interest: None

[Objectives] Although “Treat to Target” strategy improved treatments of rheumatoid arthritis (RA) remarkably, functional remission is still difficult to attain due to pre-existing joint destruction. To improve function, rehabilitation or surgery would be necessary but controversial because RA is an intricate multi-joint affecting disease. A health assessment questionnaire (HAQ) is often used for functional evaluation. However, in regards to hand function, a HAQ is ineffectual to determine interventions. [Methods] We evaluated HAQ, hand deformity and an open-ended style questionnaire from June to July, 2012. We enrolled 57 patients (13 males, 44 females). The mean age was 67.0 (35-95) and mean affected period was 152.0 months (7-444). We studied the hand deformity, dysfunctions and complaints in the questionnaires. [Results] Thirty-two patients had hand deformities. The findings of the open-ended questionnaires were 31.2% (5/16) of the patients (HAQ score < 1), and 69.2% (9/13) of the patients (1 < HAQ score < 2), and 50% (3/6) of the patients (2 < HAQ score), complained about hand dysfunctions. [Conclusion] The patients with hand deformities frequently had dysfunction even if their HAQ score was low. We concluded that therapeutic intervention is necessary to treat hand deformities.

P2-174

The effect of a novel system of insoles using styrene foam beads on foot deformities in RA patients

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Conflict of interest: Yes

[Objectives] Foot deformities in RA patients decrease their ADL and QOL because of pain and corns. Insoles are prescribed

for the patients with these deformities. However, the effect of these is not enough because of their difficulties of casting and adaptation. Therefore, we developed a novel system of insoles using styrene foam beads for deformities of foot, and analyzed the gait of the RA patients with foot deformities wearing our novel insoles. [Methods] 8 RA patients were enrolled in this study. The novel insoles were inserted into slippers (Grizzly Michel, HAFLINGER, Germany). We compared their gaits with bare feet, our novel insoles or low rebound slippers (Daiso, Japan) using a mat type load distribution sensor (Allow Industry, Japan). The parameters of our analysis were gait speed, step length, width of center of sole pressure and max load of sole pressure. [Results] The data of VAS during their gaits and max load of sole pressure were decreased by using the novel insoles compared with bare feet.The data of gait speed, step length were increased compared with bare feet. The width of center of sole pressure was decreased by using the novel insole compared with low rebound slippers. [Conclusion] Our novel insoles were useful for the treatment of foot deformities in RA patients.

P2-175

The assessment of quality of life using the patients-derived outcome scales in the patient with rheumatoid arthritis after bilateral or unilateral total knee arthroplasty

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Conflict of interest: None

[Objectives] The aim of this study was to assess quality of life in the patients with rheumatoid arthritis (RA) after bilateral or unilateral total knee arthroplasty (TKA). [Methods] We have assessed 31 patients with rheumatoid arthritis who had had unilateral TKA(group U, n=15) or bilateral TKA(group B, n=16). Average age was 61.0 years old at the final operation and 66.4 at the assessment. WOMAC and SF-36 were used as the patient-derived outcome scale. [Results] The WOMAC pain score was 92.7 in group U and 97.5 in group B, respectively. The WOMAC functional score was 83.0 in group U and 74.5 in group B, respectively. In the assessment using SF-36, physical functioning in group U was higher than that in group B. Other items in physical component summery were almost same level in group U and group B. In mental component summery, vitality and role-emotional were higher in group B. Mental health was almost same level as normal in both groups. [Conclusion] RA patients who underwent bilateral TKA show better pain score and lower functional score in WOMAC, but almost same level of SF-36 score as unilateral TKA group. The patients with bilateral TKA could maintain their quality of life as same as the patients with unilateral TKA.

P2-176

Investigation of the height of chair in patient guidance after total hip arthroplasty

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Conflict of interest: None

[Objectives] Total hip arthroplasty (THA) is performed for an improvement of ambulatory ability and pain relief for hip joint dysfunction. Since dislocation of THA is occured with relatively high frequency, patient guidance is important to prevent dislocation. But the height of the chair posturing dislocation is not clear. So, we made investigation of this study. [Methods] 51 healthy women were engaged in our study. We measured the height of the chair (A) necessary to stand up with hip and knee joints at 90 degrees flexion. At that time, we also measured the degree of hip flexion (α). On the other hand, we measured the height of the chair (B) necessary to take a standing position in a state that allows for 100 degrees hip flexion. [Results] A correlation was found between height and A, and α was greater than expected. We also observed correlation between height and B, that could be calculated at y = 0.2775X +0.09. [Conclusion] Individual guidance based on this research is considered to be helpful for preventing dislocation.

P2-177

Cooperation in Rheumatic Disease between Acute Care Hospital and Rehabilitation Hospital

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Conflict of interest: None

Rheumatic disease is a chronic and progressive disease, and there are many cases that the patients occur with various complications. Since the decay of ADL has been found in them, there is a great frequency of protracted hospitalization resulting from exacerbation of collagen disease and complicating illness. In cases where such patients want to live at home after discharging, it is necessary to introduce rehabilitation to them with proper timing for an appropriate period. Because of the difficulty of management referring from specificity of illness and varied complications, however, they often find difficulty in changing hospital to receive rehabilitation for a period of time. For this reason, we has started to cooperate with a rehabilitation hospital since August, 2011, and has asked it to rehabilitate 11patients. In order to work together smoothly, we have tried to reduce the worries of the rehabilitation hospital's stuff by checking medicines such as steroid that they are not familiar with and providing thorough instruction in medication, by making our stuff visit and examine patients twice a month. We will develop this effort and deepen the regional cooperation. At the same time, we hope our effort will provide a spark for being introduced as a model case in other areas.

P2-178

A case of PRES(posterior reversible encephalopathy syndrome) in SLE patient with severe lupus nephritis

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Conflict of interest: None

【Case】 36 y.o. female. Since she had SLE at 27 y.o.. She sometimes stopped treatment. She presented with high fever etc. to our clinic. Since then, she had deep hypocomplementemia resistant to therapy and persisted. On Dec. 2,010, massive proteinuria have appeared. DFPP, methylprednisolone and cyclophosphamide pulse therapy were started. On Aug. 2,011, hypocomplementemia and proteinuria improved considerably, and renal histopathology was classIV-G(A) + V. On Febr. 24, 2,012, Tacrolimus was administered 3 mg/day. On Apr. 9, in the afternoon, she had headache and vomiting. On Apr. 10, early in the morning, after she felt visual disturbance, convulsion occurred, then on emergency she was transported to the hospital. She has recovered with no sequelae with diazepam and antihypertensive treatment. On brain MRI at admission, she was diagnosed PRES(Posterior Reversible Encephalopathy Syndrome). 【Clinical significance】 Recently, there were rarely reported that PRES were complicated in the clinical course of SLE. We presented such patient with severe lupus nephritis and

discussed about pathophysiology.

P2-179

Meningoencephalitis as the initial presentation of systemic lupus erythematosus

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Conflict of interest: None

A 17-year-old man was admitted to the other hospital because of headache and consciousness disturbunce.Head CT and MRI showed a mass lesion(8cm) in the right parietal lobe.After 6 hours,his consciousness got worse.Head CT revealed cerebral herniation.Emergency internal and external decompression was performed.The pathology showed remarkable infiltration of neutrophil in cerebral medullary substance and subarachinoid cavity with micro abscess. They diagnosed meningoencephalitis and started MEPM 6g/day.Next month, leucocytopenia was appeared.Three months later,he got a high fever, shoulders' pain,discoid rash,and oral ulcer.Laboratory data indicated ANA positive,high anti-dsDNA antibody,proteinuria.Then he was reffered to our hospital.Predonisolone 0.6mg/kg/day was started,but proteinuria didn't improve.We increased predonisolone dosage to 0.8mg/kg/day and added tacrolimus 3mg/day. His symptoms,laboratory data improved.SLE sometimes causes central nervous system complications.Sometimes we are difficult to discriminate the CNS disorders caused by SLE or infection.In this case,although he didn't take immunosuppressant, meningoencephalitis was considered to be caused by susceptibility to infection which was derived from immune response abnormality from SLE.

P2-180

Two cases of coagulation factor deficiency complicated with systemic lupus erythematosus

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Conflict of interest: None

[Case 1] In January 2011, a 22-year-old woman underwent emergency cesarean section due to suspected acute fatty liver of pregnancy. Coagulation abnormality (PT 18%, APTT 132.1 s) was observed, but was thought to be due to hepatopathy (ALT 102, T-Bil 21.6). The patient was later diagnosed with autoimmune hepatitis based on liver biopsy and recovered with prednisolone (PSL) treatment. The patient was referred to our department in August 2011 due to leucopenia, anti-ds-DNA antibody positivity, and exacerbation of coagulation abnormality, and a diagnosis of systemic lupus erythematosus (SLE) was made. Coagulation function returned to normal with increased PSL dose. **[Case 2]** In January 2011, a 19-year-old woman was diagnosed with pericarditis. Aspirin treatment was begun, and she experienced marked alimentary canal bleeding. The patient was positive for anti-ds-DNA antibody and was referred to our department. Abnormality in coagulation test and clotting factor inhibitors were present. The patient recovered with strong immunosuppression. In clinical practice, differentiation between SLE and blood disease is sometimes difficult. Here, we report 2 cases of SLE accompanied with coagulation factor deficiency, which were difficult to diagnose and treat.

P2-181

Subcutaneous flexor tendon rapture of the ring and little finger complicated with SLE

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Conflict of interest: None

Subcutaneous tendon rapture complicated with systemic lupus erythematosus (SLE) is very rare. We report one case of the subcutaneous flexor tendon rapture of the ring and little finger complicated with SLE. A 68-years–old woman diagnosised SLE at 22 years old was started to treat with steroid. After 43 years, she noticed disturbance of flexion of her right little finger. After 2 years, she noticed disturbance of flexion of her right ring finger.Therefore she saw a doctor.The bone erosion and joint destruction was not seen on x-ray films. For the operative findings,flexor tendon of the ring and little finger degenerated.The FDP tendon of the ring and little finger and the FDS tendon of the little finger were raptured at proximal A1 pulley. We performed FDP of the ring finger tendon transfer to FDS tendon of the ring finger, furthermore tendon grafting between FDP tendon of the little finger and FDS tendon of the ring finger. Postoperative approximately thirteen months have passed, active flexion of her ring and little finger is possible. We thought that SLE, Jaccoud arthrosis and the long-term steroid administration and mechanical irritation by the hook of the hamate led to flexor tendon subcutaneous raptures in this case.

P2-182

A case of systemic lupus erythematosus complicated with aseptic meningitis showing marked decrease of cerebrospinal fluid glucose level

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Conflict of interest: None

A 22-year-old man was diagnosed with SLE in August 2012 because of butterfly rash, photosensitivity, positive test for antinuclear antibody, positive test for anti-Sm antibody and leukocytopenia. Initial therapy with 30 mg/day of prednisolone (PSL) was started. However, because his condition was worsened, the dose of PSL was increased to 50mg/day in September 20th. He showed impaired consciousness in September 21st. So he was transferred to our hospital in September 24th. He had stiff neck and his cerebrospinal fluid (CSF) showed pleocytosis and marked decrease of glucose level (9 mg/dl). He was diagnosed with meningitis. He also suffered from acute pancreatitis and peritonitis. Because we considered the possibility of septic and aseptic meningitis, we started antibiotics and continued with steroid. Gradually he became conscious and his CFS findings were improved. His CSF culture results were negative and he had positive test for anti-dsDNA antibody and low serum level of complement. So we diagnosed aseptic meningitis due to SLE. Though, in the case of aseptic meningitis due to SLE, CSF glucose level is usually normal or slightly decreased, CSF glucose level may show marked decrease.

P2-183

Excessive activation of macrophages caused erythema followed by hemophagocytic syndrome and neuropsychiatric syndrome in a patient with systemic lupus erythematosus

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Conflict of interest: None

[Objectives] To characterize the pathogenic profile in a patient with diverse clinical features of macrophage activation syndrome as initial presentation of systemic lupus erythematosus (SLE). **[Methods]** Several specimens from a newly-onset and untreated SLE patient presenting with erythema and fever followed by pancytopenia and neuropsychiatric syndrome was analyzed pathologically and immunologically. **[Results]** Skin biopsy obtained from one lesion showed an infiltration of the dermis with a predominance of interstitial CD68-positive macrophages with degenerating collagen bundles. Phagocytic histiocytes were found in the bone marrow smears. The integrity of the blood-brain barrier assessed by the Q-albumin was abnormal. Laboratory tests revealed hyperferritinemia and increased cytokines in serum and cerebral spinal fluid. **[Conclusion]** These results indicate that macrophage activation syndrome played pivotal roles in the pathogenesis in the disease course. Characteristic skin histology might be an early indicator of this syndrome in SLE.

P2-184

A case of rhupus syndrome with IgG4-related liver disease

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Conflict of interest: None

A 71 year-old woman with decades history of rheumatoid arthritis (RA) was admitted for acute arthritis with proteinuria and hematuria. She had over 30-year history of RA, episodes of posterior spinal fusion for atlantoaxial subluxation at age 50, unknown inflammatory pseudotumor of the liver at 69, and left total knee replacement at 70. She was diagnosed as systemic lupus erythematosus with oral ulcer, renal disorder, ANA and double strand DNA antibody positivity. Furthermore, her liver dysfunction was thought to be associated with IgG4-related disease because of elevation of serum IgG4 (179 mg/dl). The clinical coexistence of RA and SLE was termed 'rhupus syndrome', and is estimated to be present in 0.01 and 2.0% of SLE patients. IgG4-related disease in a patient with rhupus seems very rare. We would present this case and discuss the association between rhupus syndrome and IgG4-related disease.

P2-185

A case of pneumatosis cystoides intestinalis with Systemic lupus erythematosus

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Conflict of interest: None

The patient was a 37-year-old woman. Polyarthritis and pleuritis developed at 33 years. The patient had leukopenia and tested positive for anti-DNA antibody and antinuclear antibody. Systemic lupus erythematosus was thus diagnosed. Her condition improved after treatment with 40 mg of prednisolone. The maintenance dose was set at 10 mg. The patient was admitted to the hospital because of pollakiuria and repeated episodes of diarrhea and vomiting. Abdominal computed tomography (CT) showed left hydronephrosis, intestinal edema, and ascites. Lupus cystitis and colitis were thus diagnosed. The patient was forbidden to eat or drink, and the dose of prednisolone was increased to 40 mg. Pollakiuria, diarrhea, and nausea improved promptly, and oral intake became possible. After 4 weeks, abdominal distension developed. Abdominal CT showed improvements in intestinal edema and hydronephrosis, but subserosal gas cysts were found in the intestinal wall, and pneumatosis cystoides intestinalis was diagnosed. There were no gastrointestinal symptoms besides abdominal distension. Oral intake was continued, and the dose of prednisolone was tapered. After about 1 month, the amount of subserosal gas had not decreased. Treatment with oxygen and cyclosporine was begun, and the gas retention resolved.

P2-186

SLE with autoimmune pulmonary alveolar proteinosis worsened by immunosuppressive therapy

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Conflict of interest: None

Case report: 27-year old woman was admitted to our hospital because of worsened pulmonary infiltration. Nine month before admission, she felt malaise and noticed facial edema, and were diagnosed as having SLE with rash and thrombocytopenia at a previous hospital. Moderate dose glucocorticoid was given. Two month later, she developed cough and chest CT scan revealed diffuse ground glass opacities (GGO). She was diagnosed as having interstitial pneumonia and was treated with cyclosporine and cyclophosphamide in addition to high dose GC. However, her condition was worsened and transferred to our hospital. On admission, CT scan revealed patchy areas of GGO and interlobular septal thickening. Bronchoscopic examination was performed, milky fluid was yielded and she was diagnosed as having pulmonary alveolar proteinosis (PAP). Anti-GM-CSF antibody was positive in sera and BALF. **Implication:** Few cases of autoimmune PAP associated with systemic autoimmune diseases have been reported. This is a first case of PAP in SLE. Moreover, this case suggests that immunosuppressive therapy might worsen autoimmune PAP.

P2-187

A case of systemic lupus erythematosus with arterial hemorrhage in the retroperitoneum, gluteus, and brachial muscle

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Conflict of interest: None

A 46-year-old woman with systemic lupus erythematosus (SLE) had been stable with prednisolone at a dose of 10mg. She was admitted in a hospital because of high fever and severe leg pain. Computed tomography showed a mass lesion near iliopsoas muscle and anemia was getting worse rapidly, so she was transferred to our hospital. Angiography revealed retroperitoneal bleeding from a pseudoaneurysm of the branch of right internal iliac artery, and it was treated with embolization. Since possibility of

infectious aneurysm or primary vasculitis was supposed to be low, the bleeding was thought to be attributable to vasculitis associated with SLE, intravenous methylprednisolone pulse therapy followed by high dose steroids was started. At the same time, she exhibited psychiatric symptoms and examination of cerebrospinal fluid and brain magnetic resonance imaging strongly suggested neuropsychiatric SLE. Arterial hemorrhage occurred again from the branch of right superior gluteal artery, so intravenous cyclophosphamide therapy was also started. These therapies suppressed subsequent episode of arterial hemorrhage and improved her psychiatric symptoms. We report a case of SLE who developed arterial hemorrhage from retroperitoneum and proximal site of limb.

P2-188

Interstitial pneumonia as an initial manifestation in a patient with late-onset Systemic Lupus Erythematosus

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Conflict of interest: None

A 70-year-old Japanese man had productive cough and painful purpura of fingers and toes. Computed tomography of the chest showed consolidations in bilateral lower lung fields. On admission, he was diagnosed as SLE because of arthritis, thrombocytopenia (7.2×10^4/μl), anti-dsDNA antibody(>400IU/ml), anti-nuclear antibody(320 titer), and hypocomplementemia. Anti-SS-A antibody was negative. Video-assisted thoracoscopic surgery revealed nonspecific interstitial pneumonia (right S2) and usual interstitial pneumonia (right S6). His clinical symptoms improved after commencement of PSL(40mg/day). SLE is often described as a disease that most often sitikes reproductive-age women. The onset of SLE beyond the age of 50 years is reported to occur in only 3-18% of patients. In comparison with younger patients, elderly patients with SLE are reported to have more insidious onset of disease and a different symptomatic state. He had a medical history of membranous nephropathy, idiopathic thrombocytopenia and normal pressure hydrocephalus. His past medical history may be associated with late-onset SLE.

P2-189

Successful treatment of two cases of systemic lupus erythematosus complicated with pulmonary arterial hypertension with combination of corticosteroids, endothelin receptor antagonists, and phosphodiesterase-5 inhibitors

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Conflict of interest: None

Case1: 25-year-old woman. The patient was diagnosed with SLE complicated by lupus nephritis 6years ago, and then the corticosteroid (CS) treatment was initiated. Pulmonary infarction (PI) associated with APS occurred 5years ago, and warfarinization was started. Because dyspnea appeared rapidly, right heart catheterization (RHC) was practiced and showed PA mean 48mmHg, CI 2.11, PVR 1106, RVSP was 100mmHg by echocardiography. There was no evidence of PI by lung perfusion scintigraphy and pulmonary angiography. We were diagnosed with pulmonary arterial hypertension (PAH) associated with SLE. After the steroid pulse therapy, she has been received in order of CS, endothelin receptor antagonists (ERA), phosphodiesterase-5 inhibitors (PDE-5), and sustained-beraprost. One year after the treatment, PA mean 33mmHg CI 3.75 PVR 363, RVSP 47mmHg, PAH were improved. WHO functional class has recovered from class III to I. Case2: 73-year-old man. He had dyspnea, pleuritis, anti-ds-DNA antibody positive. RHC showed PA mean 40mmHg, CI 2.66, PVR 335, and RVSP was 84mmHg. We were diagnosed with PAH associated with SLE. After the steroid pulse therapy, he has been received CS, ERA, and PDE-5. Six months after the treatment, RVSP decreased to 45mmHg. WHO functional class has recovered from class III to II.

P2-190

The effect of cyclophosphamide pulse therapy for protein-loosing enteropathy associated with systemic lupus erythematosus

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Conflict of interest: None

【Case1】A 24-year-old man was treated with prednisolone, tacrolimus, and mizoribine against pancytopenia, serositis and nephritis associated with SLE. Although his illness was temporally ameliorated, massive ascites appeared during duration of the therapy. ^{99m}Tc-labeled albumin scintigraphy revealed protein-loosing enteropathy (PLE) associated with recurrence of SLE. He received additional treatment such as cyclophosphamide pulse therapy (500mg/day), but it was not effective. After escalation of cyclophosphamide from 500mg/day to 750mg/day, the patient revealed an amelioration.【Case2】A 50-year-old female, who have previously diagnosed with lupus nephritis, began to increase ascites. The scintigraphy revealed PLE associated with recurrence of SLE. Although she was treated with several immunosuppressants, the ascites did not reduce. The patient was successfully treated by the high dose cyclophosphamide pulse therapy (750mg/day).【Conclusion】The high dose cyclophosphamide pulse therapy was effective for the refractory PLE. 9 patients have been diagnosed with PLE in our hospital. 6 patients achieved a remission by standard therapy. 3 patients were considered to be refractory case, however all patients was successfully treated by the high dose cyclophosphamide pulse therapy.

P2-191

Case report: Diverse therapeutic effects of tocilizumab on multiorgan involvements of systemic lupus erythematosus including refractory pericarditis, macrophage activation syndrome, and nephritis despite high-dose corticosteroids, tacrolimus, and etanercept

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Conflict of interest: None

We report on a 41-year-old woman with refractory systemic lupus erythematosus with fever, pericarditis, nephritis, and pancytopenia with hyperferritinemia suggesting macrophage activation syndrome successfully treated with combination therapy with tocilizumab. High dose corticosteroids and tacrolimus resolved her arthritis, but non-infectious pericartditis exacerbated with pancytopenia and elevation of serum ferritin, which required pericardiocentesis for symptom relief. Add-on etanercept could not improve pericarditis. Then we switched etanercept to tocilizumab 8 mg/kg each other week which could dramatically improve fever, pericarditis, pancytopenia, and hyperferritinemia; and enable tapering the dose of cortiscosteroids. However continued nephrosis had been

observed despite add-on tocilizumab therapy. We subsequently switched tacrolimus to intravenous pulsed cyclophosphamide while continuing tocilizumab that resulted in decrease of proteiuria. Add-on tocilizumab produced a dramatic effect on intractable pericarditis and macrophage activation syndrome despite high-dose corticosteroids and tacrolimus, however, a little effect on nephrosis, both of which were considered to be associated with disease activity of SLE in this patient.

P2-192

Successful treatment of acalculous cholecystits and multiple complications such as pericarditis, pleuritis and lupus nephritis with IVCY in a patient with SLE

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Conflict of interest: None

Acalculous cholecystitis is a extremely rare and refractory manifestation of systemic lupus erythematosus (SLE). We report a 23-year-old woman with SLE presenting with a 3-month history of polyarthritis and a month of high fever, facial erythema and general malaise (no history of abdominal pain). Several antibiotics were initiated without any improvement. The diagnosis of SLE was made based on these clinical findings along with positive antinuclear and anti dsDNA antibodies. CT and US showed acalculous cholecystitis (with serositis) by accident. The disease activity was very high such as SLEDAI 21 scores and BILAG index 33 scores. She received intravenous methylprednisolone 1g daily for 3 days followed by 60mg oral predonisolone daily. She then received intravenous cyclophosphamide (IVCY) 15mg/kg biweekly that led to markedly improvement in acalculous cholecystitis with serositis and SLE diease activity over next 2 weeks. The case report of acute acalculous cholecystitis is few, and most are needed to cholecystectomy. IVCY can be an effective alternative for SLE patients with acalculous cholecystitis. Furthermore we recommended that the screening in CT or US make it possible to speedy diagnosis of acalculous cholecystitis without operation, even if abdominal appearace is poor.

P2-193

MPO-ANCA positive lupus nephritis in a patient with overlap syndrome of SLE and SSc

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Conflict of interest: None

A 64-year-old woman was admitted to our hospital due to polyarthralgia, facial numbness, and Raynaud's phenomenon. Interstitial pneumonia had been identified 3 month before admission. She exhibited scleroderma as well as polyarthritis and multiple lymphadenopathy. Urinalysis showed proteinuria with microscopic hematuria. Serological examination revealed MPO-ANCA (32.2 IU/ml), anti-RNP antibody (270.8 Index), anti-DNA antibody (9.5 IU/ml), and anti-Sm antibody (44.9 Index) were all positive. Anticentromere antibody and anti-Scl-70 antibody were not ditected. Renal histological findings were compatible with lupus nephritis class III (A/C). She was diagnosed with overlap syndrome of systemic erythematosus (SLE) and systemic sclerosis (SSc). Predonisolone (1mg/kg/day) was administered. The urinalysis and titer of ANCA and anti-DNA antibody became normal soon. In this case, renal biopsy showed that mesangial proliferation was only mild, while some glomeruli had prominent crescent formations. This suggests association of ANCA to the renal involvement.

P2-194

Association Between Once-Daily Mizoribine Therapy and Peak Drug Level (C3)

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Conflict of interest: None

[Background] Sufficiently high peak drug level (C3) and sufficient drug efficacy are difficult to achieve with the approved dose regimen of mizoribine (150 mg/day in 3 divided doses). [Objectives/Methods] We evaluated 193 patients with kidney/collagen disease who underwent blood mizoribine level measurement at our hospital (20 children and 173 adults). The peak drug level and goal achievement rate expected from once-daily mizoribine (100-300 mg) treatment and their association with background variables was analyzed retrospectively. [Results] Multivariate analysis of factors affecting peak drug level showed association with renal function and mizoribine dose (mg and mg/kg) but no association with age or gender. Among patients with compromised renal function, none had a peak level exceeding 5 μg/mL, and the trough level was below the detectable limit in most cases. The association between mizoribine dose and goal achievement rate was as follows: (1) 1 μg/mL goal achieved by about 90% at 4 mg/kg dose (about 200 mg) and (2) 2 μg/mL goal achieved by about 60% at 6 mg/kg dose (about 300 mg). [Conclusion] Once-daily mizoribine treatment ensures sufficient efficacy (peak drug level) and safety (trough level) at doses up to 6 mg/kg (300 mg) in patients with kidney/collagen disease.

P2-195

Efficacy of tacrolimus for induction therapy in patients with active lupus nephritis

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Conflict of interest: None

[Objectives] To evaluate efficacy of tacrolimus (Tac) for induction therapy with active lupus nephritis (LN). [Methods] We evaluated the efficacy and safety of Tac in six patients with active lupus nephritis(1 men and 5 women, mean age 33.8) who were treated with Tac for more than one year. Two patients were treated for LN flares. Five patients underwent renal biopsies :1 with class I, 3 with class IV, 1 with class IV+V. Mean daily proteinuria levels, serum albumin and serum creatinine were respectively 3.1(0.7-6.7) g/day, 2.7(1.7-3.4) g/dl and 0.69(0.45-1.25) mg/dl. The mean doses of prednisolone at the time of starting Tac were 35.8(30-50) mg/day. [Results] At 12 months after the initiation of Tac, 5 patients achieved complete remission (CR) and 1 patient showed no response (NR). The mean doses of prednisolone and serum albumin were 12.1(7-17.5) mg/day and 3.6(2.5-4.4) g/dl. Five patients continue the treatment of Tac, and 1 patient discontinued due to the pregnancy at 23 months. One patient discontinued prednisolone at 2.5 years after the initiation of Tac. All patients showed no serious infection as adverse event, but 1 patient developed myocardial infarction. [Conclusion] We consider that Tac is effective for induction therapy with active LN.

P2-196

Outcome of Combined Mizoribine, Tacrolimus, and Corticosteroid Therapy to Induce Remission of Lupus Nephritis: Analysis by Histological Type

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Conflict of interest: None

[Objectives/Methods] The standard treatment for lupus nephritis is still unclear. At Himeji Red Cross Hospital, multitarget therapy with a combination of steroids and 2 immunosuppressors (mizoribine and tacrolimus) with different mechanisms of action was attempted to induce remission of lupus nephritis. We present the treatment results analyzed by biopsy-proven histological type in 14 patients and the characteristics of patients indicated for this therapy. [Results] The study involved 14 patients (mean age, 46.0 years; 14 women; 12 new cases; urinary protein, 4.3 ± 2.6 g/day; 1 case of ISN/RPS class II, 5 of III or IV, 5 of V, and 3 of III+V). Complete nephritis remission in 64.3% and 100%, systemic lupus erythematosus disease activity index (SLEDAI) remission in 28.6% and 75.0% were observed with steroid doses of 12.5 and 8.7 mg/day at 6 and 12 months, respectively. At 6 months, complete nephritis remission (60.0%, 80.0%, and 33.3%) and SLEDAI remission (40.0%, 20.0%, and 33.3%) was observed with the steroid doses of 11.6, 13.8, and 11.7 mg/day for class III or IV, V, and III+V, respectively. The therapy was highly effective and tolerable. [Conclusion] Favorable outcomes of multitarget therapy at our hospital in each histological type suggest its diverse applicability.

P2-197

Placement for tacrolimus in lupus nephritis

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Conflict of interest: None

[Objectives] We research for existence or non-existence of remission and exacerbation by tacrolimus (Tac) administration against lupus nephritis (LN) and examine the usability. [Methods] We subjected the cases at our hospital as we diagnosed LN, executed the kidney biopsy, and used Tac for the treatment. We analyzed the clinical information retrospectively such as WHO pathological tissue classification, treatment, and outcome. The average observation period was 5.0 years. [Results] Tac was administered for 12 cases of SLE patients. We have acquired remission in 3 out of 4 cases with using Tac as remission-induction therapy and all of the tissue types were either type V or mixture of type V+III/IV. In addition, only 1 out of 7 cases (14%) with using Tac in remission-induction therapy was recognized as exacerbation and 4 out of 6 cases with maintaining remission were either type V or mixture of type V+III/IV. We did not recognize even 1 case for the shifted example of chronic kidney failure and artificial dialysis. [Conclusion] In the examples of Tac administration, both remission induction rate and long-term prognosis were favorable and the usability is expected particularly in the case of type V and type V complication.

P2-198

Two cases of type IV lupus nephritis treated with the combined therapy of cyclophosphamide and tacrolimus

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Conflict of interest: None

[Case 1] 62 years old, woman. Leukocytopenia and malar erythema appeared in September, 2011.Then she was diagnosed as SLE with proteinuria, ANA and anti-ds-DNA antibody-positivity, and was diagnosed as type IV lupus nephritis by the kidney biopsy. PSL (50mg) and TAC (3mg) were administered from December, 2011, and after two weeks when leukocytopenia was improved, IVCY 500 mg/month was started. Proteinuria decreased dramatically after the 3rd IVCY. After the sixth IVCY, proteinuria became negative. Renal dysfunction probably due to TAC developed in August, 2011 which recovered after the dose reduction of TAC. [Case 2] 29 years old, woman was diagnosed as SLE because she had polyarthritis, lymphocytopenia, ANA and anti-DNA antibody positivity in May, 2002. PSL (30mg) was started. TAC (3mg) was added for the newly develoed proteinuria in September, 2008. Though proteinuria decreased, TAC was terminated because she wanted a baby. Proteinuria got worse and kidney biopsy revealed type IV lupus nephritis. In March, 2011, PSL (50mg) and IVCY (500mg/2w) were started after ovary preservation. Proteinuria disappeared soon and after terminating TAC again, she got pregnant and had a baby by artificial insemination in May, 2012.

P2-199

A fulminant case of systemic sclerosis complicating thrombotic microangiopathy and acute respiratory failure

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Conflict of interest: None

A 59-year-old woman presented to her primary care doctor with extreme fatigue, elevated CPK, exacerbation of hypertension in April, 2012. She was suspected with thrombotic thrombocytopenic purpura (TTP) because of progressive renal dysfunction, thrombocytopenia, decreased ADAMTS13 activity(40%), and decreased haptoglobin levels. In August, she was referred to our hospital for diagnosis and treatment of TTP. On admission, we suspected IVL(intravascular lymphoma) because of abnormally high liver damage, anemia, thrombocytopenia, atypical lymphocytosis. But IVL was denied as a result of examinations. Renal biopsy showed Onion-skin lesion, indicated TTP or scleroderma renal crisis (SRC). Systemic sclerosis diagnosis was made based on a sclerodactyly and nailfold thrombi. A final diagnosis was SRC with TTP. Although she was treated by fresh frozen plasma infusion and intensification of antihypertensive treatment, renal function continued to worsen significantly. Hemodialysis was initiated on September 15. On the early morning of the 17th, she had a high fever and sudden-onset dyspnea. She developed cardiac arrest, and the patient died. We report a case with a review of the literature and autopsy findings.

P2-200

Monozygotic twin sisters with lupus-scleroderma overlap syndrome presenting various clinical symptoms

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Conflict of interest: None

A 35 year-old woman admitted to the hospital for oliguric renal failure and congestive heart failure in July 2012. Severe hypertension, aphthous ulcer, enlarged thyroid, finger tremor, microcytic anemia, and hyperthyroidism associated with anti-nuclear antibody (ANA) (160-folds), direct Coombs test, lupus anticoagulant, and anti-SSA antibody. Hemodialysis was introduced. A renal biopsy showed findings for renal scleroderma; irregular-shaped intimal thickening and obliterations of small arteries. Findings for lupus nephritis were not observed. Her monozygotic twin sister diagnosed as systemic lupus erythematosus at the age of 15 suffered from painful digital ulcers in July 2012. She revealed serum creatinine of 1.52 mg/dL with proteinuria associated with ANA (1280-folds), lupus anticoagulant, anti-SSA antibody, and anti-Scl-70 antibody. A renal biopsy showed lupus nephritis with vascular lesions similar to those observed in her sister. Her renal function and finger pain improved by the treatment with mizoribin, beraprost and bosentan. These findings are very interesting when we consider genome background and familial risk of autoimmune disease occurrence.

P2-201

A case of scleroderma renal crisis in the patient with diffuse systemic sclerosis after long-term clinical stability

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Conflict of interest: None

A 50-year-old man was transferred to this hospital because of right visual impairment. Seven years before admission, he developed fever, proximal skin sclerosis and Raynaud's phenomenon, and the diagnosis of diffuse cutaneous systemic sclerosis was made. He had been clinically stable for 7 years. One month before admission, he was found to have elevated blood pressure (BP) of 170/90 mmHg, however, antihypertensive medications were not given. On the day of admission, he was aware of right visual impairment and saw his physician. The BP was 190/110 mmHg, and the serum creatinine was 4.78 mg/dl. The patient was admitted to our hospital. Fundoscopy showed Grade IV (Keith-Wagener) changes. He was diagnosed as scleroderma renal crisis (SRC). Enalapril and intravenous nicardipin were started. He underwent 3 sessions of plasmapheresis, however, renal function deteriorated and temporal hemodialysis was instituted. On the 10th day, renal biopsy was performed, which demonstrated severe intimal thickening and luminal narrowing of small renal arteries. He discharged without renal replacement therapy. Most cases of SRC occur within the first 12 months after the onset of scleroderma. This case illustrates the importance of blood pressure monitoring even with the long-term clinical stability.

P2-202

A case of scleroderma renal crisis that renin inhibitor was effective for the treatment with plasma exchange and ACE inhibitor

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Conflict of interest: None

A 72-year-old man developed systemic scleroderma (SSc) in April 2010.He had low grade fever on August and his examination showed slightly high CRP level. Chest CT scan showed pericardial and pleural effusion. We diagnosed serositis complicated with SSc, and he was treated with prednisolone(PSL:20mg/day).We taperd PSL because it was effective. His blood pressure (BP) elevated in mid-September regardless of the treatment with ARB and he had facial edema and dyspnea on exertion with high serm Cr (sCr) level(1.3 mg/dl). Then he admitted to our hospital. Since his test showed high renin level(renin activity;16.2 ng/ml) and minor proteinuria, we diagnosed scleroderma renal crisis (SRC).Furthermore, his test showed low haptoglobin level, hemolytic anemia and thrombocytopenia. He was treated with ACEI,but his condition was not improved.Then we administered plasma exchange and added renin inhibitor, since hypertension, anemia and thrombocytopenia continued and sCr increased. After administration of renin inhibitor his BP and test values were improved.He has been followed by medication for two years after SRC on-set. His sCr shows about 3.0 mg/dl. First choise of the treatment of SRC is ACEI,but in addition to ACEI,renin inhibitor was effective in this case. It may be useful for SRC.

P2-203

A case of diffuse Cutaneous systemic sclerosis complicated by rapidly progressive skin lesions, interstitional pneumonia and renal crisis

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Conflict of interest: None

[Objectives] We introduse an example of diffuse SSc who develop rapidly progressive skin lesions and early onset interstitial lung disease and renal crisis. [Methods] The case is 61 y.o man. Dyspnea appeared from April 2012, he was aware of the darkening of skin. There were diffuse pigmentation which were partially decolorized. Because of telangiectasia of the nail fold, the pitting of the fingertip, positive of ANA and anti Scl-70 antibody, he was diagnosed with diffuse SSc. When he was admitted to the hospital, impaired renal function without the rise of blood pressure was pointed out. Because of thrombocytopenia, elevated LDH, positive red blood cells crushed, and reduced haptoglobin, we diagnosed with renal crisis and started ACEI. Renal biopsy diagnosis was scleroderma renal crisis. We started IVCY500mg/2week+ PSL20mg for interstitial pneumonia. But we hed to change the treatment to MMF+PSL, because cytopenia occured.Because of side effects of MMF, now we treated with IVCY500mg/4W+ PSL+lower dose MMF. [Conclusion] Rapidly progressive skin lesions is one of the risk factors for renal crisis.In addition, normal blood pressure renal crisis,and early onset interstitial lung disease such as in this case tends to be bad for prognosis. We report the course of treatment of such cases.

P2-204

A woman with diffuse cutaneous systemic sclerosis (dsSSc) involving gastric emphysema

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Conflict of interest: None

Gastric emphysema encompasses a broad spectrum of diseases. A 72-year-old woman with dsSSc was followed up in our hospital. She showed marked dilatation of the esophagus had lost body weight for several years. She was treated for dyhidration and decubitus in April 2012. After admission, she had bleeding at the upper digestive canal. Then the enhanced abdominal CT showed gastric emphysema. Although SSc cause contraction of the whole diges-

tive canal, it is almost recognized esophagus and some cases with pneumatosis cystoides intestinals has been reported. To our knowledge, our case is the first report of gastric emphysema in SSc, so we present our case.

P2-205

Normotensive scleroderma renal crisis with anticentromere antibody-positive onset of lung cancer

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Conflict of interest: None

A 68-year-old Japanese woman with 30-year history of Raynaud phenomenon began to have her finger tip ulcers 2 months ago. She noticed a right cervical mass a month ago and admitted because of her renal function worsening. Physical examination revealed blood pressure of 134/81 mmHg, bilateral cervical anterior hard lymphadenopathy about 2 cm in diameter, skin sclerosis distal to her wrist, nail fold capillary dilatation and finger tip ulcers with cyanosis. Laboratory data were as follows; WBC 6400/μl, Hb 9.8g/dl, platelet 28.5×10^4/μl, creatinine 3.38 mg/dl (1.3 mg/dl a month ago), positive ANA (discrete speckled 640×), positive anti-centromere antibody, negative MPO- and PR3-ANCA. Renal function gradually worsening, hemodialysis was started. Renal biopsy revealed severe gromeruli collapse with fibrinoid necrosis, and arterial internal membrane thickening like onionskin lesion. We diagnosed normotensive renal scleroderma crisis. Diagnosis of lung adenocarcinoma with cervical lymph node metastasis was made according to the findings of lymph node biopsy and chest CT. Her cervical lymph nodes were remarkably reduced with gefinitib, which was stopped because of new interstitial pneumonitis. She was died a month later. Limited scleroderma renal crisis is very rare.

P2-206

Five cases of clinically amyopathic dermatomyositis

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Conflict of interest: None

[Objectives] Clinically amyopathic dermatomyositis (CADM) is a subtype of dermatomyositis (DM), characterized by the absence of muscle weakness and the presence of normal muscle enzyme levels. Patients with CADM have anti-CADM-140 antibody and often make progress to rapidly progressive interstitial lung disease (ILD) with fatal course. [Methods] We compared clinical data prior to initiation of therapies in 5 CADM and 5 DM patients. [Results] There were no significant differences in frequency of sex and muscle weakness between CADM and DM patients. All patients with CADM had ILD but only one DM had it (P=0.0476). SerumCK and myoglobin levels, and initial dose of prednisolone in patients with each CADM and DM were 83 ± 21 IU/L(mean ± SE) and 795 ± 178 IU/L (P=0.0041), 38 ± 10 ng/mL and 234 ± 47 ng/mL,(P=0.0086), and 0.98 ± 0.08 mg/kg and 0.71 ± 0.08 mg/kg, respectively (P=0.0348). Anti-CADM-140 antibody was positive in all of 4 CADM patients examined. [Conclusion] Measurement of anti-CADM-140 antibody helps us to make a diagnosis of CADM in DM patient with normal serum CK and myoglobin. We have administered a larger initial dose of prednisolone for CADM patients because they have been complicated with ILD more frequently than DM patients and often develop to rapidly progressive ILD.

P2-207

Atypical case of antiCADM-140 antibody positive dermatomyositis with purulent arthritis

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Conflict of interest: None

The patient is a 30 years man. In November, 2011, the patient complains to his physician of wrist ache with the fever of 39°C. In February, 2012, it becomes hard to walk by the pain of the right knee, and receives this hospital. On examination, erythema on face, Gottron sign, and slight muscle weakness on deltoid, iliopsoas, and both intrinsic muscle. And chest CT films show interstitial lung disease (ILD) in the lower lung. Laboratory tests show a serum CK of 61IU/l, aldolase of 16 U/l, AST of 272IU/l, and LDH of 434IU/l. On muscle biopsy, I recognized changses of the muscular fibers and expression of the MHC-class I antigen (HLA - ABC), lymphocytosis at the perimysium and endomysium. It was diagnosed dermatomyositis, with purulent arthritis due to the bacteroides. After the remission of the arthritis, we prescribe PSL50mg. Because antiCADM-140 antibody positive, I put on 3mg of FK by combination. We taper PSL afterward, but the condition is stable without aggravation of ILD. The antiCADM-140 antibody is specifically found in CADM(clinically amyopathic dermatomyositis), lacking of muscle symptom and develops rapidly progressive ILD(RP-ILD) frequently. This case did not follow the ordinary course. The antibody measurement is useful for the confirmation of the treatment.

P2-208

Polymyositis with psoriasis vulgaris: a difficult case to make a differential diagnosis with dermatomyositis

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Conflict of interest: None

Dermatomyositis (DM) is differentially diagnosed form polymyositis (PM) by the specific skin rash in addition to the features of inflammation and degeneration of muscles. Here, we report a case of PM with psoriasis vulgaris (PV), who was needed to be differentiated from DM by skin biopsy. [Case] A 76-year-old male was admitted to our hospital because of proximal muscle weakness, CK elevation (1580U/L), dysphagia, hoarseness, and emergence of rash. He had erythema keratodes on the extensor surface of his extremities, Gottron's sign-like erythema keratodes on his fingers, and facial erythema on his cheek. His serum anti-Jo-1 antibody was negative, but anti-Ro/SS-A52 antibody was positive. Although asymmetrical muscle inflammation showed in MRI was atypical for PM, muscle biopsy indicated typical histology of PM. Skin biopsy partially showed pathological features of DM such as mucin deposition, liquefaction and vacuolar degeneration, but hyperkeratosis and acanthosis with neutrophils invasion in the stratum epidermis were more prominent. We finally diagnosed as PM with PV rather than DM. [Discussion] This case suggests the importance of histological assessment of skin and muscle biopsy to differentiate between PM and DM. We will report this case with bibliographical consideration.

P2-209

Three cases of anti-PL-12 antibody and anti-SS-A/Ro-52 antibody positive anti-aminoacyl tRNA synthetase antibody syndrome

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Conflict of interest: None

Anti-PL-12 antibody is one of anti-aminoacyl tRNA synthetase (ARS) antibodies and third frequent antibody specific to inflammatory myopathy in Japanese following to anti-Jo-1 antibody and anti-PL-7 antibody. On the other hand, anti-SS-A/Ro-52 antibody is found in Sjogren syndrome, which is known as an antibody associated with inflammatory myopathy. One report shows that approximately 40% of anti-PL-12 antibody positive patients had anti-SS-A/Ro-52 antibody, but the clinical features are not clarified. We experienced three anti-ARS antibodies syndrome cases with positive anti-PL-12 and anti-SS-A/Ro-52 antibodies. They demonstrated eosinophilia and atypical clinical findings. We will report the clinical courses and the consideration with literature review. Case 1: A 58-year-old man preceding eosinophilia and eosinophilic pneumonia showed mechanic's hand, Gottron's sign and myopathy and had anti-PL-12, anti-PM/Scl-75, and anti-SS-A/Ro-52 antibodies. Case 2: A 36-year-old woman preceding eosinophilia and eosinophilic pneumonia showed arthralgia and muscle pain and had anti-PL-12, anti-PM/Scl-75 antibodies. Case 3: A 47-year-old woman preceding eosinophilia and showed mechanic's hand, Gottron's sign and myopathy and had anti-PL-12 and anti-SS-A/Ro-52 antibodies.

P2-210

An autopsy case of amyopathic dermatomyositis with lupus-like clinical features

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Conflict of interest: None

Forty-year-old woman developed polyarthralgia, followed by erythematous rash on the face and extremities. One month late she was admitted to our hospital because of fever and progressive malaise. Mild elevation of CK was noted without autoantibodies, including anti-Jo-1 antibody. Amyopathic dermatomyositis (ADM) was made according to myalgia, arthralgia, electromyogram and skin biopsy. CT of the chest revealed interstitial pneumonia (IP), and oral steroid was started. During the course she was found to have hypoalbuminemia and nephrotic-range proteinuria. She demonstrated clinical features compatible with SLE but revised criteria for SLE was not fulfilled. Renal biopsy was performed, which revealed mesangial proliferation, endothelial cell swelling and thickening of capillary wall. Immunofluorescence study showed the deposition of IgM, C3, and C1q in the mesangial area and of IgG, IgM, and C1q in the tubular epithelial cells. Deterioration of IP was found on chest CT, and plasmapheresis, steroid and cyclophosphamide pulse therapy were stated. She died on the 238th hospital day with respiratory failure. This case demonstrated ADM with massive proteinuria and SLE-like features. We will discuss the case according to the finding s with renal biopsy and autopsy.

P2-211

A case of dermatomyositis during interferon alpha therapy for hepatitis C

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Conflict of interest: None

A 52-year-old man was diagnosed as hepatitis C, and pegylated interferon alpha-2b (PEG-IFNα-2b) and ribavirin were initiated in June 2011. He noticed weight loss and erythema on his neck, chest and back in September 2011. The pain and atrophy of his proximal muscles, exacerbation of erythema and increased level of creatine kinase (CK 23,365 IU/L) were pointed out by home doctor, and PEG-IFNα-2b and ribavirin were discontinued. He was referred to our hospital in February 2012. Skin biopsy of his back showed perivascular infiltration of lymphocyte, especially of CD4+ lymphocyte. Diagnosis of dermatomyositis was made and prednisolone (1mg/kg) was started with unfavorable response. Intravenous immunoglobulin (IVIG) and tacrolimus (3mg/day) were initiated on the 7th and 13th hospital day, respectively. Four additional treatment of IVIG were performed during 5 months, because of refractory myositis. His symptoms were improved and CK level was reduced to the normal level (CK 137 U/L). We report a rare case of dermatomyositis during IFNα therapy, and review the reported literatures.

P2-212

Analysis of the clinical features of refractory dermatomyositis and polymyositis

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Conflict of interest: None

Objectives:To assess the clinical features of refractory dermatomyositis and polymyositis (DM/PM). Methods: Adults with refractory DM/PM patients were enrolled to this study. These refractory patients need prednisolone and more than two immunosuppressive agents. Clinical records were reviewed retrospectively. Results: 12 patients (all DM, 2 male, 10 female) had refractory DM with 7 severe skin lesions, 6 severe arthritis and 11 elevation of CK levels continuously. Glucocorticoid and immunosuppressive agents include 2 MTX, 3 TAC, 1 CsA and 5 AZA were given as the initial therapy. Additional immunosuppressive agents, 5 MTX, 4 TAC, 3 CsA, 2 AZA, 2 MZR, 1 MMF, 1 RTX and 6 IvIg, were added for the refractory symptoms. Improvement rate of severe skin lesion and continuously elevated serum CK level were 64% and 86% respectively. Conclusions: The intensive treatment using various immunosuppressant agents should be chosen for refractory DM/PM patients with severe skin lesions and continuously elevated serum CK level.

P2-213

Predictor of the presence or absence of malignant tumor in dermatomyositis

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Conflict of interest: None

<Background> Dermatomyositis was complicated with malignant tumor at high frequency more than polymyositis. Therefore presence of malignancy is an important factor because of influencing poor prognosis. <Method> Forty-one dermatomyositis patients were studied and separated by the A group (complicated with malignant tumor; 14 patients) and the B group (complicated without malignant tumor; 27 patients). Age, sex, fever, arthritis and eruption (Gottron's sign, heliotrope sign, V neck sign, shawl sign, limbs extensor side erythema, mechanic's hand, skin ulcer) were examined. Serum levels of CK, LDH, myoglobin, aldolase, AST, ALT, the LDH/CK ratio, ESR, CRP and anti Jo-1 antibody were examined. <Results> There were significant difference into two groups, 64.4±14.4 years old (A group) and 52.1±19.1 (B group) (P = 0.031). Five of 14 patients (35.7%) (A group) and 19 of 27 patients (70.4%) (B group) (P = 0.036) were significant difference in the merger ratio of the interstitial pneumonia. In the LDH/CK ratio, 0.51±0.55 (A group) and 1.53±1.81 (B group) (P = 0.029) were significant difference. <Conclusions> Older age, complicated without interstitial pneumonia and low titer of the LDH/CK ratio were risk factor of the malignant tumor in dermatomyositis.

P2-214

Three cases of limited granulomatous polyangiitis (GPA; Wegener's) in elderly patients

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Conflict of interest: None

We have recently experienced 3 elderly patients with limited GPA. Case 1.-A 79-year old woman was admitted with fever, emaciation and dry cough; CRP 14.0mg/dL, WBC 12,500/μL, RF(+) and ANCA(-). Chest CT showed multiple pulmonary nodules. GPA was diagnosed by biopsy of maxillary sinus revealing granulomatous vasculitis. Initiation with GC (PSL 60mg/day) and IV cyclophosphamide (IVCY:300-400mg) brought about early disappearance of granuloma. Because of fracture complications, PSL has been tapering with IVCY. Case 2.-A 80-year old woman was admitted with ear pain and hearing loss; CRP 13.7mg/dl,WBC 10,550/μL and MPO-ANCA 170U/mL. GPA was diagnosed based on antibiotic-resistant otitis media and mastoiditis. PSL 30m/day and 3 x IVCY (500mg) improved ear inflammation and hearing loss, followed by MTX and low dose GC. Case 3.-A 79-year old woman was admitted with fever, emaciation and eye pain; CRP 6.91mg/dL and ANCA(-).Her consensus for biopsy was not obtained, but bilateral episcleritis and CT-detectable sinusitis suggested GPA. With no evidence of infection, PSL20mg/day reduced episcleritis, but mild inflammation remained with AZA addition. CY combined with GC may be essential for remission induction in GPA, even in elderly patients who must need modification of CY dosing.

P2-215

A case of granulomatosis with polyangiitis(Wegener's granulomatosis)with seronegative for PR3- ANCA

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Conflict of interest: None

An 83-year-old man was admitted with antibiotics-resistant high fever and subacute renal failure. The patient was seronegative for PR3-ANCA and high titer positive for MPO-ANCA(1330EU). We performed a renal biopsy to achieve diagnosis. The renal specimen showed necrotizing vasculitis and inflammatory granulation tissue. Granulomatosis with polyangiitis(Wegener's granulomatosis) was deagnosed. Initial treatment with oral predonisolone at 30mg daily was started and high fever was soon improved. A month after initial treatment, we started gradual tapering of dose and added on cyclosporine at 75mg daily. Renal failure got better gradually and the titer of MPO-ANCA was significantly declined.

P2-216

A man with granulomatosis with polyangiitis (GPA) involving perforation of the small intestine

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Conflict of interest: None

A 79-year-old man presented itchness and ulcers on his lower legs. He was initially treated with oral predonisorone 30mg/day following diagnosis of pyoderma gangrenosum in dermatology in our hospital. Despite initial therapy, he presented hematochezia and perforation of the small intestine, and underwent emergency surgery. Laboratory findings included markedly elevated acute-phase reactants, positivity of PR3-ANCA, renal dysfunction and cellular sedimentations, which suggested the diagnosis of GPA. Predonisorone 1mg/kg after steroid pulse therapy followed by cyclophosphamide pulse therapy were initiated. Inflammatory findings, skin ulcers and the small intestine involvement were improved. These are few reports of GPA involving perforation of the small intestine.

P2-217

A case of cerebrospinal fluid (CSF) leakage during glucocorticoid therapy for granulomatosis with polyangiitis (GPA) with hypertrophic pachymeningitis(HPM)

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Conflict of interest: None

A 67-year-old man was admitted to our hospital because of headache, right arm paralysis and dysarthria. Brain MRI revealed the findings of HPM. He also had abnormal chest radiograph and upper airway symptoms; serous otitis media, chronic sinusitis and saddle nose. And he was diagnosed as rapid progressive glomerulonephritis of unknown etiology 12 years ago, then perfomed maintenance hemodialysis. In consideration of high titer of PR3-ANCA, we diagnosed him as GPA with hypertrophic pachymeningitis. All of his symptoms remarkably improved with methyl prednisolone pulse and a large amount of prednisolone. However, he complained of splitting headache and nasal hydrorrhea on the 19th

day. Pneumocephalus was shown by Brain CT. Nasal endoscopy demonstrated disappearance of nasal granuloma, while bone and mucous of skull base were defect, being exposed dura matter. Endoscope assisted surgery of fistula closure was underwent on the 21th day. Then, there was no relapse of CSF leakage, subsequently we succeeded remission induction of GPA with glucocorticoid therapy only. We thought CSF leakage was caused by regression of osteoclastic granuloma, enlarged gradually for years, due to glucocorticoid therapy. There were no reports that CSF leakage during glucocorticoid therapy for GPA with HPM.

P2-218

A case of granulomatosis with polyangiitis complicated with eosinophilia and pulmonary hemorrhage: clinical course of cytokine profile

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Conflict of interest: None

A 25-year-old woman complained of fever, polyarthralgias, both lower limbs edema, dyspnea and hemoptsis in early March 2012. The patient was admitted to our University Hospital on March 28. Physical examination showed scleritis, bilateral midlung field crackles, and purpura. Laboratory tests on admission gave the following results: white blood cell count, 16,100 /μL; eosinophil count, 4,267/μL; hemoglobin, 9.4 g/dL; serum C-reactive protein, 2.5 mg/dL; negative antinuclear antibodies, high-titer PR3-ANCA (40EU), and negative MPO-ANCA. Her chest radiography showed patchy bilateral alveolar infiltrates. Rhinoscopy revealed perforation in the nasal septum. Bronchoscopy revealed alveolar hemorrhage. Renal biopsy revealed crescentic glomerulonephritis. She had no history of asthma. Therefore, she was diagnosed as granulomatosis with polyangiitis complicated with eosinophilia and pulmonary hemorrhage. She was improved by methylprednisolone pulse therapy, high dose glucocorticoid therapy and intravenous pulsed cyclophosphamide. Her serum IL-4 levels before and after therapy were 9.4 and 5.0 pg/mL. Her serum INFγ and IL-17 levels did not change before and after therapy. The pathogenesis of this case might be influenced by eosinophilia associated with Th2 cytokine as IL-4.

P2-219

A case of polyarteritis nodosa with Castleman's disease and positive PR3-ANCA complicated by intraperitoneal bleeding and renal infarction

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Conflict of interest: None

A 63-year-old man presented with itchy cutaneous nodules and systemic lymphadenopathy. Lymph node and skin biopsy showed IgG4-positive plasma cell infiltration with IgG4/IgG >50%. Although IgG4-related disorder was initially suspected, clinical features and elevated IL-6 and CRP were more compatible with Castleman's disease. Skin nodules and lymph nodes swelling resolved with the moderate dose of predonisone. His clinical course was complicated by proteinuria with positive PR3-ANCA and re-elevation of IL-6. Renal biopsy showed necrotic tissue and disappearance of essential kidney structures, and the diagnosis of renal infarction was made. Anticoagulation and tocilizumab were started, however, cerebral infarctions and intraperitoneal hemorrhage developed. Hepatic and gallbladder artery angiography showed aneurysms, fusiform expansion and stenosis in the intraperitoneal arteries, including renal arteries. Ruptured artery was successfully embolized. The diagnosis of polyarteritis nodosa was made. The treatment according to the EULAR recommendation was instituted. We could have prevented intraperitoneal hemorrhage with earlier recognition of vasculitic process. This case illustrates complicated management of the case which has multiple immune-related disorders.

P2-220

Infliximab As an Alternative Therapy to the refractory localized GPA (two case reports)

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Conflict of interest: None

A 62-year-old female was diagnosed as PR3-ANCA negative granulomatosis with polyangitis (GPA) 8 years ago. Her brain MRI showed enhanced lesion within the left orbit. Her disease was resistant to the therapy with several kinds of drugs such as prednisolone, cyclophosphamide, azathioprine, ciclosporin and the radiation therapy. Finally the combination therapy with Infliximab, methotrexate and prednisolone was very effective. A 68-year-old female was diagnosed as GPA with the high titer of PR3-ANCA (93EU). Her brain MRI showed swelling of pituitary pathologically injured. She was diagnosed with pituitary diabetes insipidus due to GPA. Her disease was resistant to the drugs such as prednisolone and cyclophosphamide. No treatments caused favorite response. Finally she was treated with the combination of Infliximab, methotrexate and prednisolone, then her symptom was improved. Infliximab could be an alternative therapy to the refractory localized GPA.

P2-221

Visceral dissemination of varicella zoster virus occurred after rituximab therapy for granulomatosis with polyangiitis

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Conflict of interest: None

We present a case of granulomatosis with polyangiitis (GPA) diagnosed at 18 years old. Although cyclophosphamide was not effective on right upper lung granulomas, rituximab responded well at 28 years old. At age 30, she was admitted for recurrence of lung granulomas and development of pituitary diabetes inspidus. The granulomas were well controlled by treatment of prednisolone 50 mg/day and rituximab 375mg/m2 for day 35, 42, 55 and 62. But she complained of abdominal pain from day 63 and arthralgia from day 69. Bleeding tendency, thrombocytopenia and significantly elevated d-dimer indicated severe disseminated intravascular coagulation. In spite of using thrombomodulin, antibiotics and ganciclovil, she got worse and died at day 71. Skin rash was never

observed throughout the course. After her death, cytomegalovirus (CMV) antigenemia and positive serum varicella zoster virus (VZV) DNA were detected. Histopathologically, inclusion bodies in liver, stomach and ovary were observed. VZV in pharynx, esophagus and liver, and CMV in stomach and ovary were positive by immunohistochemistry. It should be noted that disseminated VZV infection is sometimes developed in visceral organs without skin rash.

P2-222

Multiple intraperitoneal aneurysms in eosinophilic granulomatous angiitis were disappeared with the remission of angiitis

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Conflict of interest: None

A 34-year-old man who was diagnosed of eosinophilic granulomatous angiitis, and admitted to our hospital because of steroid resistance. For the purpose of examining a cause of the abdominal pain, contrast enhanced CT was performed. Multiple aneurysms in the intestine were detected in contrast enhanced CT and angiography. Because of the aneurysms were active changes of angiitis, steroid pulse therapy, conventional therapy (PSL 1mg/kg/day) and IVCY were treated. On the 7th day, an intestinal tract necrosis was detected by CT and small intestine partial excision was performed. Plasma exchange (PE) therapy was appended to IVCY. For concurrence of sepsis, a toxin adsorption treatment and the antibiotics were performed, and the inflammatory change was negative on the 22nd day. On the 38th day, inflammation of the gallbladder was developed. At that same time, angiography findings were disappearance of the aneurysms. On the 94th day, the symptom of cholecystitis was showed again, and cholecystectomy was performed. Complications of eosinophilic granulomatous angiitis and aneurysms were very rare. Combination therapy of the IVIG, IVCY and PE might be effective for the remission of angiitis and coexisting aneurysms.

P2-223

A case of allergic granulomatous angitis on hemodialysis

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Conflict of interest: None

We report a case of 72 year female who was diagnosed with allergic granulomatous angitis (AGA) on hemodialysis. She has had an asthma for 5 years, which is in therapy of inhaled steroids. 3 years ago, she also had psoriasis vulgaris. In 1990 hypertension revealed, 3 years later microproteinuria, renal dysfunction was pointed. In 1995 a hemodialysis therapy started. 1 years ago, she had a diarrhea, abdominal pain. On the next day, her both feet were swelling with purpura, numbness. 10 days later she was admitted to a hospital because of melena. Laboratory findings showed a titer of CRP was 2.1mg/dl, IgE was 1920IU/ml. Nerve conductions study of sural nerve was abnormal, a velocity was 50m/s, an amplitude was 0.5μV. A skin biopsy was performed. Pathological examination revealed microscopic polyangitis without eosinophilic invasion. There were no immune deposits on immunofluorescence study. Colonoscopic findings were normal. Intravenous pulse methylprednisolone therapy(250mg/day for 3days) was performed for the treatment of AGA. After that her prednisolone decreased to 30mg, her symptoms recovered. Many patients on dialysis have several skin lesions and symptoms caused by orthopedic diseases. But we have to consider about vasculitis like her when we see these patients on dialysis.

P2-224

A case of ANCA negative Churg-Strauss syndrome with diagnostic difficulties because of cerebral palsy

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Conflict of interest: None

[Clinical significance] Churg-Strauss syndrome (CSS) is relatively an uncommon disorder. We present a rare case of CSS because we could follow up chronologically before clinical diagnosis of CSS. In addition, cerebral palsy made it hard to diagnose as CSS neurologically in this case. [Case report] A 41-year-old woman who had cerebral palsy had been able to walk. In 2004, she was diagnosed with bronchial asthma and allergic rhinitis. Eosinophilia existed since 2010. In August 2012, she could not stand because of paresthesia, pain, and weakness of lower limbs. She was admitted for fever, bloody diarrhea, abdominal pain and foot livedo. Her laboratory tests showed as follows; WBC 25170/μL, Eos 8809/μL, PLT 500,000/μL, serum IgE 2690 U/mL, and rheumatoid factor 222 IU/mL. Anti-neutrophil cytoplasmic autoantibody was negative. The finding on colonoscopy was like ulcerative colitis. Histopathologically, eosinophilic infiltration in rectum and focal axonal degeneration in nerve were shown. In nerve conduction velocity test, waveform was totally absent in both upper and lower limbs; it showed peripheral nerve disorder. Therefore, she was diagnosed with CSS. After treated with predonisolone and intravenous cyclophosphamide therapy, her neurological finding improved in the upper limbs.

P2-225

A Case of Central Diabetes Insipidus Associated with Positive MPO-ANCA

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Conflict of interest: None

A 53-year-old women with a history of epilepsy and memory impairment developed difficulty walking due to generalized myalgia in June 2011. She was referred to our hospital in May 2012. Inflammatory response was observed (CRP8.2mg/dL ESR80mm/hr) and MPO-ANCA was 142IU / L. Neither lung lesions nor renal lesions were observed. After treatment with PSL10mg, low-grade fever and muscle pain has improved. However, the inflammatory response was prolonged. It has been found that the amount of more than 4 liters of urine per day in the course of reviewing the diagnosis. Although the details are not clear on the questionnaire because of the memory impairment, sudden onset of polyuria and polydipsia and about the same time to generalized myalgia appeared. ADH was less than the detection level. MRI revealed findings that were compatible with hypophisitis. After six courses cyclophosphamide pulses, urine volume and titer of MPO-ANCA improved.

P2-226

A case of MPO-ANCA-positive thoracic hypertrophic pachymeningitis

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Conflict of interest: None

[Introduction] Hypertrophic pachymeningitis (HPCM) is characterized by thickening lesions of inflamed dura mater and resultant nerve disturbance. This is a rare case of HPCM that was localized in the thoracic region and presented positive MPO-ANCA. [A case report] A 69-year-old man complained of back pain, gait disturbance, and difficulty in urination and defecation. Since MRI disclosed thickened thoracic dura mater, he had decompression surgery. A biopsy of the removed specimen showed only chronic nonspecific inflammation. Because of positive MPO-ANCA, we considered HPCM as a manifestation of ANCA-related vasculitis after careful examinations, and started a steroid therapy (PSL 0.8mg/kg day). After 4 weeks, the dura mater lesion recovered original thickness and released symptoms along with the reduction of MPO-ANCA. [Discussion] There are an increasing number of case reports on ANCA-positive HPCM, and some described that the prevalence of MPO-ANCA amounted to 71%. In ANCA-positive HPCM, vasculitis was generally diagnosed based on other tissue lesions than dura mater, and there have been reported no cases that proved dural vasculitis. HPCM is not included in BVAS and VDI items. It needs future discussion whether HPCM should be one of the vasculitis manifestations.

P2-227

Two cases of anti-thyroid drugs 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 vasculitis, and there are a few reports of methylmercaptoimidazole (MMI) induced-vasculitis. [Methods] I report on two cases of both PTU and MMI induced MPO-ANCA-associated vasculitdes (AAV). [Results] One patient is a 19-year-old woman with Basedow's disease treated with PTU for 4 years. She admitted to our hospital with pulmonary hemorrhage. Because her legs were edematous with purpura since two months, PTU was withdrawn and she had taken oral PSL 20mg/day and MMI. On the laboratory examination, her MPO-ANCA was positive, and she was diagnosed as PTU induced AAV. Oral PSL 50mg/day was started and her symptom was improved. The other patient was a 50-year-old man with Basedow's disease treated with MMI for 10 years. He was having livedo reticularis on his legs since one year. Recently, polyarthralgia and myalgia with sural muscle occurred. His MPO-ANCA was positive, and he was diagnosed as MMI induced AAV. Although we recommend him to withdraw MMI and to get the surgery, he rejects them. Now he has taken low dose MMI and Potassium Iodide. His symptoms are reduced. [Conclusion] Clinical abnormalities are heterogenous and less severe in patients with drugs induced AAV, and they may have a good prognosis.

P2-228

Three cases of aortitis syndrome above 60-year-old

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Conflict of interest: None

[Objectives] Aortitis syndrome (AOS) commonly presents in younger population with a ratio of males to females of 1 to 10. We report three cases of AOS which onset in elderly patients above 60-year-old. [Methods] The patients were 62-year-old female, 69-year-old female, and 87-year-old male. They had examinations including blood test, echocardiography, abdominal ultrasound, CT for fever of unknown origin (FUO). PET-CT was carried out because of the hypertrophic aortic wall found in CT and MRI. Although the difference in blood pressure between arms was not remarkable, the uptake at wall of thoracic aorta and ventral aorta in 62-year-old female, thoracic aorta, ventral aorta, brachiocephalic artery, subclavian artery, and common carotid artery was detected by PET-CT in 69-year-old female and 87-year-old male. They were diagnosed as AOS and treated with 30 mg/day of oral prednisolone. Their fevers were gone in 3 days and CRP improved in 8 days. [Results] While about 30% of FUO in elderly patients is due to collagen disease, AOS is a rare cause. However, AOS should be considered as an origin of FUO in elderly patients, when contrast CT image finds hypertrophic aortic wall or diffusion MRI finds high signal intensity of aortic wall. [Conclusion] AOS may cause FUO in elderly patients.

P2-229

The usefulness of ^{18}FDG-PET for the early diagnosis or evaluation of the disease activity in the patients with Takayasu's arteritis (TA): a report of three cases

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Conflict of interest: None

【Case 1】A 24-year-old woman had pulseless of bilateral upper limb in 2009. She was admitted because of elevated inflammatory reactions etc. Enhanced CT demonstrated wall thickening of aorta and its branches, thus she was diagnosed as TA. Although operation was considered due to the cerebral ischemic symptom, we preceded steroid therapy since ^{18}FDG-PET revealed the active inflammation of aortic wall. After the improvement, she was followed without the operation.【Case 2】A 17-year-old woman was admitted due to FUO in 2011 and diagnosed as TA by the finding of enhanced CT and ^{18}FDG-PET. Steroid therapy was effective and then low disease activity was maintained. She had suffered diarrhea and slight fever from June 2012. ^{18}FDG-PET revealed the relapse of TA by abnormal uptake of aortic wall. Then increasing dose of steroid and additional methotrexate improved her symptoms.【Case 3】A 17-year-old woman had suffered sustained fever and cough from January 2012. She was admitted because vasculitis was suspected due to intimal thickening of carotid artery. Although her symptoms was already resolving, enhanced CT and ^{18}FDG-PET revealed mild aortic wall thickening and abnormal uptake, thus diagnosed as TA. She was followed without therapy since her symptoms were spontaneously improved.

P2-230

FDG-PET/CT Revealed Aortitis in 5 Elderly Cases of High Serum CRP Levels

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Conflict of interest: None

We recruited 5 patients (3 male, aged 53-88 years) with Takayasu arteritis in our department (general medicine) over a recent 3-year period. Their symptoms were non-specific. None of them had symptoms of polymyalgia rheumatica, heart murmur, bruit, or visual impairment, and none showed significant difference in systolic blood pressure between both arms. The laboratory findings showed persistent elevated serum CRP levels (5-17 mg/dl). Blood and urinary cultures, a variety of immunological tests and major tumor markers were also negative. We performed CT, brain MRI, endoscopies, and Ga-67 Scintigraphy, but the resulting data could not define diagnoses. Finally 18F-FDG-PET/CT revealed FDG abnormal uptake in the aorta, indicating aortitis. In 3 of 5 cases, the CT angiography showed arterial wall thickening and some range of stenosis consistent with FDG uptake region. We initiated therapy with prednisolone in 3 cases, and their clinical symptoms and serum CRP levels rapidly improved. In elderly patients, we often experience cases with non-specific symptoms and elevated inflammatory serum markers. When routine investigations fail to determine the etiology, we propose that clinicians should suspect aortitis. FDG-PET may be useful for the early diagnosis of Takayasu arteritis.

P2-231

On classification of IgG4 related diseases with malignancy

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Conflict of interest: None

[Objectives] Nowadays we can easily measure the IgG4 value for the purpose of diagnosis of AIP. So we can encounter many clinical situation which shows IgG4 elevation except for typical IgG4 related disease, such as tuberculosis and malignancy. [Methods] This time, we tried classify our own cases to for the further understanding of the IgG4 related diseases. [Results] Classification was as follows; 1. Malignant lymphoma developing from IgG4 related diseases, 2. Malignant lymphoma associated with IgG4 related diseases. 3. Simple comorbidity of malignant diseases and IgG4 related diseases, 4. wide spread malignant condition which showed IgG4 elavation. [Conclusion] Considering these classification, we must gather much more cases and investigate the true pathophysiology of this disease.

P2-232

The clinical character of 16 patients suspected to be IgG4-related disease

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Conflict of interest: None

[Objectives] To examine the clinical characters of IgG4-related disease patients in our hospital. [Methods] 16 patients were analyzed about their involved organs, laboratory data, and histological examinations referring to the criteria proposed by Umehara et al in 2011. [Results] 13 of 16 patients were diagnosed as definite IgG4-related disease. Among the three not diagnosed as definite disease, two were not revealed either typical organ involvements or high level of serum IgG4, though having IgG4-positive cells histologically. Another one showed typical organ involvement, but IgG4 couldn't be proved. 10 of 13 defined patients had Mikulicz disease. Involvements of orbital tissue, but not lachrymal glands, were seen in other two cases. Mean serum concentration of IgG4 was 676±452mg/dl (175-1580mg/dL) in 13 definitive patients. In 5 of 12 patients examined histologically, IgG4-positive plasma cells were increased sufficiently. Four patients had malignancy, gastric carcinoma (2 patients), prostate cancer (1), and malignant lymphoma (MALT lymphoma)(1). [Conclusion] In our hospital, orbital involvements including Mikulicz disease were the majority of the IgG4-related disease. The patient of MALT lymphoma was treated only by glucocorticoid and achieved remission without chemotherapy.

P2-233

The Diabetes management of IgG4 related disease

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Conflict of interest: None

[Back ground] Autoimmune pancreatitis (AIP) patients have Diabetes mellitus by 42-85%. The pancreatic function was improved by steroid therapy. In this case, we managed to assess the blood glucose during therapy. [case] 74 yo male. He was diagnosed by Mikulicz disease on July in X. He had the swelling of the lymph node of Mediastinum and Pulmonary hilum by CT on Feb in X+1. IgG4 was higher at 454 mg/dl. He was diagnosed by AIP and treated by prednisone 30mg/day. After the therapy, Blood glucose level was improved. [Conclusion] Diabetes Mellitus with AIP was improver by steroid therapy, so we have to pay attention of the low glucose.

P2-234

2 cases difficult to distinguish from retroperitoneal fibrosis

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Conflict of interest: None

【Background】Retroperitoneal fibrosis (RPF) is now recognized to be within the spectrum of IgG4-Related Disease (IgG4-RD). We experienced 2 patients with image findings similar to RPF by other disease.【Case 1】72 year-old man visited with history of fever, low back pain and weight loss. CRP:14.4mg/dl, ESR(1h):100 and IgG:2438mg/dl. Abdominal CT showed the hypodense tissue around the aorta with right hydronephrosis. MSSA cultured from blood. By MRI, he diagnosed lumbar vertebral osteomyelitis.【Case 2】62 year-old woman with past history of breast cancer and adrenal insufficiency was introduced to us suspected of IgG4-RD. Pancreatic tumor and para-aortic low density tissue with left hydronephrosis were pointed by CT. IgG4:155mg/dl. Brush cytology of pancreas proved no malignant cell. Steroid therapy started. About 6 months later, bilateral leg edema appeared with ascites, and adenocarcinoma was proved from ascites. She was diagnosed breast cancer disseminated into the abdominal cavity.【Clinical Significance】Image findings similar to RPF are presented by not only IgG4-RD but also other disorders such as some infection or malignancy. Diagnosing of RPF should be comprehensively through the clinical information such as time course, past medical history and physical examination.

P2-235

The clinical Study of immuno-supplesstant therapy for IgG4-related disease

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Conflict of interest: None

[Objectives] The purpose of this study is to clarify the efficacy of glucocorticoid (GC) and immune-suppressive drugs (IM) combine therapy for IgG4-related disease. [Methods] Th retrospective observational study for the patients with high serum IgG4 rate in- and out-patients in Kyorin University hospital from 2010 to 2012. [Results] Total number of the patients showed the high degree of IgG4 were 60 people. Most of them were treated with moderate dose of GC. The efficacy of GC using for IgG4-related disease was favorable, and half of them were achieved to complete remission. Some patients showed the relapsing during the tapering of GC. The seven cases of the patients were treated with IM and GC concomitant therapy. The combine therapy was inhibit the disease activity, but serum IgG4 levels were remained over the cut-off range. [Conclusion] The further study would be necessary to evaluate the efficacy and safety of GC and IM combined therapy for IgG4-related disease.

P2-236

A Study of Characteristics of IgG4-related Cardiac Tumor through Four Cases

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Conflict of interest: None

Objective:A study of the characteristics of IgG4-related cardiac tumor. Methods:Four patients who were diagnosed as IgG4-related by a biopsy and had cardiac tumors were evaluated with L/D and images(CT, MRI, echo cardiogram, and FDG-PET). Results: [Age] Mean age 53±2 years. [Sex] Two men and two women. [Cardiac lesions] Case1;Left atrium, right atrium, atrium septum, and around RCA and LCA. Case2; Right atrium. Case3; SVC, right atrium, and epicardium. Case4; Left atrium and around LCA. [Non-cardiac lesions] Case1; Bilateral lacrimal glands and spleen. Case2; Bilateral renal pelvises. Case3,Case4;None. [Histopathological findings] Lymphoplasmacytic tissue infiltration with more than 40-50% IgG4+ plasma cells accompanied by fibrosis was observed. [L/D] Mean IgG4 608mg/dl. [Image] CT:The cardiac tumors were detected clearly and the lesions were enhanced slowly. MRI:The cardiac tumors were slowly enhanced in enhanced T1WI. US: The cardiac tumors were detected in three cases and abnormal flow was detected in one case. PET: SUVmax2.3-4.4 was observed in each lesions. Conclusions:IgG4-related cardiac tumor should be one of the differential diagnosis of cardiac tumors, although it is rare. PET is useful for screening to detect cardiac tumor in patients with IgG4-related disease.

P2-237

A case of IgG4-rerated disease (Mikulicz disease) with the remarkable swelling of bi-lateral major Salivary glands, pancreatitis and thickening of the bronchial wall

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Conflict of interest: None

[Objective and Methods] Recently Mikulicz disease is categorized in IgG4-related disease, differ from Sjogren syndrome. This disease show various systemic symptoms, and the effect of therapy for salivary glands function on both diseases are different too. [Results] A 52-year-old man noticed remarkable swelling and hardening of his bi-lateral Parotid glands and submandibular glands from 6 months before. We suspected Mikulicz disease and performed several examinations. His serum IgG4 level was elevated, 1610 mg/dl,and the anti SS-A antibody and the anti SS-B antibody were negative. The computed tomography scans showed severe swelling of the Parotid grands, the submandibular glands, the lacrimal glands, findings of autoimmuno-pancreatitis and remarkable thickening of the bronchial wall. Histopathological examinations by biopsy of salivary glands and the bronchial mucosa showed remarkable infiltration of IgG4-positive plasma cells. After the therapy of corticosteroids, the patient's all symptomes, include salivary flow rate and his serum IgG4 level were rapidly improved. [Conclusion] There was a case of IgG4-rerated disease (Mikulicz disease) with diagnostic symptomes. The all symptomes were rapidly improved by corticosteroids therapy.

P2-238

Spontaneous remission of hypophysitis in IgG4-related disease

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Conflict of interest: None

A 87-year-old male was diagnosed with IgG4-related disease because of bilateral swelling of parotid and submandibular glands and a compatible biopsy result of a submandibular gland. He had been successfully treated with moderate dose of prednisolone and stable until prednisolone was tapered to 1mg/day. Then he started to feel fatigue and lose appetite and was diagnosed with central hypothyroidism and hypoadrenalism. A brain MRI showed hypophysitis. A month later, his symptoms and hormonal abnormalities were spontaneously recovered along with the improvement of hypophysitis on MRI. We herein report the first case of spontaneous remission of hypophysitis in IgG4-related disease.

P2-239

Clinical and pathological features of patients with IgG4-related disease complicated with orbital involvements

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Conflict of interest: None

[Objectives] IgG4-related disease (IgG4-RD) is characterized by IgG4+ plasmacytic infiltration and fibrosis in various organs. Orbital involvements in IgG4-RD affect not only lachrymal glands but also others such as inflammatory pseudo tumors, muscles, and nerves. The purpose of this study is to clarify the features of IgG4-RD complicated with orbital involvements. [Methods] We examined the 9 patients with IgG4-RD who underwent orbital tissue biopsy from April 2010 to August 2012 at our hospital retrospectively. We studied their clinical features, pathological findings, and response to treatment. [Results]1) In 9 patients, 8 had dacryoadenitis,

one complicated with infra-orbital nerve swelling, and the other one had inflammatory pseudo tumor. All patients had other organ involvements. 2) All biopsy samples showed lymphoplasmacytic infiltrations and fibrosis, and ratios of IgG4+ / IgG+ plasmacytes were higher than 40%. 3) Every patient was treated with corticosteroid and well responded in early phase. As tapering corticosteroid, two patients had relapse with swelling of lachrymal glands. [Conclusion] Patients with IgG4-RD complicated with orbital involvements often had other organ involvements. Corticosteroid was effective for orbital involvements as well as for others in IgG4-RD.

P2-240

A case of AS patient with CIDP

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Conflict of interest: None

Present illness: He was diagnosed juvenile rheumatoid arthritis (JRA) in 8 years old and had been followed up without medication, diagnosed RA in 11 years old and administered with PSL and NSAIDS, diagnosed ankylosing spondylitis (AS) in 23 years old and administered with gold drug and NSAIDS for 6 months, and because of improvement, medication had been finished. In 28 years old, right necrosis of head of femur occurred to him. In 59 years old (2009 September), numbness of limb, disturbance of gait occurred, he had a medical examination in our hospital, and he entered the hospital at 5th in January 2010. Progress after hospitalization: He was doubted polyradiculitis because of existence of disturbance of sensory and nerve in nerve conduction velocity. He was diagnosed with CIDP because of remarks by biopsy of nerve. He was administered with massive γglobulin therapy, and after that, was administered with PSL100mmg every other day. He improves disorder of sensory and motor even after tapering of PSL, and was discharged the hospital 30th in March 2010. Conclusion: We experienced the case of AS with CIDP, which was improved with massive γglobulin therapy and PSL. There are some reports that the case of SjS with CIDP. We report the rare case which supervenes CIDP with AS with literature,

P2-241

Hemophagocytic syndrome associated with methotrexate-associated lymphoproliferative disorder in a patient with spondylarthritis

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Conflict of interest: None

We report a case of spondylarthritis treated with low-dose MTX therapy suffered from HPS associated with lymphoma. A 51-year-old man was referred to our hospital because of Raynaud's phenomenon, arthralgia, joint swelling. He suffered from ileosacral arthritis, psoriasiform dermatitis, enthesitis. He was diagnosed with spondylarthritis and treated with PSL 6mg/day and MTX 14mg/week and SASP 1000mg/day. His arthralgia resolved, but he developed cervical lymphadenopathy 5 months after the beginning of MTX therapy. Although MTX therapy was interrupted, the lymphoadenopathy did not improve, and developed fever, thrombocytopenia (17.3 x 10^4/μL→3.7 x 10^4/μL), hepatosplenomegaly, and DIC. Bone marrow examination revealed increase of phagocytosis, and cervical lymphnode biopsy showed diffuse large B-cell lymphoma. The diagnosis of lymphoma-associated HPS (LAHS) was made. Treatment with steroid pulse was started, and his thrombocytopenia and DIC resolved immediately. MTX-associated lymphoproliferative disorders (MTX-LPD) are categorized as other iatrogenic immunodeficiency-associated LPDs in the recent WHO classification. Our case developed LAHS after withdrawal of MTX, therefore we have chosen chemotherapy. Our case indicated that careful follow-up after the cessation of MTX is important.

P2-242

Thrombotic Thrombocytopenic Purpura (TTP) developed after MTX and NSAIDs administration in a case of spondyloarthritis (SpA)

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Conflict of interest: None

[Case Report] A case, 46 years-old woman, was consulted to our clinic because of limbs and truncal pain. She had inflammatory back pain, and laboratory findings revealed CRP 0.1 mg/dl, ESR 6mm/h, MMP-3 34.9ng/ml, RF 4 U/ml, and anti-CCP negative. We diagnosed her as SpA because of typical clinical features and multiple enthesitis by imaging. A cough developed after MTX and NSAIDs administration for two weeks. She noticed hematuria and nausea followed by vomiting and admitted to our hospital. Laboratory findings revealed LDH 1,582 IU/l, I-bil 3.1 mg/dl, Plt 13000 / ul, Coombs' test negative, haptoglobin <10 mg/dl, ADAMTS-13 activity undetectable. Fragmented red cells were also found in peripheral blood and we started PSL administration of 50mg/day suspicious of having TTP. On the sixth day, however, loss of consciousness developed and we added pulse therapy of methylpredonisolone for three days and 10 times of plasma exchanges. Following treatment, her symptoms and signs disappeared and we finally diagnosed her as having TTP after MTX and NSAIDs administration for SpA. There was no previously reported cases in which MTX caused TTP. We could not detected the cause of TTP in this case, but we discuss some consideration about a cause of TTP.

P2-243

THA and TKA in Patients Suffering from Psoriatic Arthritis -a Case Report-

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Conflict of interest: None

[Objectives] Psoriatic arthritis (PsA) is a chronic inflammatory arthropathy that affects approximately 7% to 42% of patients with psoriasis. The aim of this paper is to evaluate the results of total hip arthroplasty (THA) and total knee arthroplasty (TKA) in patients suffering from PsA. [Methods] Material included 3 patients, 1 female and 2 males, on whom 1 THA and 2 TKAs were performed at the Department of Bone and Joint Surgery, Ehime University Hospital. The age of patients ranged from 47 to 80 years (mean 68.7). Follow-up ranged from 1 to 7 years (mean 4.7 years). The patients were evaluated clinically and radiologically [Results] All patients had increased function and decreased pain. The radiograms of all patients revealed that prosthesis were correctly positioned with no radiographic evidence of loosening in the last examination. Arthritis and skin lesions were well controlled with

medicine of DMARDs. [Conclusion] Clinical and radiological evaluation of our material showed THA and TKAs allows regaining good lower limb function. As it is necessary to recognize the potential complications (eg, poor wound healing and increased risk of infection) associated with PsA, careful attention should be paid to prevent these conditions.

P2-244

A case of psoriatic arthritis actualized by PEG-IFN treatment

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Conflict of interest: None

64 years old female suffered from arthralgia visited rheumatology clinic. She was patients of dermatology due to chronic dermatitis. DIP joints was suspected bone erosion by x-rays, and her nail presented foveation, but her skin lack of psoriatic skin. Because of ESR and CRP was within normal range, she was prescrived NSAIDs. She reffured to hepatology, because she suffered from chronic hepatits due to HCV infection. After the start of combination therapy by PEG-IFN, ribavirin and teraprevir, psoriatic lesions appeared on her upper arm, where were injection sites of PEG-IFN. Arthritis was flared at the same time with the appearance of psoriasis.

P2-245

Relapsing polychondritis: a report of three cases and literature review

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Conflict of interest: None

[Objectives] Relapsing polychondritis (RP) is a chronic rare immune-mediated disorder characterized by recurrent episodes of inflammation in cartilaginous structures, particularly the ears, nose, eyes, joints, and respiratory tract. We report 3 cases of RP at our medical center. [Methods] Clinical features, course, and treatment given were analyzed. [Results] Two men and one woman were included. The mean age at diagnosis for male was 63.5 years, whereas the one for female was 32 years. The mean duration of symptoms, before diagnosis, was 3.7months, ranging from 1month to 6months. Clinical features were as follows: auricular chondritis (100%), laryngotracheobronchial chondritis (100%), ocular involvement (66%), hearing loss and vestibular dysfunction (66%), and dermatologic manifestation (66%). Laboratory findings were as follows: elevated MMP-3 level (100%), antibodies to type II collagen (33%), and histologic examination of an affected auricular cartilage (33%). All of the patients received systemic prednisone with MTX. Mild RP of the female patient improved, whereas two male patients with floppy ears were under poor control with moderate improvement. [Conclusion] We report 3 cases of RP and review the literature.

P2-246

A Case of relapsing polychondritis in which FDG-PET/CT was of great value for early diagnosis

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Conflict of interest: None

A 54-year-old man had a sensorineural hearing loss in December 2011. Fever and cough developed with increased levels of CRP (>10 mg/dl) in February 2012. Computed tomography (CT) of his chest showed thickening of the tracheal and central bronchus wall. FDG-PET/CT demonstrated the accumulation of FDG in the trachea, bronchus, nasal septum, and laryngeal cartilage. He was transferred to our hospital on 9 April 2012. He had clinical features such as respiratory tract chondritis, nasal chondritis, cochlear and vestibular dysfunction. He was diagnosed with relapsing polychondritis (RP). Serum level of antibody against type II collagen was highly elevated (>99EU/ml). Prednisolone (PSL) 50 mg/day was initiated on the 13th hospital day followed by the treatment of azathioprine 50mg/day on the 30th hospital day. His symptoms disappeared and CRP was reduced to 0.02mg/dl. CT revealed improvement of thickening of the tracheal and central bronchus wall. PSL was tapered to 27.5mg/day on the 73th hospital day. This case suggested that FDG-PET/CT was a useful tool for the early diagnosis of RP.

P2-247

Relapsing polychondritis complicated with aortitis: a case report and literature review

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Conflict of interest: None

A 68-year-old man presented with meningitis and uveitis 3 years ago. He treated with antibiotics, antiviral agents and a pulsed steroid. The oral administration of corticosteroid was taken for a year. Two years ago, he was aware of softening auricle. He also experienced redness and swollen of auricle occasionally. The symptoms improved and worsened without medication. Two years later, he had polyarthritis and hyperemia, and visited our hospital. At the initial visit, he had external ear inflammation, conjunctivitis, neurosensory hearing loss and polyarthritis. An auricle biopsy demonstrated chondritis. According to the diagnostic criteria for relapsing polychondritis (RP) by Damiani et al. in 1979, he was diagnosed with RP. He didn't have nasal and laryngotracheal disease. He also showed wall thickness from ascending to descending aorta in CT and MRI, which were compatible with aortitis. He didn't show physical findings of aortitis. The therapy started with 60mg (1mg/kg) PSL a day. The symptoms disappeared and inflammation markers normalized immediately. RP is a very rare autoimmune disease characterized by the recurrent inflammation of cartilaginous structures. We experienced a case of RP complicated with aortitis. We will present with a literature review.

P2-248

A case of the relapsing polychondritis that treatment with Tocilizumab was effective

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Conflict of interest: None

A 63-year-old male, who has past history of malignant lymphoma, was admitted to our hospital complaining of polyarthralgia in November, 2011. He was suspected as rheumatoid arthritis because of synovium thickening of both wrists and increase of bloodstream signal detected by joint sonography. After administration of salazosulfapyridine and 7.5mg daily of prednisolone (PSL), his symptoms were improved. In February, 2012, high fever, hoarse-

ness and precordial pain appeared. FDG-PET/CT demonstrated increased FDG activity in tracheal cartilages and rib cartilage, and anti-Type II collagen antibody was strong positive, so he was diagnosed as relapsing polychondritis. He received mPSL pulse therapy, followed by combination therapy with 40mg daily of PSL and cyclosporine. In April, his symptoms recurred, so he was treated with intravenous cyclophosphamide (IVCY). Abdominal CT showed lymph node swelling, so we performed lymph node biopsy and diagnosed a malignant lymphoma (ML) recurrence. Chemotherapy including Rituximab was provided, and ML was in remission. In August, dyspnea and polyarthralgia recurred under 25mg daily of PSL, so he was treated with IVCY and mPSL pulse therapy. However, his symptons did not improve. Finally, we administrated Tocilizumab, so he was improved completely.

P2-249

Acute phase reactant is really necessary include 2012 EULAR/ACR classification criteria for polymyalgia rheumatica?

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Conflict of interest: None

[Objectives] Polymyalgia rheumatica (PMR) is a common disease. 2012 EULAR / ACR classification criteria for PMR is published. It is merely provisional, I give it a try to validate it. [Methods] All factors include EULAR/ACR criteria were validated. We retrospectively evaluated all cases that we suspected PMR at first during 10 years in our facilities. [Results] As 2012 EULAR/ACR criteria itself, the specificity was 60%, sensitivity was 71%. The most unnecessary factor is acute phase reactants. 2012 EULAR/ACR criteria without acute phase reactant, the specificity was 58%, sensitivity was 74%. [Conclusion] There is no need to measure the inflammatory response findings at the first visit. But 2012 EULAR/ACR criteria is not enough for diagnosis, because the sensitivity is still low. We wil evaluate ultrasound findings instead of acute phase reactants.

P2-250

Is steroid the best treatment of polymyalgia rheumatica? According to ultrasound findings

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Conflict of interest: None

[Objectives] Polymyalgia rheumatica (PMR) is common disease in the elderly. The first choice of PMR is steroids, and its treatment is long.The reactivity of the treatment is based on the reaction and inflammatory pain overall. Ultrasonography (US) of both shoulders hips were adopted as classification criteria of 2012EULAR/ACR, it has been widely used in clinical routine. We evaluate disease activity using US, and the association between US findings and the effect of steroids. [Methods] We studied prospectively in 19 PMR consequence patients who underwent steroid medical treatment for half a year. We evaluated general visual analogue pain scale (VAS),acute phase reactant(CRP, ESR) and US findinds of both shoulders and hips(evaluated by OMERACT) at baseline, week 2, month 1, 2,3,4,5. We evaluated the correlation between them. [Results] There are no correlation between US findinds, acute phase reactant, and VAS (Spearman correlation coefficient: 0.06; p = 0.46.). 2 cases with VAS 0/100 at 5months, and no inflammatory response had remarkable US positive findinds.These case has led to relapse after 8 months with treatment in the low-dose maintenance steroid. [Conclusion] Accoding to this study,it may not be sufficient in the current steroid therapy and regimen.

P2-251

The risk of relapse in polymyalgia rheumatica

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Conflict of interest: None

[Objectives] To determine climical parameters that may be useful in identifying polymyalgia rheumatica (PMR) patients who relapse during treatment with glucocorticoids. [Methods] A retrospective follow up study of 26 untreated patients with PMR were assessed for relapse. Patients were monitored for erythrocyte sedimentation rate (ESR), C-reactive protein (CRP),MMP-3, period before the start of treatment and thickening of the vessel wall at four aortic segments (ascending aorta, aortic arch, descending thoracic and abdominal aorta) in contrast *CT* image. [Results] Seven of 26(27%) patients relapsed during tapering glucocorticoids. In relapse group, vessel wall of aortic artery in contrast CT image before treatment is significantly thicker than that of no relapse group(median: 2.52mm vs1.85mm, P=0.004). Though, elevated ESR lebels at diagnosis were not correlated to increase the risk of relapse(median;61mm vs 63mm, p=0.28). CRP,MMP-3 levels at diagnosis were not also correlated to increased risk of relapse. [Conclusion] The aortic wall thickening found in the patients who relapse during treatment suggested that they may have large vessel vasculitis. It is important to perform PET-CT or temporal artery biopsy in addition to CT image before treatment.

P2-252

A case of localized nodular myositis which presented corticosteroid-resistant PMR like symptoms

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Conflict of interest: None

A 69-year-old woman developed uchal pain, left shoulder arthralgia and low-grade fever in January 2012. The symptoms persisted and worsened in August. Laboratory exams revealed normal CK value, CRP 11.8 mg/dl, RF negative, ACPA negative. MRI showed inflammation around the cervical vertebra. As antibiotics were invalid and no other obvious causes were detected, we administered PSL 15 mg / day orally, based on the diagnosis of polymyalgia rheumatica (PMR). But therapeutic effect was poor. She underwent further investigation in our department. MRI detected right shoulder bursitis, and myositis around lumbar vertebrae. Ga scintigraphy showed patchy accumulation in the right vastus lateralis muscle. There were mild tenderness and induration in the right leg as the scintigraphy indicated. The muscle biopsy proved fasciitis and myositis with lymphocytic infiltration. Excluding other diseases, we made the diagnosis of localized nodular myositis (LNM). Symptoms markedly improved with PSL 40 mg / day. LNM is a rare inflammatory muscle disease which causes localized painful swelling of the limbs and trunk. It may occur in proximal muscles, often without increased serum CK values. When a patient

with PMR presents resistance to low-dose corticosteroid, LMN should be differentiated.

P2-253

Two cases of atypical SAPHO syndrome that took a long time to diagnose

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Conflict of interest: None

[Cases] Case 1. A 50-year-old female complained of headache due to inflammation of skeletal bone. Although culture was negative, infectious osteomyelitis (OM) was suspected and she underwent a long-term antibacterial therapy, but the efficacy was unclear. After one year she complained of pain and difficulty of swelling. As MRI revealed strong soft tissue inflammation (STI) anterior to the cervical spine, retropharyngeal abscess was suspected, but its rapid disappearance in response to steroid ruled it out. STI adjacent to bone, together with aseptic OM and skin eruption, suggested SAPHO. Case 2. A 65-year-old female complained of severe low back pain and high fever of 40°C. Severe inflammatory response (IR), and inflammation of vertebrae on MRI suggested infectious spondylitis, although culture was negative. Antibiotics were sufficiently used, but ineffective. Tuberculous or fungal infection was unlikely. Albeit asymptomatic, the right sternocostoclavicular hyperostosis was observed. Although marked IR and lack of skin eruption were atypical, aseptic osteitis in two distant sites suggested SAPHO, which was confirmed by marked efficacy of minocycline. [Conclusion] Our cases showed that SAPHO, presenting with various symptoms, should be reminded of when we encounter refractory OM.

P2-254

Young case of SAPHO syndrome; association between various infection and clinical symptoms

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Conflict of interest: None

[Introduction] SAPHO syndrome is overlapping dermatologiacal and musculoskeletal conditions. The etiology remains unclear, but mivroves involvment might be a pivotal role for the pathogenesis. We report a young case of SAPHO with various infection with clinical symptoms. [Case] An 8- year-old girl resented with pustulosis, sternalgia, recurrent croup syndrome and mediastinal emphysema. The symptoms did not respond with antibiotics. She admitted for evaluation of exacerbation of PPP and joint pain. MRI and bone scan showed right sacrum and light fibula osteomyelitis. Ga scintigraphy revealed active inflammation of lachrymal gland and nasal cavity. Her condition had been deteriolated after recurrent otitis media (*P. aureginosa*) and dacryocystitis (*S. aureus*). MTX seemed to be effective, but anti-TNFα therapy would be considered. [Discussion] The unproved hypothesis, "auto-amplified reaction for low-virulence microorganisms " is still controvertial. Immune over-reaction with neutrophil dysfunction might be important for aseptic inflammation.

P2-255

A case of refractory MAGIC syndrome treated with Infliximab

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Conflict of interest: None

A 44-year-old woman with a history of auricularis, nasal root inflammation, uveitis, and scleritis was admitted to our hospital. She was positive for anti-type II collagen antibody. She also suffered from recurrent oral and genital ulcerations. She was diagnosed as mouth and genital ulcers with inflamed cartilage syndrome (MAGIC). Oral prednisolones (PSL) were prescribed (1mg/kg) and the symptoms were resolved. When PSL was tapered to 0.5mg/kg, the symptoms were returned. The effects of steroid pulse therapy and intravenous cyclophosphamide therapy were transient, and the symptoms of scleritis returned. Methotrexate (MTX) was added to PSL and titrated up to 16mg/week. When PSL was tapered to 0.25mg/kg, the symptoms of scleritits were returned again. Infliximab (INF) was initiated for her refractory RP in addition to PSL and MTX. The symptoms improved. She remains on INF and had no recurrence of symptoms. MAGIC syndrome is a rare disease and includes the clinical manifestations of Bechet disease (BD) and RP. Treatment includes corticosteroid and immunosuppressive agents. In this report, we showed the successful treatment of refractory MAGIC syndrome with INF. As RP and BD are mediated by the proinflammatory cytokines, anti-TNF therapy can be effective in refractory MAGIC syndrome.

P2-256

Interstitial pneumonia in a patient with Behçet's disease

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Conflict of interest: None

A 65-year-old man was diagnosed as Behçet's disease (BD) based on the presence of refractory stomatitis, erythematous nodosum on bilateral extremities, arthritis, ileocecum ulcers, and the positive result of HLA-B51 type. He was prescribed with prednisone 30mg/day combined with mesalazine and colchicine. He had been getting better after initial therapies, however, he was admitted to our hospital complaining of exertional dyspnea. The chest CT showed the ground-glass opacities on bilateral lungs, mesalazine-induced acute lung injury was considered. Although the administration of mesalazine was suspended, dyspnea and dry cough persisted. Another three months had passed, he admitted to our hospital again due to the deterioration of dyspnea, and the CT showed the spread of interstitial infiltrations compared with previous one. We concluded the interstitial pneumonia (IP) caused by BD. The therapy was initiated with methylprednisolone pulse followed by prednisone 50mg/day by oral. The maintenance therapies with cyclophosphamide and azathioprine were administered. Until now (November in 2012), the disease activity has been well-controlled. The IP associated with BD is extremely rare case, we are going to report academically.

P2-257

A case of Bechet-like fever

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Conflict of interest: None

A 39 year-old man was admitted to our hospital, because of UFO, He was operated aortic valve replacement by cardiovascular surgeon 17 years before. Episodic fever recurred several time with tonsiltis. Tonsilectomy was not done because of taking anticoagulant therapy. Each episode of fever, he was admitted for ruling out of infectious endocarditis. In October 2009, he was admitted to hospital because of atypical cerebral hemorrhage, which might be complicating cerebral abscess or crebritis.Fever continued after a few weeks, which disappeared for prescription of Colchicine.We considered that this patient pathophysiology.

P2-258

Reduced efficacy of infliximab and pharmacokinetics in Behcet's disease patients

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Conflict of interest: None

[Objectives] To determine the relationship between efficacy of infliximab (IFX) and the pharmacokinetics in Behcet's disease (BD) patients with uveitis. [Methods] WWe studied 24 BD patients receiving IFX for uveitis. IFX was given at 0, 2, 6 wk and then every 8 weeks. IFX concentration and antibody towards IFX (ATI) prior to the next infusion were determined by ELSIA. [Results] IIFX significantly suppressed ocular attacks (2.6±2.1 to 0.4±0.5/6M), leading to improved or stable visual acuity in 16 patients, whereas in 8 patients visual acuity was further deteriorated due to attacks which appeared at 1.5±1.6 wk before the next administration. The attack frequency was significantly decreased by shortening infusion interval to 5-7 wk. However, 6 patients who had ocular attacks, extraocular symptoms and infusion reaction along with undetectable IFX (<0.1mg/ml) and positive ATI required additional immunosuppressive agents besides shortening of the infusion interval or switching to adalimumab. [Conclusion] IFX efficacy is reduced due to the low trough level, which is overcame by shortening the infusion intervals in part, whereas additional immuonosuppressive agents or switching to another biologics should be considered especially in patients with positive ATI.

P2-259

Safety and efficacy of infliximab in the treatment of Behçet's disease up to 5 years

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Conflict of interest: None

[Objectives] To assess safety, efficacy and retention rate and to identify factors contributing to incomplete response. [Methods] Retrospective cohort study at Osaka University Hospital. Observed variables were patients' characteristics (age, sex, disease duration and HLA-B51 positivity), drug retention time, adverse events, visual acuity, CRP, serum compliment (C3) and drug usage. [Results] Twenty-eight patients (21 men and 7 women) were administered between March 2007 and May 2012. Median age was 37 years and median disease duration was 68 months. Retension rates were 76.5% at 3 year and 71% at 4 year. Severe adverse events were bacterial pneumonia, infusion reaction, intestinal perforation, heart failure and renal artery aneurysm. Among 21 patients over 2-year period, there were no eyes whose visual acuity worsened evidently. Factors such as long disease duration, low visual acuity, small deviation of visual acuity and serum C3 contributed to incomplete response. [Conclusion] Infliximab therapy is effective for ocular disease in Behçet's disease, however intervention considering 'windows opportunity' is important.

P2-260

Successful remission by adalimumab in a secondary infliximab - resitant intestinal Behçet's disease case under supportive therapy for myelodysplasia with granulocyte-colony stimulating factor

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Conflict of interest: Yes

[Objectives] Remission induction by adalimumab (ADA) in a secondary infliximab (IFX) - resitant intestinal Behçet's disease (BD) case under supportive therapy for myelodysplasia (MDS) with granulocyte-colony stimulating factor (G-CSF). [Methods] Case: A 33 year-old woman with MDS with trisomy 8 complained of abdominal pain in May 2011, and perforations occurred in her ileum the next month. After an emergency surgery, she was diagnosed with intestinal BD. She began oral cyclosprin A (CYA) and colchicine. The level of CRP became negative. However, it elevated again in 3 months and an endoscopy through her ileal stoma showed ulcers in the ileum. CYA was suspended and IFX was introduced without immunosuppressants. After 6 months, She became resitant to IFX, and ADA was started. At the same time, recurrent febrile neutropenia occurred, so G-CSF was begun. The negative CRP level was maintained without recurrence of sepsis and she had no abdominal pain. An endoscopy in September 2012 showed a great improvement of the ulcers. [Results] Remission induction by ADA in a secondary IFX - resitant intestinal BD case was achieved under supportive therapy for MDS with G-CSF. [Conclusion] This case suggests the remission of intestinal BD can be maintained by ADA even with the use of G-CSF.

P2-261

A case of chronic progressive neuro-Beçhet's disease successfully treated with infliximab

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Conflict of interest: None

A 36 year man, already diagnosed as Beçhet's syndrome because of his uveitis, had been treated by cyclosporin A. However, he sometimes complained of headache with fever at 2005. He became to be angry and complained numbness on his right side of the body at 2011. On January of 2012, he had dementia and difficulty in walking, he had hemiparesis on next month, and his consciousness became drowsy, so he was transported to emergency department. Cerebrospinal fluid (CSF) showed slightly increased cell count and remarkable elevation of interleukin-6 (IL-6) (1270pg/ml). CT scan of the brain showed low density area on his left lentiform nucleus, thalamus, and crus cerebri. He was diagnosed acute type neuro-Beçhet's syndrome (NBD) based on chronic progressive NBD and treated by high dose corticosteroid and MTX. However their effect was limited, and according to a sustained elevation of IL-6 in his CSF, administration of Infliximab was considered. After treatments with MTX (16mg/week) and Infliximab (5mg/kg on 0, 2 w, 6mg/kg on 6,12 w), his IL-6 levels in CSF was decreased transiently and he came soften. Infliximab was effective

for chronic progressive NBD in this case. However, further strategies including increasing the dosage and shortening the interval would be necessary for this case.

P2-262

MTX and Infliximab succeeded for chronic progressive form neuro-Behcet

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Conflict of interest: None

A 47-year-old Japanese female.They had a diagnosis of complete form Behcet by aphthous ulcer, iritis, jeniter, erythema nodosum in 2000. We showed a cognitive function decrease in 2005. However, it was with introduction hospitalization to our department because of cognitive function decrease.We showed on admission, bilateral pyramidal tract lesions, pseudobulbar palsy, the neurologic symptoms of the cerebellum disorder and the cognitive function decrease of HDS-R 20. Atrophy and both sides deep part white matter of both inferior horn showed diffuse ischemic change by the MRI. There was IL-6 209 pg/ml and high level and diagnosed it with chronic progressive form neuro-Behcet. We start treatment in MTX 6 mg/week and Infliximab 5 mg/kg and inhibit a decrease of cerebrospinal fluid IL-6 and exacerbation of HDS-R. The cerebrospinal fluid cell count does not increase, and the chronic progressive form that neurologic manifestation progresses to slowly often shows increase of cerebrospinal fluid IL-6. As for the treatment, it is proved that MTX leaves a decrease of IL-6 and psychoneurotic progress. Chronic progressive form neuro-Behcet was diagnosed from clinical manifestations and cerebrospinal fluid findings, and treatment succeeded.

P2-263

A case of *Mycobacterium tuberculosis* infection with an extremely high neutrophil CD64 expression

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Conflict of interest: None

[Case] 63-year-old man [Chief complaint] Fever [Present history] The patient felt malaise and loss of appetite of a month duration. He was admitted to the hospital with vomiting of blood, fever, weight loss, pancytopenia and inflammatory findings in blood. The CT scans revealed the nodules scattering around the bronchi, liver cirrhosis and splenomegaly. He was initially treated with Minocycline but not responded, with the suspected diagnosis of Chlamydophila pneumonia because of the positive for *C. pneumoniae* IgM of 1.96 C.O.I. Lack of physical findings denied rheumatic diseases, no sign of malignancy was detected. Although the smear of sputum for acid-fast bacterium and tuberculin reaction were negative and inconclusive QFT results, *M. tuberculosis* infection was suspected because the level of neutrophil CD64 was extremely high at the 27215 / cell. He was treated with REP, EB, PZA, INH that resulted in the prompt fever resolution. After 20 days of culture, *M. tuberculosis* was detected from the sputum collected at the admission. [Discussion] Neutrophil CD64 expression is a useful marker for bacterial, fungal and viral infection. The extremely high neutrophil CD64 level may be helpful to identify a case with *Mycobacterium tuberculosis* infection.

P2-265

Serum Procalcitonin Could be a Useful Serologic Marker for the Differential Diagnosis between Acute Gouty Attack and Bacterial Infection

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Conflict of interest: None

[Objectives] We investigated whether procalcitonin levels are elevated in patients with acute gouty attack and the availability of those in differential diagnosis between acute gouty attack and bacterial infection. [Methods] This study included 41 patients with acute gouty attack and 75 age-matched patients with bacterial infection. Clinical and laboratory data were collected at the time serum samples were obtained. Their serum levels of procalcitonin were measured by enzyme-linked fluorescent assay. [Results] Patients with acute gouty attack had significantly lower serum procalcitonin levels than the patients with bacterial infection (0.078 ± 0.066 ng/mL vs 5.401 ± 14.982 ng/mL, $p = 0.003$). However, there were no significant differences between these two groups in serum ESR, CRP levels, and WBC counts. There was a larger number of patients in the acute gouty attack group who had serum procalcitonin levels greater than the reference range than in the bacterial infection group (11/41, 26.8 % vs 63/76, 82.9 %, $p < 0.001$). [Conclusion] Serum procalcitonin levels were lower in the acute gouty attack group than in the bacterial infection group. The serum procalcitonin level could be a useful serologic marker for the differential diagnosis between acute gouty attack and bacterial infection.

P2-266

Study in patients with rheumatic disease (RD) complicated with infection who required hospitalization

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Conflict of interest: None

Background: RD treatment has recently advanced dramatically. Especially for RA, MTX & biologicals can prevent joint destruction, leading to remission. Increased infection rates and possible serious infection should be considered. Methods: In hospitalized patients with RD complicated with infection from 2010 to 2012, we assessed disease states, immunosuppressive therapy and pathogenic microorganisms. Pneumonia accounted for about 60% of the all cases, about 40% of penumonia were bacterial pneumonia and about 30% were atypical pneumonia. Therapy with steroid or MTX was more often performed than that with potent biologicals. The infection rate was relatively high for ETN among biologicals. Results: Therapy with oral steroids or MTX, mainly controlled by patients, was associated with higher infection risk than that with biologicals adequately controlled at the hospital. Similarly, there were relatively more patients using self-injected biologicals among those using biologicals. Very high infectious complication rate among patients using a single steroid was noteworthy. Conclusion: The recent treatment for collagen disease & RD makes prognosis more favorable than the past. However, infectious complications sometimes suddenly become lethal. Precautions are more necessary than ever.

P2-267

Role of IRAK2 in the cellular reactivity of macrophages after stimulating by lipoteichoic acid

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Conflict of interest: None

[Introduction] Septic arthritis due to gram positive cocci is a very harmful destructive joint disease and may occur in the patients with rheumatoid arthritis under immune-suppressive status. Macrophage stimulated by Lipoteichoic acid (LTA) could produce some inflammatory cytokines and enhance the immune reactivity. IRAK2 is one of adaptor molecules maintaining immune response in TLR cascades. But it is not clearly how IRAK2 can work on TLR2 cascades. This study is designed to clarify the function of IRAK2 in LTA-mediated response of macrophages. [Methods] 1) RWA264.7 were stimulated by soluble LTA (sLTA) (100 ng/ml). mRNA levels of TNF-α, IL-1β, TLR2 and IRAK2 was quantified by real-time qPCR. 2) RAW264.7 were transfected Irak2-siRNA and stimulated by sLTA. mRNA expression levels were compared between wild type cells and knockdown cells. [Results] 1) sLTA increased significantly mRNA levels of TNF-α, IL-1β and TLR2 ($p<0.05$). 2) mRNA levels of IRAK2 was significantly suppressed by siRNA. mRNA expression levels of TNF-α and IL-1β were also suppressed, but mRNA of TLR2 was not suppressed. [Discussion] LTA enhance the immune reactivity of macrophages through TLR2 cascade. IRAK2 is essential for expression of inflammatory cytokines, but it has no effect on mRNA expression of TLR2.

P2-268

2 cases of connective tissue disease complicated with cryptococcus meningitis

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Conflict of interest: None

Case 1: 68-year old male was admitted because of progressive unconsciousness and fever. He was diagnosed as Sjogren syndrome and interstitial pneumonia 3 years ago and had been receiving 7.5mg of oral prednisolone. CSF analysis revealed positive test results for Cryptococcus. Antimicrobial drug was successful. Case 2: 72-year old man was transferred due to rapid progressive glomerulonephritis. Diagnosis of microscopic polyangitis was made because of positive result test for MPO-ANCA. Though corticosteroid treatment was administrated, fever of unknown etiology appeared and both blood culture and CSF culture revealed positive test results for Cryptococcus. Though antimicrobial drug was initiated, he lead to death, complicating with cytomegarovirus infection. Cryptococcosis should be considered as possible cause of opportunistic infections in immune suppression therapy.

P2-269

The clinical characteristics of pneumocystis pneumonia (PCP) patients in the biologics era

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Conflict of interest: None

[Objectives] To assess the incidence of PCP in patients with rheumatic disease under treated with strong immunosuppressive drugs (ISDs) in recent years. [Methods] The PCP cases that admitted to our hosipital were analyzed from 2002 to 2011 retrospectively, using the medical record. We compared clinical characteristics of PCP between patients treated after 2007(in the biologics era: BE) and before 2006(pre-BE). [Results] 26 PCP patients were included (female 17), who diagnosed with Vasculitis(8), RA(7), SLE(5), AOSD(2), PM/DM(2), HSP(1), and SSc(1). The mean age was 63±14.3 years (mean±SD).The average dose of PSL at diagnosis of PCP in BE group was significantly lower than in pre-BE group (14.6±11.9 VS 36.8±26.5 mg/day; $p=0.01$). The patients in BE group were received more ISDs and biologics (2 adalimumab, 1 infliximab). Three patients using biologics were treated with concomitant administration of MTX and low-dose PSL. No one received the primary prophylaxis of TMP/SMX. 4 patients were given aerosolized pentamidine. One patient developed PCP after primary prophylaxis with TMP/SMX in BE. [Conclusion] Under the circumstances that strong ISDs are available, the prophylactic use of TMP/SMX against PCP may be administered in patients treated with low dose PSL.

P2-270

***Pneumocystis Pneumonia* in Patients with Rheumatoid Arthritis in the Era of Biologic therapy**

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Conflict of interest: None

[Objectives] We conducted a comparative study on PCP patients before and after the marketing of BIO. [Methods] We studied 15 RA patients with PCP, who received MTX between March 1994 and March 2005 (before BIO), and 13 patients who received MTX or BIO between April 2005 and July 2012 (after BIO). [Results] Three patients received BIO in the after-BIO group. Three patients died in the before-BIO group, but only 1 patient died in the after-BIO group. In the before- and after-BIO groups, the age of onset was 68 years vs. 72 years; used volume of MTX, 6.8 vs. 6.3; used volume of PSL, 6.9 vs. 5.8; βDglucan, 155 vs. 68.1; KL-6, 571 vs. 427; lymphocyte count at the time of onset, 1301 vs. 1002; time required until the use of combined ST, 9 days vs. 5 days; and treatment length, 34 days vs. 22 days. There were many patients with complications such as amyloidosis, existing lung disease, and diabetes in both before- and after-BIO groups. No onset was observed in the patients who received preventive treatment with combined ST. [Conclusion] Combined ST preventive treatment was performed, but PCP was observed in 13 cases. In both before- and after-BIO groups, many patients were old with complications; therefore, it is important to administer the preventive treatment of combined ST thoroughly.

P2-271

The potentially fatal predictor caused by the PCP in the rheumatic disease

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Conflict of interest: None

【Purpose】 Complication of the PCP is one of the fatal predictor in rheumatic disease. We examined the potentially fatal predictor caused by PCP in the rheumatic disease. 【Method】 From 2010 to 2012, 23 patients were complicated with PCP, and divide into two groups, surviving patient (group A; n=18) and deceased patient (group B; n=5). Age, sex, body mass index, past history of the pulmonary disease, smoking history, serum level of albumin, LDH, CRP, IgG, IgA, and β-D-glucan, arterial blood gas level of pH, P/F ratio, PCO2, HCO3 were examined. 【Results】 There were significant differences about the following; Age: 72.8±10.5 (group A), 83.2±9.2 (group B) (years old) (p=0.029) Sex: male/female=2/16, male/female=3/2 (p=0.048) Alb: 2.9±0.5, 2.5±0.2 (g/dl) (p=0.008) CRP: 8.3±6.9, 19.3±10.0 (mg/dl) (p=0.01) IgA : 282.8±103.9, 178.8±61.1 (mg/dl) (p=0.024) P/F ratio: 267.9±97.0, 120.1±88.6 (p=0.014) Otherwise, there were no significant difference in other factors. 【Conclusion】 Male, elderly people, high level of CRP, low level of serum albumin, IgA and P/F ratio were potentially fatal predictor caused by PCP in the rheumatic disease.

P2-272

Pentamidine-induced hypoglycemia in patients with Pneumocystis pneumonia: Two case reports

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Conflict of interest: None

【Case1】A-75-year-old female who had a history of rheumatoid arthritis (RA) treated with adalimumab (ADA) and methotrexate (MTX) was admitted to our hospital complaining of fever. We diagnosed with Pneumosystis pneumonia (PCP). The patient was started treatment with trimethoprim-sulphamethoxazole (TMP-SMX). But we changed the medication fromTMP-SMX to pentamidine for vomiting. 7 days later hypoglycemia occurred after changed to pentamidine. We were considered to be drug-induced hypoglecemia and stopped pentamidine. The hypoglycemia persisted and the patient required glucose infusion for a week. 【Case2】A-67-year-old female who had a history of RA treated with ADA and MTX was admitted to our hospital complaining of fever. We diagnosed with PCP. The patient was started treatment with TMP-SMX. But we changed the medication from TMP-SMX to pentamidine for vomiting. 5 days later hypoglycemia occurred after changed to pentamidine. We were considered to be drug-induced hypoglecemia and stopped pentamidine. The hypoglycemia persisted and the patient required glucose infusion for 2 days.【discussion】Threre are few reports of pentamidine-induced hypoglycemia. We report two rare cases in addition to the literature.

P2-273

Analysis of the polymyalgia rheumatica(PMR) and RS3PE syndrome in our hospital

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Conflict of interest: None

[Objective] We examined clinical characteristics and usefulness such as MMP-3, or anti-CCP antibody in polymyalgia rheumatica (PMR) and RS3PE syndrome. [Methods] It was aimed at 32 patients, who diagnosed as PMR or RS3PE syndrome at the first medical examination or finally diagnosed in our hospital. [Results] Three patients diagnosed as RS3PE at the first time shifted to all rheumatoid arthritis (RA). Among patient for it to have been considered as PMR at the first time, four have been diagnosed as RA finally (one have a merger of fake gout contains), and One patient for it to have been considered as RA doubt at the first time to have been diagnosed as PMR finally. Although CRP was going up in all patients, it was a reference interval in five in a final-diagnosis PMR group about MMP-3. The anti-CCP antibody was going up by four in finally RA group, no case rise in a PMR group. There were eight cases succeeded PSL withdrawal in which nine cases which Tried PSL secession among 25 cases diagnosis finally PMR. While of withdrawal PSL success cases MMP-3 was 56.6 (32-78) at the time, the case of exacerbation were a high price (155.7 ng/ml). [Conclusions] MMP-3 may be useful as a predictive factor of a success of the PSL withdrawal in PMR.

P2-274

Small intestine bacterial overgrowth as the cause of fever of unknown origin (FUO) in a woman with positive anticentromere antibody test

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Conflict of interest: None

A 47-year-old woman, who had been healthy, complained of constipation and postprandial abdominal. Laxatives were ineffective. After one month, fever of 39 degrees Celsius emerged and persisted. She couldn't eat and lost weight by 14 kg. She got gastroscopy and colonoscopy exams in another hospital, but no obstruction was found. Laboratory studies showed positive anticentromere antibody (ACA). She was admitted to our hospital. Physical examinations showed tenderness in the right upper quadrant, erythemas on the extremities and swollen cervical lymph nodes. Blood cultures, biopsies of the cervical lymph node, skin and liver, bone marrow aspiration, capsule enteroscopy, echocardiography, CT and ^{18}F-FDG PET didn't reveal the cause yielded nothing about the cause. Neither of low gluten diet, NSAIDs, colchicine and prednisolone (1mg/kg=50mg) was effective. Positive ACA and her characteristic clinical history made us suspect small intestine bacterial overgrowth (SIBO) with systemic sclerosis sine scleroderma. After oral cephalexin and metronidazole were initiated, her body temperature became lower than 38 degrees Celsius and the abdominal symptoms were gradually improved. A month later, nail fold bleeding emerged. This case suggested that SIBO could be a cause of FUO.

P2-275

A review to evaluate the effectiveness of switching to esomeprazole (EPZ) in collagen disease patients taking NSAID who have persistent gastrointestinal symptoms following treatment with PPI

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Conflict of interest: None

<OBJECTIVE> PPI has been used for the prevention of peptic ulcer caused by NSAID in RA patients. We previously reported

that gastrointestinal symptoms persisted despite the use of PPI in 152 collagen disease patients using GOS scale (GOS) and GSRS questionnaire (GSRS). Especially, QOL decreased in the patients taking ≥10 mg/day of PSL. EPZ is expected to show more efficacy than other PPIs. To investigate the efficacy of EPZ, we examined short switching study from another PPI to EPZ in patients taking NSAID and persisting gastrointestinal symptoms. **<METHOD>** EPZ was given to twenty-nine outpatients for 2 weeks from other PPIs. We examined the changes of gastrointestinal symptoms with GOS and GSRS questionnaire before and after treatment with EPZ. **<RESULT>** Six of the 29 patients (20.7%) improved their symptoms based on GOS questionnaire ($p<0.001$), especially stomach heavy feeling significantly improved ($p=0.018$). QOL evaluation based on GSRS showed that the mean total score significantly improved from 2.36±0.71 to 2.05±0.58 ($p=0.011$). Each item except diarrhea and constipation significantly improved respectively. **<CONCLUSION>** Our results show that switching to EPZ 20mg improved some upper gastrointestinal symptoms. EPZ 20mg is expected to have better preventive effect than other PPIs.

P2-276

A case report of EBV -associated hemophagocytic syndrome in a Rheumatoid Arthritis patient treated with a small dose MTX

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Conflict of interest: None

A 54-year-old woman with Rheumatoid Arthritis treated with MTX 2 mg/week, suffered from malaise, diarrhea, and oral erosions two weeks before visiting emergency room in our hospital. She had fever (over 38°C), and laboratory data showed severe pancytopenia(WBC 240/μl, Hb 4.7g/dl, Plt 5000/μl) and abdominal CT suggested neutropenic enterocolitis. Hemophagocytosis were obsereved in her bone marrow, and the level of Epstein-Barr virus (EBV) DNA in peripheral blood mononuclear cells elevationed, We diagnosed EBV-associated hemophagocytic syndrome. Treated with prednisolone, cyclophosphamide and etoposide, she was recovered gradually and went back home 125 days after her hospitalization. Increasing patients treated with immunosuppressive therapy, many cases of reactivation of virus which establishes latency after primary infection like Hepatitis B virus are reported. It was surprising and interesting that the patient who had not recieved intensive immunosuppression suffered from serious disorder caused by reactivation of EBV in our case. We review some literatures and discuss EBV infection in immunocompetent patients and how to treat them.

P2-277

A profile of patients with rheumatoid arthritis who required hospitalization for infections

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Conflict of interest: None

[Objectives] To clarify the property of patients with rheumatoid arthritis (RA) who required hospitalization for infections. [Methods] We reviewed the records of the RA patients who admitted for infections in our hospital from April 2011 to March 2012. Clinical data were collected from patient's medical records. We examined the Charlson Comorbidity Index (CCI). [Results] We studied 55 patients (43 females and 12 males), with 77 episodes. They had mean age of 71.4 years and a mean duration of RA symptoms was 17.0 years. 23 patients(41.8%) had Steinbrocker classification class III or IV. RA treatment was corticosteroids (n=50, 90.9%), MTX (n=17, 30.9%), and Anti-Tumor Necrosis Factor-α agents (n=9,16.4%). Among 77 episodes of infections, the frequently occurring events were respiratory infections (n=42), urinary tract infection (n=13) and skin/soft tissue infections (n=4). 30 patients (54.5%) had interstitial pneumonia, and 12 patients (21.8%) had diabetes mellitus. The mean CCI scores were 4.5. 30 (54.5%) cases of patients had experienced recurrent infections during followup. [Conclusion] RA patients with admission for infections had long disease duration, steroid administration and high CCI scores. High frequency of recurrent infections in RA patients was remarkable.

P2-278

Assessment of two cases of Sweet's disease-associated arthritis with ultrasonography

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Conflict of interest: None

Case 1: A 48-year-old male patient had had recurrent fever, edematous erythemas, pustules, and arthralgias for 10 months. He admitted to our hospital because of severe ankle pain. On examination, he had arthritis with swelling, redness and feverish, in many joints such as fingers, hands, elbows and ankles. Furthermore, he revealed several oral ulcers and a genital ulcer. We then also suspected he might have Behcet's disease, but the result of skin biopsy was typical for Sweet's disease. Case 2: A 77-year-old male patient had had circular erythemas since 1 year and 5 months ago. The result of skin biopsy was compatible for Sweet's disease. Then he was treated by oral corticosteroid and the symptoms disappeared soon. As decreasing corticosteroid, he tended to complain of joint pain with joint swelling, redness, and feverish. We focused on the joint findings of the two Sweet's disease patients. Joint ultrasound proved that they didn't have synovitis or intraarthritis, but did have apparent subcutaneal inflammation on the joints. We will discuss the details with bibliographical considerations.

P2-279

A case of Erdheim-Chester disease that was presented with systemic pain and fever of unknown origin and that was treated with interferon-α effectively

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Conflict of interest: None

A 75-year-old woman had bone pain of both legs in April 2011. Her pain exacerbated to systemic pain with fever above 38°C in July 2011. She was given diagnosis of polymyalgia rheumatica and was prescribed prednisolone (PSL) 5mg/day. But she did not improve, so she was referred to our hospital in August 2011. Her physical findings were remittent fever and pain caused by pressure of both upper arms and both femurs. The C-reactive protein level was 11mg/dl. Technetium-99 bone scintigraphy showed involvement of superior and inferior limbs. Bone images of MRI showed

infiltration of inferior limbs. Bone marrow aspiration showed dry tap. Left tibia biopsy gave fibrosis and foam cell, consequently we diagnosed as she was having Erdheim-Chester disease (ECD). PSL treatment was not effective. We treated her with interferon-α(IFN-α) and it improved her symptoms rapidly. ECD is a rare non-Langerhans cell histiocytosis. ECD is a systemic and heterogeneous disease mainly involving the bones diffusely and symmetrically. Immunosuppressive drugs such as PSL, cyclophosphamide have poorly effect on ECD. IFN-α is the most used for ECD and improves survival. There is few case report of ECD in Japan, but ECD is cause of systemic pain and fever of unknown origin.

P2-280

Clinical features of haemophagocytic syndrome in our hospital

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Conflict of interest: None

[Objectives] We investigated 9 cases with haemophagocytic syndrome (HPS) in our hospital from 2007 to 2012. [Cases] The male:female ratio was 1:8.The average age of diagnosis was 54.2±20.6 years.9 patients included 1 with SLE,1 with AOSD,1 with RA,3 with Malignant lymphoma (ML)/1 with suspected ML,(1 patient was diagnosed as dermatomyositis with ML), 1 with PN associated with candidemia,1 with hereditary spherocytosis associated with parvovirus B19 infection.The average period from onset to diagnosis was 23.8±20.7 days.All patients showed fever(average 38.5±0.9°C) and had progressive cytopenia at least two cell lineages.Each of the average laboratory findings was followed;AST/ALT 203.4±198.7/107.8±99.5 IU/l,LDH 987.2± 632.9 IU/l,ferritin 16392.2±30330.7 ng/ml.The average IL-2R was 20777U/ml in patients with ML,1379 U/ml in patients with not. High IL-2R values were more frequent in ML than not ML.6 cases had hepatomegaly and splenomegaly.7 patients were treated with corticosteroid,additional cyclosporine in 3,plasmapheresis in 2. [Prognosis] Five patients were dead,four out of five patients were included 3 with ML and 1 with suspected ML.one with AOSD was dead by sepsis. [Conclusion] The prognosis was poorer HPS with ML than not ML.We thouht that ML was important as a cause of HPS.

P2-281

Successful tocilizumab treatment in a patient with adult-onset Still's disease complicated by interstitial pneumonitis

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Conflict of interest: None

We report successful tocilizumab (TCZ) use in a patient with adult-onset Still's disease (AOSD) complicated by interstitial pneumonitis (IP). Treatments with prednisolone (PSL), various types of immunosuppressants including cyclosporine and cyclophosphamide, and infliximab were unsuccessful. TCZ was then started. By TCZ treatment, arthritis, fever and IP improved. Moreover, Normalization of inflammatory markers and ferritin level were confirmed. KL-6 also decreased from 7238 U/ml to 500 U/ml. TCZ is an excellent treatment for refractory AOSD complicated with IP. We demonstrated and considered this case with some literature.

P2-282

The education of self evaluation of the joints in patients with rheumatoid arthritis by nurses

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Conflict of interest: None

[Background] The activity of rheumatoid arthritis is evaluated by the composite measurement including the number of swollen joints, tender joints and the patient global assessments using the VAS. The aim of this study is to examine the outcome of the patient education by nurses for the evaluation of the affected joints. [Methods] The patients were asked to fill in the questionnaire that included the self assessment of the swollen and tender joints in the body figure. The rheumatologist also assessed the joints and the differences between the patients and doctors were evaluated. In 46 cases, the records were collected form the patients who were educated by the nurses how to evaluate the swelling and tenderness of the joints. Those were compared with the 38 cases without the education by nurses. [Results] The number of the swollen joints matched better in patients with the education by nurses ($P<0.01$). There were no statistical difference in the assessment of the number of the tender joints between the presence or absence of the education by nurses. [Conclusion] The nurse's education improved the self assessment of the swollen joints of patients which can lead to the better practice of T2T for rheumatoid arthritis.

P2-283

Adoption of shortened infliximab (IFX) infusion time and comparison of the incidence of infusion reactions (IRs)

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Conflict of interest: None

[Objectives] IFX has been used in our clinic since 2007, but the 2-hr infusion and lengthy monitoring was a burden on both patients and nurses. Changing infusion time from 2 hrs to a minimum of 36 mins, we analyzed the association between the shortened infusions and the patients' IRs. [Methods] Primary infusion was given over 3 hrs, followed by 2-hr infusions (Group 1). If there were no IRs in the first 3 infusions, they were shortened to 1 hr.(Group 2). Patients without IRs the following 3 times were shortened once again to 36-min infusions (Group 3). All patients received antihistamine prophylaxis, and were monitored once every 15 mins. [Results] 27 of 34 patients received shortened infusions. A total of 163, 223, and 8 infusions were given in Groups 1, 2, and 3. The rate of IRs in each group were 3.1%, 1.0%, and 0.0%. Mean methotrexate (MTX) dose in each group were 4.4mg, 5.7mg, and 6.3mg, showing an inverse relationship with IR incidence. [Conclusion] Infusions shortened up to 36 mins proved to be an acceptable option, since IRs did not increase in the patients in Group 3. However, the dose of MTX may be related to the incidence of IRs in IFX infused patients. Shortened IFX infusions are feasible with the nurses' proper drug guidance and patient monitoring.

P2-284

The investigation of efficacy on intervention by nurses when patients with rheumatoid arthritis choose their biologics for the first time

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Conflict of interest: None

[Objectives] Patients with rheumatoid arthritis have a variety of anxiety, and they are at a loss which biologic to choose the best. We evaluated the efficacy that nurses provided the drug information and gave some advices with the aid of a drug comparative chart when the patients choose their biologics. [Method] We conducted the questionnaire study. The questionnaires had been done at pre and post interview by nurses. The questionnaire was done at 3 months later in both groups. We used Decisional Conflict Scale (DCS) to evaluate patients' conflicts. [Result] 10 patients for intervention group and 20 for control group were collected. The "knowledge" score on DCS was getting lower after our interview, but was rising after 3 months later in the intervention group. And the score after 3 months later is same in intervention group and control group. The "satisfaction" score on DCS tended to be grater in patients who made out that "patients" decided their drugs than that "doctors" made choice of their biologics. [Conclusion] We believe that continuous intervention reduce patients' conflicts with biologic treatment. The cognition that patients decided the biologics for themselves makes their satisfaction. We need to modify the way of interview in order to encourage self-determination.

P2-285

Approach for improvement in the knowledge of nurses on biological agents

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Conflict of interest: None

[Background] In the 56th JCR, we reported that nearly half of the patients remained anxious,despite sufficient effect of biologic therapy. [Objectives] In order to understand how nurses can meet patients' concern in the current situation, we used a questionnaire and held a study meeting. [Subjects] Subjects were 76 nurses. [Methods] The following methods were used: (I) survey on current patient guidance and information on BIO; (II) holding a study meeting 3 times; and (III) creating a pamphlet. [Results] The survey revealed that among 76 nurses, 64% felt uneasy because of knowledge deficiency. The survey was performed using 26 nurses after completing the study meeting. In terms of feelings that a nurse can explain and/or think she can explain a little to patients, the percentage changed as follows: drug administration (63%→ 84%), inquiry of patients (48%→ 86%), explaining the disease condition (before 27%→after 81%), examination (35%→ 61%), cost (19%→58%), and pregnancy (23%→50%). [Conclusion](1) Knowledge and understanding increased by holding the study meeting. Because the level of understanding on cost, examination, and pregnancy was low, there is a need for creating a pamphlet to supplement the knowledge of the nurses. (2) Creating the pamphlet is a useful method.

P2-286

The role of nurse care for patients with rheumatoid arthritis in center of rheumatology Social Insurance Chukyo Hospital

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Conflict of interest: None

[Objectives] In the treatment of patients with RA, not only drug therapy and surgery, the need for intervention by the care and rehabilitation therapy is the current focus. We opened center of rheumatology consisting of member physicians, nurses, pharmacists, physical and occupational therapists. Members of the nurse is five, including rheumatism care nurse and head. In this study, we examined the role of nurses involved outpatient care. [Methods] In patients with RA who visited our center, rheumatism care nurse was measured DAS28(CRP). We also conducted interviews with HAQ. From data analysis of HAQ, we extracted the difficulties of daily life of them. [Results] DAS was evaluated 135 cases, and the average value was 3.295. HAQ was evaluated 152 cases, and the average value was 0.919. Gradual improvement trend was observed in both the DAS and HAQ. [Conclusion] By measuring the DAS, we were able to actually feel the pain, swelling the joints, to empathize with the suffering. As we conducted interviews method when measuring the HAQ, we could communicate with the patient, and know the background of their daily life more specifically. We could provide individual guidance based on them. We believe by measuring clinical indicators in plans and can now be shared treatment goals with them.

P2-287

Treatment experiences narrated by rheumatoid arthritis patients receiving biological agents

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Conflict of interest: None

[Aim] This study aimed to clarify subjective treatment experiences narrated by rheumatoid arthritis patients receiving biological agents. [Methods] Participants were 5 female patients receiving biological agents through outpatient treatment at the Saga Medical School Hospital. Interviews were conducted on "opinions about condition and treatment" and "lifestyle"; recorded data were analyzed using qualitative inductive methods. [Results] The three phases were evident in the narratives of the 5 participants. In terms of "life before introduction", issues such as anxiety about side-effects of medication emerged, along with uncertainty about the future. "Indecision and decision regarding introduction" included costs versus benefits of biological agents and financial burden, as well as anxiety about side-effects. Reasons for deciding on introduction were deterioration in ADL, accounts of experiences of other people who had undergone the same treatment, and family support. "Life after introduction" revealed issues such as improvement in ADL, as well as tiredness and reduced immunity. [Conclusion] The present findings suggest the importance of medical professionals' full understanding of the psychological and financial situation of patients in order to support decision-making regarding treatment.

P2-288

Analysis of the questionaire with rheumatoid arthritis

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Conflict of interest: None

Objective:To do positive RA nursing intervention by treatment based on T2T, we understand RA pts social, physical and mental

backgrands so improve consideration as the RA caring specialty nurse through this research. 0bject and method: We executed the research for the outpatient care RA 106person in seven participation facilities. The questionnaire survey was executed to the pts of biologics agent (Bgroup 59people) and conventional DMARDs (Dgroup 47people) Result :Average DAS28-CRP - HAQ-DI B and D group was (2.8,0.9) and at the time of the investigation, Dgroup was (2.8,0.9) and (2.3,0,4) respectively.HAQ was lower in the Dgroup.Having understood from the social background is as follows. (1)There are a lot of workers in D group and pensioners in Bgroup. (2)The physical disability certificate class of first and second in Bgroup are much more than in B. (3)A lot of nursing care requirements was in Bgroup.62% of the D group's copayment and deductible was 10,000 yen /month. Though there was roughly no difference of the body and mental background. there were only intentionally a lot of answers with "RA is an obstacle of usual work" in B group. Conclusion:In the future, RA caring specialty nurse will think that they should teach to Pts for improvements of consideration to the pts treatment.

P2-289

Examination of guidance for the patients with rheumatoid arthritis (RA) by rheumatology floor nurses in induction of treatment with biologics

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Conflict of interest: None

[Objectives] In the treatment of RA with biologics, patient's self-care, prevention of infection are very important. Therefore, nurses have to give them guidance. We clarified the actual conditions of initial guidance by rheumatology floor nurses (RFN) and examined the subjects. [Methods] 23 RFN (average years as RFN; 2.6±1.4) were surveyed on the guidance of procedure, daily life, infection control and cooperation with outpatient department. [Results] The reason why they find the difficulty at the time of guidance was classified into 3 groups as follows, lack of knowledge, lack of time and patient's conditions. 90% of guidance for oral care, hand-wash and wearing-masks had been done, however, as for prevention of both herpes zoster and pneumonia, guidance varied among different individuals. 90% of RFN felt the necessity of cooperation with outpatient department. [Conclusion] We need to build the common guideline in the hospital. Internship for nurses who belong to different working systems should be held. Well-developed guidance is thought to be able to improve self-care ability of patients and expected to improve the safety and efficacy of medical treatment. Besides, the construction of collaborative tools in the hospital which can support without interruption should be required.

P2-290

Establishment of the KURAMA (Kyoto University Rheumatoid Arthritis Management Alliance) cohort that can be used for both clinical investigation and daily practice

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Conflict of interest: None

[Objectives] To establish a system which extracts clinical data of RA patients to be used for both clinical investigation and daily practice. [Methods] All patients admitted to our hospital with rheumatic diseases were included in the KURAMA (Kyoto University Rheumatoid Arthritis Management Alliance) cohort using paired medical interview sheets filled by both patients and doctors. The clinical data was automatically extracted from the sheets by Optical Character Recognition system. Medications and laboratory data were collected by the electrical medical record system. More detailed data were also obtained through distributing RA questionnaire sheets (10 pages 19 items) once a year. [Results] From May 2011 to August 2012, 5410 medical interview sheets were used and 970 patients including 681 RA patients were registered in the cohort. RA questionnaire sheets were distributed to 402 RA patients and recovered from 381 patients (95.5%). We were able to utilize the collected data for clinical investigations, and also for informing individual RA patients with reports showing the changes in disease activities. [Conclusion] In KURAMA cohort, we could collect clinical data from daily practice with relatively low labor costs.

P2-291

Establishment of the RA network in G prefecture;GRN

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Conflict of interest: None

[Purpose] The evidence creation for performing better treatment for rheumatoid arthritis (RA) is needed. Since we established the multi-institution database with five institutions, to which the specialist who performs RA treatment in G prefecture belongs. [Method] The name of this database was made as GRN, and it aimed at building the medical-examination database within /around G prefecture. Participation of 1 university hospital, 3 orthopedics hospital, and 1 RA clinic was planned, then the approval of the Ethics Committee was received [Result] Establishment of GRN was performed by participation of five institutions of a schedule. As a collection method of data, after anonymity of patient information, each institution scanned with the scanner the view tables (a medical examination view, laboratory data, HAQ, etc.), and sent to a GRN secretariat via cloud service (online storage). Data transmission used and carried out the scanner and PC only for a database with each institution. Moreover, collected data was inputted into form which the GRN secretariat created using database management software. [Consideration] This database is used to collect the clinical data of multiple institutions, therefore the collected clinical data would be expected to become useful.

P2-292

Report on Regional Medical Collaboration in the Treatment of Rheumatoid Arthritis

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Conflict of interest: None

【Objectives / Methods】 Changes in regimens like Bio intro-

duction & evaluation techniques of diagnostic imaging such as MRI & ultrasonography enabled remarkable advance in rheumatoid arthritis (RA) treatment; however, inter-district variances are occasionally seen. In order to offer standard treatment (ST) to RA patients (pts) w/out causing excessive burdens on the limited no. of RA specializing physicians, promotion of close linkage between specialists & home doctors is essential. A regional linkage aiming joint care of rheumatism pts including Bio-use cases is presented. **【Results】** About 3 years have passed since regional RA network was launched. Over 20 facilities are now members. Case evaluation meetings have been held about 40 times. Although pts referred to core hospital via this network is increasing, a system to promote ST across the community w/out excessive loads on a particular facility is being established. **【Conclusion】** To reduce inter-regional treatment variances & provide ST w/ little stress also to pts living distant from RA expertise care facilities & elderly pts difficult to make frequent visits, medical collaboration between home doctor & expertise facilities will become further more important into the future.

P2-293

Challenge of regional medical cooperation between clinics and hospitals in north area of Osaka city on rheumatic diseases

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Conflict of interest: None

[Objectives] As performed in regional critical pass on various diseases, medical cooperation; hospitals and/or clinics cooperation, has become a trend in regional medicine. [Methods] We have formed a meeting of medical cooperation on rheumatic disease in northeastern area of Osaka city, begun working. Constituent members were 2 hospitals and 4 clinics. First meeting was to discuss patients with rheumatoid arthritis (RA) who had been referred from clinic for biotic treatment. Second meeting was to discuss patients with RA who suffered from MTX peumonitis, participated in respiratologost. [Results] Through these face to face meeting, we were able to understand from the standpoint of each other, and to interact well. Patients are relieved because they knew that he will be referred to a nearby hospital even if complications occurred. Problems to be resolved were as follows: Members are not all rheumatologists. So there is a difference between the doctors about understanding of the rheumatic disease and of the patient's rheumatic condition. [Conclusion] Patients with RA, their mobility is reduced in flare of disease activity, progression of disease. Healthcare organizations work together in each region, is working to become a town continued rheumatoid patients live with confidence.

P2-294

Analysis of improvement effect by Health Assessment Questionnaire (HAQ) input / totaling system in rheumatoid arthritis (RA) with tablet devices

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Conflict of interest: None

[Objectives] HAQ is self-report functional status measures of daily activities in RA patients. However, it is difficult to total HAQ because there are so many items. In order to reduce the burden of patients and medical staff, we developed the system in which patients input HAQ directly into tablet device, and data can be easily totaled statistically using the automatic sum function. [Method] RA patients (n = 25) and healthy controls (n = 20) inputted HAQ by this system. We measured the input time. HAQ was transmitted to electronic chart and integrated into medication history and blood test data. The individual summary was created on that very day. [Result] It took 174±98 seconds for RA patients to input. Meanwhile, healthy controls spend 96±51 seconds significantly faster than RA patients. The fast group in RA possessed tablet device. On the other hand, the slow group in RA scarcely ever used it. The clinical score, with which we have been doing only clinical research until now, was able to be used also for outpatient care. [Conclusion] This system enables us to immediately inform outpatient medical information in time series including HAQ, CRP, MMP3, etc and solves time-consuming problem for medical staff. It is not only clinically useful, but also it reduce the medical expense.

P2-295

Examination of making requirement for Patient Guidance Tool

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Conflict of interest: None

Subjective The patient guidance by an original Patient Handbook is examined as one of the guidance tools of the rheumatic. An unnecessary description item felt the inconvenience in use a lot in the Patient Hand book of the manufacturer offer that had been used up to now. This time, the Handbook was examined and a necessary requirement including convenience use from each standpoint of "Side of the medical treatment was offered" and "Side of the medical treatment was received" was extracted and "Permanent Tool" was made was examined. **Result** Necessary requirement for "Permanent Tool" It is useful for the grasp of a long series of progress, and can offer high-quality treatment. Doctor - Nurse - Patient shares information, and the nurse positively bearing the patient care becomes possible.Handbook with convenience It is necessary to consider individual information. It is possible continuance use (and record), about ten years per one. **Conclusion** The patient guidance by not only the doctor but also the nurse is important in a complicated and troublesome outpatient diagnosis and treatment. A new Handbook is possible to become an important tool when the side effect when the medicine to an individual patient, and guide the transition of the disease activity.

P2-296

Current state of medical treatment for RA in our department using the iPad

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Conflict of interest: None

[Objectives] Although it seems that it is very important to evaluate RA patient in recent years, evaluating HAQ and Pt-VAS in a consultation room requires time very much. We introduced the rheumatoid arthritis oral consultation system iRIS by iPad simulta-

neously with an electronic medical recoding system this time. [Methods] Preparing iPad for patients, and iPad for doctors, before a medical examination,a patient inputs patient ID,time of morning stiffness,HAQand Pt-VAS. If a doctor inputs blood collecting results, such as joint evaluation of the patient concerned, CRP, ESR, and MMP3, in the case of a medical examination, DAS28 etc. will be calculated automatically. It connects and made it two sets of iPad(s) synchronize not by WiFi but by Bluetooth in consideration of safeties. [Results] It compared, when Pt-VAS was evaluated at the time of a medical examination, and evaluation time has been shortened considerably.Furthermore, data required of clinical study can extract as excel data easily. In the questionnaire before introduction, 90 percent or more of the patient showed interest to the system, and it seemed useful as a tool for patient evaluation after introduction.

P3-001

Enhancement of CRACM1 Expression in Functionally Aberrant Naive CD4+ T cells in Active Rheumatoid Arthritis

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Conflict of interest: None

[Objectives] A precise molecular explanation for the enhanced Ca^{2+} influx in T cells has not yet been established. To explore the molecular basis of the irregular Ca^{2+} influx in RA T cells, we performed a study to characterise the expression levels and functional status of Ca^{2+}release-activated Ca^{2+} (CRAC) channels in peripheral naive CD4+ T cells from RA patients. [Methods] To determine whether CRACM1 channels contribute to the abnormal behavior of T cells in RA, CRACM1 expression was evaluated by western blotting and immunofluorescence analysis. We also measured Ca^{2+}influx and CRAC currents in naive CD4+ T cells, as well as cytokine release by activated naive CD4+ T cells, for each of the three groups. [Results]1.Intracellular iCa^{2+}nflux is up-regulated in naive CD4+ T cells from RA patients and is associated with RA disease activity. 2.CRACM1 channel function is increased in T cells from active RA patients. 3.CRACM1 expression in naive CD4+ T cells is higher in active RA patients than in OA patients and healthy donors. [Conclusion] Functionally aberrant naive CD4+ T cells from activeRA patients exhibited an increase in Ca^{2+} influx, as well as up-regulated CRACM1 protein expression and function, indicating that CRACM1 might represent a new molecular target for novel RA therapies.

P3-002

A common mechanism of gout/hyperuricemia with decreased urate excretion from intestine

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Conflict of interest: None

[Objectives] ABCG2 is a high-capacity urate exporter and the combination of its dysfunctional variants raises risk of gout/hyperuricemia. Hyperuricemia has been pathophysiologically classified into urate "overproduction type," "underexcretion type" and "combined type." We then investigated the association between ABCG2 variants and urate excretion. [Methods] We genotyped ABCG2 in 644 Japanese male patients of hyperuricemia with their urinary urate excretion (UUE). Urate excretion is also examined with Abcg2-knockout (KO) mice. [Results] Paradoxically, ABCG2 export dysfunction significantly increases UUE. ABCG2 dysfunction is found in 75.6% of patients and raises the risk of "overproduction" hyperuricemia (risk ratio=2.3 at the maximum). KO mice show increased serum uric acid (SUA) levels and renal urate excretion, and decreased intestinal urate excretion. [Conclusion] These findings indicate a novel common mechanism of hyperuricemia that the decrease in extra-renal urate excretion via dysfunctional ABCG2 increased SUA and UUE. Here we propose that current "overproduction type" be renamed "renal overload type" which consists of two subtypes, "extra-renal urate underexcretion" and genuine "urate overproduction," providing a new concept valuable for treatment of hyperuricemia and gout.

P3-003

Expression of MUC-1, MUC-5B, Tn and sialyl Tn antigens in labial salivary gland of patients with Sjogren's syndrome

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Conflict of interest: None

[Objectives] The purpose of this study is to investigate the existence and bioactivity of tumor-associated carbohydrate antigens in Sjogren's syndrome (SS). **[Methods]** Eleven patients (females) with SS. We examined the expression of MUC-1, Tn and sialyl Tn antigens in salivary glands tissues by immunohistochemistry. In addition, saliva was subjected to gel filtration on Sepharose 6B and collected the fractions including mucins. The IL-6, tumor necrosis factor (TNF)-α production by mucin in human peripheral blood monocytes (PBMC) were also investigated using ELISA. **[Results]** We found that MUC-1, Tn and sialyl Tn antigens were strongly expressed in mucous acinar cells and infiltrating mononuclear cells on the labial salivary gland. Saliva fractions can stimulate the production of IL-6, TNF-α in human PBMC. **[Conclusion]** We revealed that MUC-1 and typical malignancy-associated mucins expressed in SS salivary glands. We found an aberrantly glycosylated mucin from saliva in patients with SS, which can produce cytokines in human PBMC. This finding suggests that the mucins exhibiting with abnormal glycosylation may be in part responsible for salivary glands inflammation, leading to the salivary glands destruction in the pathogenesis of SS.

P3-004

The role of TRIM21 as a suppressor for type I interferon induction is abrogated in systemic lupus erythematosus

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Conflict of interest: None

[Objectives] The increased expression of type I interferons (IFNs) and their inducible genes, called "IFN signature", has been suggested to have important roles in the pathogenesis of systemic

lupus erythematosus (SLE). Recently, TRIM21, one of the type I IFN-inducible genes, was shown to suppress the type I IFN expression via ubiquitylation of IRF family. In this study, we investigated the role of TRIM21 in the IFN signature. [Methods] We collected peripheral blood mononuclear cells (PBMCs) from 12 healthy controls (HCs) and 12 SLE patients. We analyzed the mRNA expression levels of genes including TRIM21, type I IFNs and their inducible genes by quantitative RT-PCR. [Results] The mRNA of TRIM21 and other type I IFN-inducible genes were increased in PBMCs from SLE patients as compared to HCs. There was positive correlations between the mRNA expression levels of TRIM21 and other type I IFN-inducible genes. Although the mRNA levels of type I IFNs showed negative correlations with TRIM21 mRNA level in HCs, these correlations were not observed in the patients with SLE. [Conclusion] These results suggest that TRIM21 functions as a suppressor for type I IFN induction in HCs, but not in SLE patients. This abrogation of the regulation system may contribute to the pathogenesis of SLE.

P3-005

Activated mast cells and their cellular stress-network involve in the early onset of rheumatoid arthritis

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Conflict of interest: None

[Objectives] D1CC mouse is a novel rheumatoid arthritis mouse model, in which a class II transactivator, master switch for MHC class II gene expression was introduced under driven type II collagen (Col2) promoter and enhancer. Inflammatory arthritis was induced by injection of lower dose of Col2 (0.05mg/mouse/injection), because D1CC mice had high susceptibility to arthritogenic stimuli (PNAS, 103:14465, 2006). Chronic and slow disease progression was observed in D1CC mouse. This feature was advantage to analyze the early onset of inflammatory arthritis. [Methods] Histological and RNA in the inflammatory lesions analyses were performed. [Results] It was revealed that synovial cells and mast cells were activated at this stage. In the blood vessels, many neutrophils as major inflammatory cells were observed simultaneously, but almost no infiltrated neutrophils at the joints. [Conclusion] A large number of studies suggested that mast cells involved in arthropathy, however it was not clear when and what kinds of crosstalk they did between mast cells and others such synovial cells and inflammatory cells Data suggested activated mast cells impact joint inflammation of rheumatoid arthritis in the early onset of rheumatoid arthritis.

P3-006

The expression of recombination-activating gene (RAG) in the patients with SLE; the generation of autoantibody-inducing $CD4^+$ T cell

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Conflict of interest: None

[Objectives] We found that SLE was induced by repeatedly immunizing the mice with any exogenous antigen and have then proposed a novel 'self-organized criticality theory' that explains the cause of SLE. The autoreactive lymphocytes, which we name autoantibody-inducing $CD4^+$ T (*ai*$CD4^+$ T) cells are newly generated *via de novo* T cell receptor (TCR) revision at peripheral lymphoid organs. They not only stimulated B cells to generate autoantibodies but also helped final differentiation of $CD8^+$ T cell into cytotoxic T lymphocyte (CTL) to induce lupus tissue injuries. Here we examine the expression of recombination-activating gene (RAG) in relation to the generation of *ai*$CD4^+$ T cell in the patients with SLE. **[Methods]** Lymphocyte was collected from the blood of the patients with SLE, and RNA was extracted from lymphocyte. cDNA was generated by reverse transcription reaction, and RAG-1 and RAG-2 was detected by PCR. **[Results]** Whereas the expression of RAG-1 was not observed in the healthy controls, RAG-1 was significantly detected in the patients with SLE ($P<0.001$). The expression of RAG-2 was also significantly increased in the patients ($P<0.05$). **[Conclusion]** The expression of RAG which is responsible for TCR revision suggests the generation of *ai*$CD4^+$ T cell in the patients with SLE.

P3-007

A novel method for measuring autophagy and identification of a protective role of autophagy as an anti-oxidant system in human primary T cells. A potential therapeutic strategy for autoimmune diseases

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Conflict of interest: None

[Background] Human activated T cell plays an important role in the pathogenesis of autoimmune diseases, and its regulation would be a new therapeutic strategy for these diseases. Autophagy is an intracellular degradation system and contributes to T cell survival, however, a precise role of autophagy in human primary T cells remains unclear. [Objective] To clarify functional roles of autophagy in activated human primary T cells and explore an autophagy-targeted strategy to efficiently induce apoptosis to these cells. [Methods] GFP-LC3, which could monitor autophagy, was retrovirally transfected into activated T cells, and the fluorescence intensity was measured using flow cytometry. [Results] Autophagy was induced after T cell receptor stimulation. Autophagy-defective T cells had higher levels of mitochondria and reactive oxygen species, and were susceptible to apoptosis. Combination of an autophagy blocker (chloroquine) and an inhibitor of mitochondrial electron transport chain (mETC, arsenic trioxide) synergistically induced apoptosis to activated T cells. [Conclusion] We identified a protective role of autophagy as an anti-oxidant system in activated T cells. Combination of an autophagy blocker and an inhibitor of mETC could be a novel therapeutic strategy for autoimmune diseases.

P3-008

Analysis of lining hyperplasia in three-dimensional organ culture of synovial fibroblasts

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Conflict of interest: None

【Introduction】 Synovial hyperplasia plays a crucial role in destruction of cartilage,bone and joint in Rheumatoid arthritis (RA). Unlike monolayer cultures of fibroblast-like synoviocytes (FLS),synovial tissue has the synovial lining layer that is composed of cell layers surrounding a meshwork of extracellular matrix.In some reports it was demonstrated that the lining layer could

be established in three-dimensional micromass organ culture.We examined the mechanism of the synovial lining hyperplasia in this 3-D culture with cytokine stimuli.【Objective】To examine the mechanism of the synovial lining hyperplasia in the three-dimensional organ culture of FLS.【Methods】As described previously,we made micromass organ cultures of FLS of RA and osteoarthritis (OA) with or without cytokine stimuli.Micromasses were fixed and sectioned,then stained with hematoxylin and eosin.To assess the hyperplasia,the lining layer was scored according to our criteria. The data from the histrogical scoring was analyzed statistically. 【Results】Obvious lining hyperplasia was observed in 3-D culture with stimuli of cytokine combination including PDGF.The lining hyperplasia was observed not only in the 3-D culture of RA FLS,but also in that of OA. We are investigating the mechanism of the lining hyperplasia.

P3-009

Expressions of microRNA-155 and its target gene MMP-3 in the patients with ankylosing spondylitis

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Conflict of interest: None

Objectives: Fibrosis and calcification of the spine and sacroiliac joints induced by inflammation were the symptoms of ankylosing spondylitis (AS). Fibrosis is consequence of excessive accumulation of extracellular matrix (ECM), matrix metalloproteinase-3 (MMP-3) also plays a part in arthritis through ECM degradation and activation of proinflammatory factors. Higher expression of miR-155 might inhibit MMP-3 mRNA. We thus evaluated the effects of miR-155 and MMP-3 mRNA in the AS development. Methods: Serum miR-155 and MMP-3 mRNA levels were detected by RT-PCR among 123 AS patients and 123 controls. Osteocalcin (OC) level was measured using ELISA. Results: Subjects with lower expression of miR-155 had 1.85-fold risk for AS development (95% C.I. = 1.01-3.41) than those with higher expression. Higher osteocalcin level was found in AS patients than healthy controls (27.9 vs. 14.5 ng/ml; $P < 0.001$). In addition, a negative correlation of miR-155 and MMP-3 mRNA was observed in AS patients ($r = -0.55$, $P < 0.01$). Correlation of miR-155 ($r = -0.21$, $P = 0.02$) and MMP-3 mRNA expression ($r = 0.27$, $P < 0.01$) with osteocalcin level were also observed in AS patients. Conclusion: Serum miR-155 and MMP-3 mRNA expressions might be associated with AS development.

P3-010

Anti-inflammatory effects of glyceroglycolipids from green algae in synovial cells

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Conflict of interest: None

[Objectives] Beppu spas are appreciated by those who suffer from arthritis. Recently, we have isolated and cultivated a series of novel green algae from the thermal waters. Monitoring tests showed that the algal extracts were practically beneficial for easing joint and muscular pains. In order to investigate the molecular basis of the effects, we have purified glyceroglycolipids and examined them using cell-based assay systems. **[Methods]** The mixture of glyceroglycolipids, containing MGDG and DGDG, was prepared from the novel green alga (Chlorophyta) according to G. Marcolongo *et al*. (2006). The anti-inflammatory effect of the mixture was examined by quantitative analysis of inflammatory cytokines and matrix metalloproteinases (MMPs) in synovial cells. **[Results]** MGDG and DGDG were observed in the glyceroglycolipids mixture by TLC/GC-MS. The glyceroglycolipid-mixture reduced both mRNA and protein levels of IL-1, IL-6 and TNF-α in IL-1 treated synovial cells. The reductions of MMP-3 were also observed dose-dependently in RA patient-derived synovial cells. **[Conclusion]** The glyceroglycolipids mixtures of the novel alga showed anti-inflammatory effects in the cell-based assays, implying it to be an application in inflammatory arthritis.

P3-011

Differences in effect between anti-IL-6 receptor antibody and JAK inhibitor on anti-inflammatory response by IL-10 in monocytes

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Conflict of interest: None

[Objectives] JAK inhibitors are promising for new treatment of rheumatoid arthritis (RA). However, it has been pointed out that JAK inhibitors could weaken the suppressive effect of IL-10 against bone destruction by inhibition of IL-10 signaling. Here, we elucidated the effects of anti-IL-6 receptor antibody (anti-IL-6R) and JAK inhibitor on the response to IL-10 in monocytes. **[Methods]** Monocytic cell line THP-1 cells were cultured with anti-IL-6R or JAK inhibitor in the presence of IL-6, lipopolysaccharide (LPS) or IL-10 for 24 h. MMP-13 and IL-8 mRNA expressions were measured by real-time PCR. Furthermore, IL-8 concentration in 24h-culture supernatant was measured by ELISA. **[Results]** IL-6 increased MMP-13 mRNA expressions and both anti-IL-6R and JAK inhibitor suppressed the induction of MMP-13 by IL-6 in THP-1 cells. Moreover, LPS increased IL-8 expressions and IL-10 suppressed the induction of IL-8 by LPS. This suppression of IL-8 by IL-10 was impaired by JAK inhibitor, but not by anti-IL-6R. None of anti-IL-6R and JAK inhibitor affected the increased expression of IL-8 by LPS. **[Conclusion]** It was suggested that JAK inhibitor can inhibit IL-10 as well as IL-6 signaling and attenuate anti-inflammatory effects of IL-10.

P3-012

A role for soluble interleukin-6 receptor as an antagonist of interleukin-27 signaling

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Conflict of interest: None

[Objectives] IL-27 is a heterodimeric cytokine composed of IL-27p28 and EBI3, which is structurally homologous to IL-6 and sIL-6R, respectively. We elucidated the role of sIL-6R in regulating IL-27 signaling. [Methods] BIAcore and competitive ELISA were performed to evaluate the binding to IL-27p28 and the dissociation of EBI3 from IL-27p28 in the presence of sIL-6R. $CD14^+$ cells were incubated with IL-27 and sIL-6R, and the phosphoryla-

tion of STAT3 was measured. $CD14^+$ cells were cultured with RANKL in the presence of IL-27 and sIL-6R, and osteoclast numbers were counted after TRAP staining. Concentrations of IL-27p28/sIL-6R complex in serum from healthy subjects and RA were determined. [Results] BIAcore analysis showed that IL-27 bound to sIL-6R, and that sIL-6R promoted the dissociation of EBI3 from IL-27p28 and formed complex with IL-27p28. In $CD14^+$ cells, IL-27 increased the phosphorylation of STAT3, and sIL-6R suppressed IL-27-induced phosphorylation of STAT3. RANKL-mediated osteoclast differentiation was inhibited by IL-27, and sIL-6R restored the differentiation. Surprisingly, IL-27p28/sIL-6R complex in RA serum was significantly higher than that in healthy. [Conclusion] We demonstrated that sIL-6R antagonized IL-27 signaling by competing with EBI3.

P3-013

IFNα is sufficient for the induction of SLE: its relation to Self-organized criticality theory

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Conflict of interest: None

[Objectives] To directly investigate the role of IFNα in inducing SLE, we generated mice that express IFNα under the control of the inducible doxycycline (Dox) promoter. [Methods] [Results] We demonstrate that IFNα expression alone is sufficient to induce disease with characteristics identical to SLE, i.e., serum anti-dsDNA antibody, immune complexes (IC) and tissue injury including glomerulonephritis accompanied by IC deposition, alopecia, epidermal liquefaction, positive lupus-band skin test and classical splenic onion-skin lesions. In these mice, activated $CD3^+CD4^-CD8^-$ double-negative T (DNT) cells, which were also $TCR\alpha\beta^+B220^+CD1d$-teteramer$^-$, expanded significantly. When transferred into naïve recipients, these DNT cells infiltrated to the glomeruli of transgenic mice and induced *de novo* glomerulonephritis and alopecia. We observed that these DNT cells had halted differentiation and had massively accumulated at the DN1 stage in the thymus. [Conclusion] IFNα expression appears to be sufficient for the induction of SLE *via* the generation of a unique DNT cell population. However, anti-Sm antibody was not induced. Thus, IFNα seems sufficient but not enough for generating SLE, and may generate or mediate the action of *ai*CD4 T cell which causes SLE.

P3-014

Serum cytokine profiles are useful for evaluating pathological conditions of rheumatoid arthritis (RA)

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Conflict of interest: None

[Objectives] Proinflammatory cytokines play significant roles in the pathogenesis of rheumatoid arthritis (RA). This study is designed to evaluate whether expression pattern analysis of multiple serum cytokines is useful for developing novel diagnostic methods for RA, including detection of anti-CCP antibody (ACPA)-negative RA patients and therapeutic monitoring. [Methods] Serum samples from RA patients, seronegative spondyloarthropathy (SNSA) patients and healthy controls (HC) were analyzed. Thirteen kinds of cytokines and chemokines (IFN-γ, TNF-α, IL-1β, IL-4, IL-6, IL-8, IL-10, IL-17A, IL-17F, IL-23, CCL20, CXCL13 and TGF-β1) were measured by chemiluminescence ELISA and their expression patterns (cytokine profiles) were evaluated for correlation with clinical parameters, including disease activities and ACPA levels. [Results] We revealed that 1) several serum cytokine levels were significantly elevated in RA patients, and 2) were significantly higher in ACPA-positive RA patients than in ACPA-negative ones. Furthermore, 3) serum cytokine profiles were shown to be associated with therapeutic efficacies after administration of bio-drugs. [Conclusion] We showed that cytokine profiling would be useful for detecting ACPA-negative RA patients and evaluating therapeutic efficacies.

P3-015

Serum interleukin-32γ in systemic lupus erythmatosus patients

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Conflict of interest: None

[Object] Interleukin-32 (IL-32) is known as a proinflammatory cytokine. IL-32γ is the most potent isoform and secreted extracellularly. IL-32γ is reported to contribute to autoimmune diseases such as rheumatoid arthritis (RA). However, the role of IL-32γ in systemic lupus erythematosus (SLE) is unknown. [Methods] Serum IL-32γ and tumor necrosis factor α(TNF-α) levels in 42 SLE patients were measured using an enzyme-linked immunosorbent assay. Gene expression of Interferon (IFN) signature (ISG15, Mx-1, OAS-1) in peripheral blood mononuclear cells (PBMCs) of 7 SLE patients were measured by quantitative PCR. [Results] Serum IL-32γlevel of SLE patients was 1700 pg/mL on average. There was no correlation between the serum TNF-α and IL-32γ. Gene expression of IFN signatures in PBMCs tended to be positively correlated with IL-32γ. [Conclusion] TNF-α is known to stimulate the secretion of IL-32γ in RA fibroblast-like synoviocytes. However, in SLE, IL-32γ may be induced by stimuli other than TNF-α. Since the positive correlation with Type I IFN was observed, TLR stimulations might be supposed as IL-32-inducing signals.

P3-016

IL-26 is produced by activated T cells and IL-26 is tend to be elevated in untreated RA compared treated RA

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Conflict of interest: None

【Objective】 We previously showed that IL-26 is expressed on synovial tissues of RA but not on those of OA. Our objective is to investigate the concentration of IL-26 in RA serum or synovial fluid (SF). **【Method】 1**) The concentration of IL-26 was measured by ELISA in serum with RA (n=13) and OA (n=4). We also measured IL-26 concentration(conc.) in SF with RA (n=2) and OA (n=3). 2) Human $CD4^+$ T cells were stimulated and IL-23 was added. After 48 hours IL-26 conc. of supernatants was mesuared by ELISA. **【Results】** 1) In untreated RA group (n=3), IL-26 conc. with serum were 774.4, 72.7, 120.1(pg/ml), respectively; however, in treated RA group (n=10), IL-26 was not detectable. Interestingly, in OA group (n=4), IL-26 with serum was not detectable at all. As well as serum, the IL-26 conc. with SF were elevated (2277.8, 243.7 pg/ml, respectively) in RA group but not OA group (not detectable). 2) IL-26 conc. was significantly elevated in activated $CD4^+$ T cells compared to non-stimulated T cells (p=0.115). IL-26 conc. was not changed by adding IL-23. **【Conclusion】** In serum,

IL-26 was detectable in only RA but not OA. In SF, IL-26 was tend to be elevated in RA compared to OA. Our findings results suggest that IL-26 produced by activated T cells is involved with the pathogenesis in RA.

P3-017

Temporal changes of serum IL-6 levels in patients with Castleman's disease treated with tocilizumab

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Conflict of interest: None

Background:We previously reported that serum IL-6 levels (sIL-6) increase shortly after tocilizumab (TCZ) therapy.But Long-term data of sIL-6 under TCZ therapy in pts with Castleman's disease are rarely reported.Objective: The purpose of this study is to analyze temporal changes of sIL-6 in pts with Castleman's disease treated with TCZ.Patients and methods: Temporal changes of sIL-6 were measured in 5 Castleman's disease pts (3 male and 2 female) treated with TCZ.Results: The average age at the beginning of treatment was 50.2 years (30-68). All pts were successfully controlled with TCZ without recurrence. Before the TCZ treatment, all pts received corticosteroid, and sIL-6 levels before TCZ therapy were undetectable in two pts, while the mean serum IL-6 level was 39.7pg/ml in the remaining 3 pts. Two months after the start of treatment, average sIL-6 increased to 383.4pg/ml (range 238-495), and 284.0pg/ml after 1-year follow-up (3 cases). In 2 cases followed by us for more than 4 years the final follow-up data were 226 and 196pg/ml respectively. Conclusion: In Castleman's disease, sIL-6 levels were persistently high in spite of good clinical control, and this fact suggests that continuous abnormal regulation of IL-6 production might be of etiological significance.

P3-018

Searching for new systemic lupus erythematosus autoantigens using proteins produced by wheat cell-free synthesis

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Conflict of interest: None

[Purpose] To discover new autoantigens associated with the disease etiology and/or prognosis of SLE. [Method] The AlphaScreen assay was used to search for new SLE autoantibodies using paired acute and convalescent serum samples of 3 SLE patients. We screened 2296 proteins based on databases of autoimmune disease susceptibility genes and membrane proteins. [Result] Proteins with positive reactions in acute samples, which declined in remission, were 6 (thrombocytopenia), 538 (nephritis), and 604 (serositis). These proteins included well-characterized autoantigens of SLE, e.g., SNRPs (Sm proteins). We chose 68 proteins and examined serum samples from patients with SLE (5, acute phase and 5, remission), dermatomyositis/polymyositis (10), and sclerosis (10). We found 19 proteins with high SLE specificity, including membrane proteins (e.g., IFITM1) and cytoplasmic proteins (e.g., PSMC2). Seven proteins had a much higher response in active SLE than inactive SLE. Studies on associations of these proteins with disease etiology and progression are underway. [Conclusion] The AlphaScreen assay using autoantigen proteins produced by the wheat cell-free translation system is useful for autoantigen screening.

P3-019

Novel autoantibodies against two membrane proteins in patients with Takayasu arteritis identified by a serological identification system (SARF)

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Conflict of interest: None

[Objectives] Anti-endothelial cell antibodies (AECA) are detected in a half of patients with Takayasu arteritis (TAK), but their target antigens remain unclear. To specifically target cell-surface molecules in identification of autoantigens, we constructed a serological identification system (SARF). [Methods] AECA activities were measured in patients with TAK, and IgG fractions were purified from AECA-positive patients. A cDNA library of human umbilical vein endothelial cells (HUVEC) was retrovirally transfected into a rat myeloma cell line, from which AECA-positive clones were sorted by flow cytometry. [Results] AECA-positive clones were isolated using serum IgG from six out of twelve patients with AECA-positive TAK. By DNA sequencing, we proved two cDNAs encoding different membrane proteins were inserted into these clones. The prototype AECA IgGs bound specifically to each protein-transfected cells, thus they were identified as novel autoantigens. One protein involves in lipid transport and atherosclerosis, and the other involves in coagulation and apoptosis. [Conclusion] We identified two membrane proteins as novel autoantigens in TAK. Further studies might enable the application of these autoantibodies for the practical use, and bring a new insight in the etiology of TAK.

P3-020

Identification of fine epitope to anti-NR1 antibody in Systemic lupus erythematosus

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Conflict of interest: None

[Objectives] We showed that the presence of autoantibodies against N-methyl-D-Aspartate (NMDA) receptor subunit 1 (NR1) is associated with systemic lupus erythematosus last year. The present study explored that which amino-acid sequence of NR1 is more specific epitope. [Methods] Sera were obtained from 33 patients with SLE and 57 healthy individuals. To demonstrate more specific epitope of anti-NR1 against original peptide, we investigated the reactivity of four kinds of shorten polypeptide composing original peptide. The sequence of these shorten peptide was determined by subdiving 82-amino acid sequence of original peptide without signal portion into 4 parts out of 25-amino acid. We called these peptide ⊿A, ⊿B, ⊿C and⊿D from N terminal tail of NR1. IgG anti-NR1 antibodies were measured by ELISA, using these peptide. [Results] Cut off value of anti-NR1 antibody was defined as 2SD above the mean of anti-NR1 levels in normal healthy individuals. Antibody prevalence rate of each peptide were shown as follows: ⊿A is 21.2%, ⊿B is 6.1 %, ⊿C is 21.2 % and⊿D is 15.2%. [Conclusion] Anti-NR1 bound more efficiently to the sequence of amino acids between position 19 and position 44 (peptide A) or position 57 and position 81 (peptide C) from the N-terminus of human NR1.

P3-021

Antibodies to the $GABA_B$ receptors in systemic lupus erythematosus

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Conflict of interest: None

Objectives: Using a random peptide display library, we explored SLE patients' sera, and identified the $GABA_B$ receptor as a candidate auto-antigen. The $GABA_B$ receptor was previously reported as a target antigen in stiff-person syndrome and limbic encephalitis. Here we report the prevalence of anti-$GABA_B$ receptors antibodies in SLE. **Methods:** Presence of anti-$GABA_{B1b}$ receptor or anti-$GABA_{B2}$ receptor antibodies (α-B1b or α-B2) was examined by ELISA. **Results:** Reactivity of α-B1b and α-B2 (ELISA-titer) was significantly high in SLE patients, compared to healthy controls. ELISA-titers of α-B1b and α-B2 in 20 SLE patients were 0.51 or 0.48, whereas those of 15 healthy controls were 0.09 or 0.06, respectively ($P < 0.001$). More than 80% of ELISA-titers of SLE samples were higher than the highest one of the controls. Moreover, the reactivity of both antibodies in 48 acute-phase SLE patients was higher than 38 chronic-phase SLE patients ($P < 0.001$). Both antibody titers were significantly decreased after treatment in 8 pairs. Neither of α-B1b and α-B2 correlated with neuropsychiatric SLE. No significant high ELISA-titers of α-B1b and α-B2 were detected in scleroderma, myositis and vasculitis. **Conclusion:** Anti-$GABA_B$ receptor antibodies could have a relation to disease activity of SLE.

P3-022

Association of Increased Frequencies of *HLA-DPB1*05:01* with the Presence of Anti-Ro/SS-A and Anti-La/SS-B Antibodies in Japanese Rheumatoid Arthritis and Systemic Lupus Erythematosus Patients

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Conflict of interest: Yes

Objectives: Autoantibodies to ribonucleoprotein are associated with a variety of autoimmune diseases, including rheumatoid arthritis (RA). Many studies on associations between human leukocyte antigen (HLA) alleles and RA have been reported, but few have been validated in RA subpopulations with anti-La/SS-B or anti-Ro/SS-A antibodies. Here, we investigated associations of HLA class II alleles with the presence of anti-Ro/SS-A or anti-La/SS-B antibodies in RA. *Methods:* An association study was conducted for *HLA-DRB1, DQB1,* and *DPB1* in Japanese RA and systemic lupus erythematosus (SLE) patients that were positive or negative for anti-Ro/SS-A and/or anti-La/SS-B antibodies. *Results:* An increased prevalence of *DPB1*05:01* was associated with the presence of anti-Ro/SS-A (Pc=0.0040, OR 1.55, 95%CI 1.23-1.96) and anti-La/SS-B antibodies (Pc=0.0069, OR 2.27, 95%CI 1.44-3.57).The *DPB1*05:01* allele was also associated with anti-Ro/SS-A (Pc=0.0408, OR 1.69, 95%CI 1.19-2.41) and anti-La/SS-B antibodies (Pc=2.48X10^{-5}, OR 3.31, 95%CI 2.02-5.43) in SLE patients. *Conclusions: HLA-DPB1*05:01* was the only allele associated with the presence of both anti-Ro/SS-A and anti-La/SS-B antibodies in Japanese RA and SLE patients.

P3-023

The diagnostic utility of line immunoassay for patients with collagen disease

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Conflict of interest: None

[Objectives] To evaluate the diagnostic utility of the line immunoassay (LIA) in patients with collagen disease. [Methods] Thirty seven patients performed myositis- and SSc-LIA tests at Okayama University Hospital in 2012 were include in this study. The diagnostic performance of myositis-LIA was evaluated using Bohan's criteria as diagnostic golden standard. We also investigated the relationship between the initial clinical symptoms and each LIA results. [Results] Among 37 patients, 24 were women and the ages of onset were 60 (30-80) including 11 vasculitis, 7 PM/DM, 5 RA, 4 SLE, and 1 SSc patients. The sensitivity of anti-Jo-1 antibody was 43% in both ELISA and LIA, and the specificity was 100% for the diagnosis of PM/DM. The sensitivity of simultaneous use of anti-Jo-1, ARS, SRP, and Mi antibodies was 100%, and the specificity was 70%. Furthermore, the sensitivity of anti-PM75, PM100, and Ku antibodies in addition to the above antibodies was 100%, and the specificity was 47%. In all patients, we found that anti-PL-7 antibody is related to pulmonary hypertension, and anti-PM100, NOR90, and RP11 antibodies are related to interstitial pneumonia. [Conclusion] The combination of LIA for myositis-associated antibodies may be useful for the diagnosis of myositis.

P3-024

Final diagnosis of 2029 cases that tested positive for anti-nuclear antibody on ELISA

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Conflict of interest: None

[Objectives] To clarify differences in quality between anti-nuclear antibody ELISA (ELISA-ANA) and F-ANA using the indirect fluorescence antibody technique, we analyzed final diagnoses of ELISA-ANA-positive cases. [Subjects and methods] Final diagnosis was checked for all of 2029 cases positive on ELISA-ANA performed for diagnostic purposes. MESACUP ANA test (MBL) using a mixture of recombinant antigens (11 types including RNP-70kD protein, Scl-70, phage l DNA) was used. [Results] The results indicated 701 cases of connective tissue disease and related diseases, 409 cases of autoimmune diseases other than connective tissue diseases, 50 cases of allergic diseases, 135 cases of infec-

tious diseases including viral hepatitis, 134 cases of cancer, and 593 cases classified as other or unknown. [Discussion] ELISA-ANA showed many positive cases in non-connective tissue diseases. Low-titer positive cases included hepatopathy, including viral type, thyroid disease, chronic renal impairment, malignant, and infectious diseases. High-titer positive cases with non-connective tissue diseases often had autoimmune hepatitis. ELISA-ANA cannot detect nonspecific ANA, but the rate of positive cases ultimately diagnosed as connective tissue diseases was high, which we believe is clinically useful.

P3-025

Evaluation of antinuclear antibody in the case of biologic switching therapy in our clinic

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Conflict of interest: None

Recently, it has been reported that the cases of positive antinuclear antibody (ANA) in patients treated with IFX may lead to secondary failure of IFX. As a general use of biologics in patients with RA, a patient who has had an inadequate response to the first biologic would be switched to another biologic. We will show a case report which indicated complete response to two biologics failures as third biologic choice. <Case report>Age: 57, Sex: female, the patient was diagnosed as RA in 2005 and treated with MTX and tacrolimus in previous clinic. When she firstly visited to our clinic in June 2009; Stage: III and Class 2, 80 times of ANA (by speckled & discrete specked).Although she initiated adalimumab (ADA) 40mg/time in May 2010, her medication was switched to IFX in August 2010 because of non-response to ADA. However, in April 2011 we further switched to abatacept (ABT) due to the secondary failure of IFX, consequently her RA disease activity was dramatically improved and her condition is doing well at this moment. We would evaluate the correlation between this case report which suggested lack of efficacy for both first and second biologics, and positive ANA or another connective tissue disease complication, based on exploring any ANAs in other biologics switchers in our clinic.

P3-026

Epitopes of low density lipoprotein receptor-related protein2 (LRP2) in thyroid diseases

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Conflict of interest: None

[Objectives] We previously reported autoantibodies to low-density lipoprotein receptor-related protein 2 (LPR-2) in rheumatoid arthritis (RA). In thyroid disease, that there is anti-LRP2 antibody is reported. Extending this study, we here investigated autoantibodies to LRP2 in patients with thyroid disease, and mapped autoepitopes on LRP2. [Methods] We prepared 7 recombinant LRP2 molecules as a fusion protein with maltose binding protein using E. coli and then used them for detection of autoantibodies and epitope mapping in the sera of patients with thyroid diseases by western blotting. [Results] The autoantibodies to LRP2 were detected in 13 (43.3%) of the 30 tested Hashimoto's thyroiditis serum samples, and in 2 (0.7%) of the 30 patients with Graves'disease. Epitope mapping using the Hashimoto's thyroiditis serum samples revealed that epitopes on LRP2 were recognized by 54% of the positive patients. [Conclusion] This study revealed that multiple epitopes of LRP2 in some patients with Hashimoto's disease. The autoantibodies to LRP2 would be produced by the antigen-driven immune response in 7 (23%) of the 30 tested Hashimoto's thyroiditis. But, 6 (46%) of positive patient react to only one fragment. This autoantibody may be cross-react for other molecules

P3-027

Availability of measuring rheumatoid factor and anti-Sm antibodies in subjects with anti-U1RNP antibodies

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Conflict of interest: None

[Objectives] To study the clinical significance of the presence of rheumatoid factor (RF) and anti-Sm in subjects having anti-U1RNP. [Subjects] 71 subjects (4 males and 67 females) with anti-U1RNP who showed persistently positive or negative for RF were enrolled. [Results] The frequencies of SSc (34.6%), IP (38.5%), and RP (84.6%) in RF+ group (n=26) were significantly higher than those in RF- group (n=45; 11.1%, $P < 0.05$; 13.3%, $P < 0.05$; 60.0%, $P < 0.05$; respectively). Meanwhile, the frequency of renal disorder (3.8%) and anti-Sm (12.0%) in the RF+ group were significantly lower (28.9%, $P < 0.05$; 34.2%, $P < 0.05$; respectively). Among the 4 groups classified according to present patterns of RF and anti-Sm, clinical features in the RF+/anti-Sm+ group and the RF-/anti-Sm- group showed having SLE (100.0%, 92.3%; respectively). The frequency of renal disorder in the RF-/anti-Sm+ group (46.2%) was highest among groups. Meanwhile, the frequencies of SSc, IP, and RP in the RF-positve/anti-Sm-negative group (40.9%, 40.9%, 90.9%; respectively) were highest among groups. The RF-negative/anti-Sm-negative group showed intermediate clinical features between the groups. [Conclusion] To examine RF and anti-Sm in subjects with anti-U1RNP is more good decisions for diagnosis.

P3-028

Expression of leucine rich α2-glycoprotein in the patients with rheumatoid arthritis and osteoarthritis

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Conflict of interest: None

[Objectives] Leucine rich α2-glycoprotein (LRG) is an approximately 50 kDa glycoprotein, and contains repetitive sequences with a leucine-rich motif. Previous study has shown that serum LRG concentrations are increased in patients with rheumatoid arthritis (RA), although its function remains unclear. We examined the expression of LRG in the patients with RA and osteoarthritis (OA). [Methods] Synovial fluid (SF) samples were obtained from knee joints in 9 patients with RA and 46 patients with OA. Sera were also collected from 46 OA patients. SF and serum levels of LRG were determined using an ELISA. Synovium were analyzed by immunohistochemistry. [Results] ELISA results showed SF levels of LRG in RA (mean 27.0 μg/mL) were significantly higher compared with OA (mean 13.4 μg/mL, p=0.012). SF levels of LRG were significantly correlated with serum levels in OA patients (R^2=0.114, p=0.023). SF levels of LRG in the patients with OA

showed significant correlation with radiographic progression (R^2=0.100, p=0.034), however, serum levels showed no correlation. Immunohistochemistry of the synovium demonstrated LRG expression was found in synovial lining cells and vessel walls in RA and OA. [Conclusion] LRG may be a useful biochemical marker of RA and OA.

P3-029

The screening-rapid test of KL-6 can aid the early detection of methotrexate associated lung injury in outpatients with rheumatic diseases

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Conflict of interest: None

[Objectives] To evaluate the clinical significance of the screening-rapid test of KL-6 (**R-KL-6**) for the early detection of methotrexate associated lung injury (MTX-LI) in outpatients with rheumatic diseases. [Methods] Data of outpatients with rheumatic diseases, who had been undergone MTX prescriptions and the **R-KL-6** at least once from April 2008 to September 2012, were picked up. To evaluate the all candidates of MTX-LI, the data of abnormal KL-6 value and the discontinuation of MTX were extracted separately. We defined the abnormal value of KL-6 as fulfilling at least one of following, 1) increase rate > 240U/ml per month, 2) 2 fold elevation from prior, 3) KL-6 value > 3fold of upper limit of normal. The result of **R-KL-6** could be reported to us in time. [Results] In the total 808 patients with MTX treatment, the **R-KL-6** were tested for 723. Forty two had the abnormal value as above, and we analyzed their clinical record and extracted 16 MTX-LI cases. The records of MTX-discontinuation could reveal the additional 2. In total, MTX-LI developed approximately 2.0%, but most cases had good clinical outcome except one fatal case. [Conclusion] The **R-KL-6** could aid the early detection of MTX-LI and the prevention of the severe lung injury in outpatients with rheumatic diseases.

P3-030

Analysis of serum immunoglobulin A in rheumatoid arthritis

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Conflict of interest: None

[Background] According to previous reports, some cases of rheumatoid arthritis show high level of serum immunoglobulin A (IgA). However, the significance of IgA in RA still remains to be elucidated. [Objectives] To evaluate the pathogenetic significance of serum IgA in RA. [Methods] We enrolled 51 RA patients with mean age of 61.7±11.4, and disease duration of 12.6±10.5 years. We measured IgG, IgA, IgM, C3, C4, CH50, RF, ant-nuclear antibodies, anti-double-strand DNA antibodies, MMP-3, KL-6, urinary proteins, urinary bloods, and urinary casts and evaluated disease activity score (DAS) 28-CRP, DAS28-ESR, and presence of interstitial pneumonia. Then we analyzed the relationships statistically between serum IgA and these clinical parameters. [Results] Mean DAS28-CRP and DAS28-ESR were 2.1±0.9 and 2.8±1.0 respectively. Mean serum IgA was 323.4±134.8 mg/dl. We detected significant positive correlations of serum IgA with DAS28-CRP, DAS28-ESR, CRP, and ESR respectively ($p<0.05$) in whole patients (N=51), and also in patients not treated with tocilizmab (N=42). [Conclusion] Serum IgA was correlated with DAS28-CRP and DAS28-ESR, respectively. Our result suggests that serum IgA may reflect clinical activity of RA. Further studies are required to clarify the pathogenetic role of serum IgA in RA.

P3-031

Renal function in patients with RA –a longitudinal study using IORRA cohort–

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Conflict of interest: None

[Objective] We have previously shown that lower eGFR was associated with disease activity, MTX dose, cardiovascular comorbidities in patients with RA in a cross-sectional study using IORRA cohort. The aim of the present study was to characterize the factors associated with decreased eGFR during a year in RA patients by a longitudinal study. [Methods] 5522 RA patients who participated in both 2009 and 2010 IORRA study were included. eGFR was determined using Japanese MDRD equation, and was corrected by body surface area (eGFR/BSA). The associations between eGFR/BSA and patients' characteristics, disease activity, medications and comorbidities were analyzed. [Results] eGFR/BSA data at both 2009 and 2010 were available in 4455 cases. In the patients with eGFR/BAS ≥ 50 ml/min at 2009, 3763 and 244 cases showed eGFR/BAS ≥ 50 ml/min (Group I) and <50 ml/min (Group II) at 2010, respectively. Univariate analysis revealed that patients in Group I were younger age, more males, shorter duration of RA, higher doses of MTX, and lower frequencies of cardiovascular comorbidities than Group II. Multivariate analysis revealed the association with DAS28. [Conclusion] It was suggested that stable renal function was associated with RA medication and improved disease activity.

P3-032

Serum levels of anti-CCP antibodies in the short term follow-up of patients with rheumatoid arthritis treated with biologics

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Conflict of interest: None

[Objectives] Antibodies against cyclic citrullinated peptides (anti-CCP) are frequently used by clinicians for diagnosis of rheumatoid arthritis (RA). However, the role of monitoring anti-CCP antibodies of patients with RA treated with biologics has not been elucidated. The aim of this study was to analyze the serum levels of anti-CCP antibodies in the six month period of follow up with RA patients who were first treated with biologics, to identify peculiarities of therapeutic response. [Methods] Fourteen RA patients with anti-CCP antibody positive were included in this analysis. Anti-CCP antibodies, CRP, ESR, MMP-3 and DAS28-ESR were determined at baseline (before use of biologics) and after use of biologics (2, 4, 6 months). [Results] In almost patients, the activity of RA was significantly reduced. However, the level of anti-CCP antibodies did not decrease during this short term follow-up after use of biologics. Three of six patients with high titer of anti-CCP antibodies (over 100 U/ml) after first biological therapies needed another biologics because of secondary failure within one year. [Conclusion] The short term assessment of anti-CCP antibodies to

biological treatment for patients with RA may provide information of secondary failure.

P3-033

Predictive value of novel method for analyzing IgG galactosylation in rheumatoid arthritis

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Conflict of interest: None

Objectives: To evaluate predictive value of agalactosyl IgG in RA, we analyze serum IgG oligosaccharide structures in early undifferentiated arthritis (UA) as a predictive marker for future development of RA. Methods: We analyzed the percentage agalactosyl IgG oligosaccharides (%G0) by high performance HPLC method in 144 patients with recent-onset UA. They were studied for whether UA progressed to RA after 2 year. Results: This study comprised 144 patients with early UA. The following parameters were assessed at baseline: %G0, rheumatoid factor (RF), autoantibody to galactose deficient IgG (CARF) and anti-cyclic citrullinated peptide antibodies (ACPA). Of the 144 patients with early UA, 58 (40.3%) developed RA, 9 (6.2%) developed collagen disease, 33 (22.9%) diagnosed as OA, 21 (14.6%) were UA as ever, and 23 (16.0%) were healthy within 2 years after registration. %G0 predicted progression of UA to RA with high accuracy (AUC=0.807) at a highest sensitivity of 79.3% among 4 diagnostic markers. Moreover, combination of %G0 and ACPA predicted progression of UA to RA with highest accuracy (AUC=0.905; 95% CI, 0.835-0.962). Conclusions: This novel method for analyzing agalactosyl IgG revealed excellent predictive value in RA. %G0 as well as ACPA would contribute to prediction of RA.

P3-034

Clinical evaluation in rheumatoid arthritis classified chronic kidney disease stages

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Conflict of interest: None

[Objectives] To investigate clinical evaluation in RA classified CKD stages. [Methods] RA patients (264; male: 63, female: 201) who medicated from July to October in 2012 were evaluated ages, disease duration, MTX, PSL, WBC, lymphocyte, Cre, MMP-3, CRP, ESR, TJC, SJC, Pt-VAS, Dr-VAS, DAS28CRP, DAS28ESR, CDAI, SDAI and MHAQ. The mean ages, disease duration, DAS28CRP, DAS28ESR were 64.4, 12.1 years, 2.06, 2.95, respectively. They were classified to 5 groups using CKD staging criteria. [Results] Numbers of stage1/2/3/4/5 were 39/146/75/2/2, respectively. Remission+LDA rates using DAS28CRP in stage1/2/3/4/5 were not different significantly (79.5/80.8/81.3/50.0/50.0%). Ages in stage1/2/3/4/5 were 52.4/62.9/73.0/83.5/69.5 years, respectively and differences between stage1/2, 2/3, 1/3 were significant. Dose of MTX in stage1/2/3 were 9.8/7.1/6.1 mg/w, respectively and differences between stage1/2, 1/3 were significant. MTX was not medicated for stage 4 and 5. [Conclusion] Renal dysfunctions over stage3 were seen in 29.9% (79/264). Although dose of MTX was reduced as CKD stage went up, RA activity kept low. Cre outliers of CKD stage3 were only 18.7% and we must be careful to check renal function using Cre value in RA patients. Renal function was dependent on not disease duration but age.

P3-035

Measurement significance of hepcidin-25 in patients of rheumatoid arthritis planned to treatment with biologics

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Conflict of interest: None

[Objectives] Hepcidin-25 is mainly induced by IL-6, concurrently involved in the pathogenesis of inflammation associated anemia via iron metabolism. We suppose that the serum hepcidin-25 level reflects the grade of IL-6 activity physiologically in each patient. The aim of this study is to assess the value of serum hepcidin -25 levels in patients with rheumatoid arthritis treated with anti-IL-6 therapy or anti-TNF-α therapy, whether the change of hepcidin-25 level during pre- and post -treatment is influence to the therapeutic effect. [Methods] RA patients were classified to three groups; Infliximab effective group, Infliximab resistant group and tocilizumab effective group. We measured the serum hepcidin-25 level before and after each treatment to evaluate the result with reference to other clinical findings. [Results] Serum Hepcidin-25 decreased at before and after therapy in each groups. It was seen the tendency that serum Hepcidin-25 level of infliximab resistance group and tocilizumab effective group are higher than infliximab effective group. [Conclusion] The measurement of serum hepcidin level of patients with rheumatoid arthritis to introduce biologics newly may help the decision of the choice of an antiTNF -α therapy or the antiIL-6 therapy.

P3-036

Validity of the screening test for hepatitis B infection in rheumatoid arthritis

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Conflict of interest: None

[Objectives] To clarify validity of the screening test for HBV infection in RA. [Methods] Levels of HBsAg, HBsAb, and HBcAb were measured in 405 RA, then again after 2 years. [Results] 375 RA patients could be followed for 2 years. At the baseline, 259 patients were diagnosed as uninfected with HBV, 110 had previous infection, and 6 were carriers. After 2 years, these numbers had shifted to 278 uninfected patients, 90 patients with previous infection, and 7 carriers ($p < 0.0001$). The sensitivity for diagnosing HBV infection decreased from 97.4% to 81.5%. Of 69 patients with HBsAg-positive/HBcAb-positive at baseline, after 2 years, 64 were HBsAb-positive/HBcAb-positive, two were HBsAb-positive/HBcAb-negative, and three were HBsAb-negative/HBcAb-positive. Of 13 patients with HBsAb-positive/HBcAb-negative, after 2 years, 10 were HBsAb-positive/HBcAb-negative and three were HBsAb-negative/HBcAb-negative. Of 28 patients with HBsAb-negative/HBcAb-positive, after 2 years, two were HBsAb-positive/HBcAb-positive and 19 were HBsAb-negative/HBcAb-negative. Of the 259 patients with uninfected, after 2 years, one patient had undergone HBsAg-positive conversion and two were HBsAb-negative/HBcAb-positive. [Conclusion] Routine screening for HBV

for RA is the complete denial of a HBV infection in them.

P3-037

Evaluated of monocyte CD64 expression in two patients with systemic lupus erythematosus (SLE)

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Conflict of interest: None

OBJECTIVE: The expression of CD64 (Fc gamma RI) on monocytes (mCD64) in SLE patients was investigated. mCD64 correlated with IFN-I-stimulated gene expression and SLE Disease Activity (SLEDAI) in patients with SLE. We measured mCD64 molecules by a quantitative flow cytometry in two SLE patients and 20 healthy controls. **Case1;** A 43-year-old woman had a history of photosensitivity, and new occurrence of high grade fever, polyarthralgia, leukopenia, antinuclear antibody (ANA) (1:640) and anti-ds DNA antibody 48 IU/ml. She was diagnosed with SLE and treated prednisolone (PSL) 10mg/day. Her condition has improved and a SLEDAI score also decreased from 4 to 2. The mCD64 molecules were down-regulated from 25000 to 10152 molecules /cell. **Case2;** A 14-year-old woman presented with butterfly rash, pleuritis, leukopenia, antinuclear antibody (1:640), anti-ds DNA antibody 2020 IU/ml and lupus nephritis WHO IV-(G/A). She was diagnosed with SLE and started PSL 50mg /day. Her clinical condition improved gradually. A SLEDAI score decreased from 21 to 12 points and the mCD64 also down-regulated from 52552 to 10152 molecules /cell. **CONCLUSION:** We conclude that mCD64 levels may be a useful in the disease activity of SLE as well as in the assessment of its response to immunosuppressive therapy.

P3-038

The current status of the treatment for rheumatoid arthritis with hepatitis B virus infection in our hospital

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Conflict of interest: None

[Objectives] We often have difficulty in the treatment for RA with HBV infection. [Subject] In case of enrolled 1,470 RA patients between Nov. 2009 and Aug. 2012 in our hospital, we have experienced 16 HBV carriers, and 49 patients who have cleared HBV infection. [Results] Sixteen HBV carriers included 7 patients treated with biological agents (BIO) and 9 patients treated with immunosuppressant except BIO (IMS). Two rises in serum transaminases were accepted from the standard value in HBV carriers treated with IMS during the observation period. Forty-nine patients who have cleared HBV infection included 31 patients treated with BIO and 18 patients treated with IMS. We have experienced no de-novo hepatitis B. [Conclusion] The HBV carrier rate of RA patients in our hospital is 1.09%, and the HBV carrier rate in Hokkaido is ranked second (2.40%) in 47 prefectures. The JCR has recommended a nucleoside analog should be given to RA patients undergoing BIO and/or IMS with HBV infection and detectable HBV DNA. Expensive medical costs sometimes disturb them to attend our hospital. Some RA patients with HBV infection require BIO and/or IMS because of high disease activity, and their history of HBV test is sometimes vague during their long progress.

P3-039

Availability of fluorodeoxyglucose positron emission tomography/computed tomography and shoulder joint magnetic resonance imaging in patients with active polymyalgia rheumatica

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Conflict of interest: None

[Objectives] Polymyalgia rheumatica (PMR) is an inflammatory disease characterized by stiffness and aches in the proximal muscles, slight fever, general fatigue in the aged, and the pathology is unknown. Although PMR is diagnosed by the exclusion of other disorders causing similar complaints and by its rapid response to low-dose corticosteroid therapy, sometimes it is difficult to differentiate with other diseses. Recently, H. Yamashita et al. showed the availability. In this study, we assessed FDG -PET/CT and shoulder joint MRI findings in seven patients with PMR. [Methods] 7 patients with PMR (4 women, 3 men; mean age 74.85± 6.76 years, range 64-83 years) had undergone FDG-PET/CT and shoulder joint MRI, before the treatment of steroid. [Results] Almost all patients showed FDG uptake at sites of shoulder joints, spinous processes, hip joints, greater trochanters, and ischial tuberosities, and 5 patients showed subacromial bursitis in shoulder joint MRI. [Conclusion] FDG-PET/CT may be useful for the diagnosis of PMR, because of its high detection sensitivity of PMR lesions and its ability to exclude malignant diseases. Shoulder joint MRI may be also useful in the detection of subacromial bursitis, which is important for the diagnosis of PMR.

P3-040

Quantitative evaluation of the shoulder inflammation in polymyalgia rheumatica by power Doppler ultrasound

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Conflict of interest: None

[Objectives] Through the clinical experience of the power Doppler (PD) ultrasound (US) of the shoulder lesions in untreated patients with polymyalgia rheumatica (PMR), we noted that there were many cases presenting hyperemia adjacent to the anterior aspect of the subscapularis tendon ("hyperemia on SubST"). We examined whether such hyperemia correlates with the disease activity of PMR. [Methods] We analyzed consecutive records of 10 PMR patients and 12 elderly-onset rheumatoid arthritis (EORA) patients mimicking PMR, whose both shoulders were assessed routinely for the "hyperemia on SubST" between July 2010 and September 2012. The areas of PD positive pixels (PD-area) were measured on representative transverse images of both shoulders and correlation with various clinical indicators was analyzed. [Results] PD-area was comparable between PMR group and EORA group. In PMR group, PD-area significantly correlated with serum MMP-3 ($|R|=0.975$, $p< 0.0001$). Although weak positive correlation was shown between PD-area and serum CRP or ESR in PMR group, it was not significant. There was no significant correlation between PD-area and MMP-3, CRP or ESR in EORA group. [Conclusion] The extent of hyperemia adjacent to the anterior aspect of SubST may serve as an index of a disease activity of PMR.

P3-041

Estimation of ultrasound assessment in polymyalgia rheumatic and correlation of matrix metalloproteinase-3 (MMP-3)

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Yumoto[2], Tomoaki Iwanaga[2], Kayo Asato[1], Toshihiko Shiga[1], Shoichi Hino[1], Tomohiro Yano[1], Kazuya Kishimoto[1], Yasuaki Nagare[2], Hideki Shimazu[3], Koji Kinoshita[2], Masanori Funauchi[1], Itaru Matsumura[1]
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Conflict of interest: None

[Objectives] The correlation of ultrasound (US) assessment and clinical symptoms and laboratory test in patient with polymyalgia rheumatica (PMR) were evaluated. [Method] Fifteen patients (Male 7, Female 8, 72.2 ± year old) were diagnosed as PMR from October 2011 to October 2012. The patients are satisfied with criteria inAmerican collage of rheumatology/European league against rheumatism(ACR/EULAR) at diagnosis. The correlation of US with clinical symptoms (VAS, morning stiffness, HAQ) and laboratory test (MMP-3, CRP, ESR). We observed bilateral shoulder (subdeltoidbursitis, long head biceps (LHB), subacrominal bursitis) of those synovium thickness and power doppller of Grade 0-3 by US. We evaluated the relationship of US with the clinical symptoms and laboratory test at baseline and 6 and 12 months. All patients were treated with prednisolone (PSL) 15mg/day without immunosuppressant. [Result] At baseline, LHB and MMP-3 were observed the positive correlation (r^2=0.782562, P= 0.0192). The thickness of the LHB and ESR were trend to be the positive correlation even though there was no significant change (r^2=0.246033, P= 0.3170). [Conclusion] We suggest that US may be a responsive additional tool in the assessment of the response to the disease activit

P3-042

Two cases of typical polymyalgia rheumatica with effusion of the atlantoaxial joint

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Conflict of interest: None

[Background] In the 50th JCR annual meeting, we reported the evidence that the crowned dens syndrome, which had been termed as acute neck pain due to calcifications surrounding the odontoid process, was essentially identical to pseudo gouty attack in the atlantaxial joint by image analysis. We accordingly found that some cases of definite polymyalgia rheumatica (PMR) might be the same. We report two representative cases. [Cases] Two females in their eighties were admitted to our hospital for acute severe pain and stiffness of their neck, nape, and shoulders. Physical examination showed neck, nape and bilateral upper arm tenderness. They had a low-grade fever. ESR and CRP were markedly increased. On cervical CT scan, the odontoid process was covered with crown-like calcification. MRI showed effusion of the atlantoaxial joint. Their medical history also revealed previous pseudo gouty attacks of their knees. Corticosteroid therapy (prednisolone 6 and 8 mg/day respectively) resulted in dramatic improvement in their condition. CRP became negative at an early date. [Discussion] PMR is a kind of clinical diagnosis. Therefore it can contain many pathogenesis, such as autoimmune disease like giant cell arthritis. Cervical pseudo gouty attack may be also a major cause of PMR.

P3-043

A case of rheumatoid arthritis complicated with polymyalgia rheumatica (Clinical usefulness of shoulder joint MRI)

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Conflict of interest: None

A 62-year-old male, who had suffered from polymyalgia rheumatica (PMR) for 2 years, was treated with 20 to 9 mg/day of oral prednisolone. He has become aware of strange noise in his left shoulder joint since 2011. However, he further felt his left shoulder joint pain with myalgia on his left upper arm since Jan 2012. Laboratory findings on visit was as follows: CRP 0.38 mg/dl, RF 3 IU/ml, anti-CCP antibody 1.1 U/ml,and ANA <40. Shoulder-joint MRI exhibited erosive changes of the head of his left humerus and thickened enhancement of the synovial membrane. Arthroscopic synovectomy revealed infiltration of lymphocytes and plasma cells and proliferation of capillaries and synovial superficial cells in the resected synovial membrane, which led to the diagnosis of monoarthritis-type rheumatoid arthritis (RA). Despite methotrexate (MTX) administration (12 mg/week) since July 2012,MRI performed on Sept 2012 showed edematous changes in bone marrow of the head of left humerus, suggesting the progression of bone destruction. Therefore, the patient was additionally treated with abatacept (750mg/body). In conclusion, MRI of shoulder joint was clinically useful for the diagnosis of RA in a complicated case with monoarthritis-type RA and PMR.

P3-044

Diachronic X-rays change of the Ankylosing Spondylitis-2 cases report-

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Conflict of interest: None

[Objectives] It is easy to recognize that it is Ankylosing Spondylitis if we can confirm Bamboo Spine in an X-ray. However, this change is not a feature to be seen early in the onset of the Ankylosing Spondylitis. And the diachronic X-rays image change of the Ankylosing Spondylitis is unknown enough. Therefore I want to consider an image change of the Ankylosing Spondylitis through two different cases of the medical history. [Methods] Case repots. [Results] [Case 1] A 56 years old man. His X-rays image change showed Ankylosing Spondylohyperostosis. However, after time more than ten years, it changed to the Bamboo Spine. [Case 2] A 42 years old man. At the first medical examination, I accepted many ankyloses in science views, however X-rays image did not show the abnormal finding. Eight years later, I accepted an enthesophyte to his hip joints. [Conclusion] I understand that the primary diagnosis with the X-rays image is difficult early in the onset of Ankilosing Spondylitis and that it was a disease to have to observe its X-ray change over time carefully.

P3-045

Ultrasound and Power Doppler Evaluation is useful for diagnosis of Psoriatic Arthritis without skin lesion

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Conflict of interest: None

[Background] Psoriatic arthritis (PsA) occur about 10-30% with psoriasis (Pso). It is difficult to be diagnosed that about 15% cases have no skin lesion. We report two PsA cases without skin lesion that was diagnosed by assisted ultrasound and power doppler evaluation. [Case 1] 48 years old woman. The nail deformity and swelling with pain of DIP joint was appeared from two years ago. It was treated as osteoarthritis by other hospital. DIP joint was swelling and there was no skin lesion. Proliferation of synovia with ultrasound and hypervascular with power doppler was showed in DIP joint. [Case 2] 65 years old woman. The swelling with pain of DIP joint was appeared. DIP joint was swelling and there was no skin lesion. Proliferation of synovia with ultrasound and hypervascular with power doppler was showed in DIP joint. The two cases were diagnosed as PsA by clinical features and imaging techniques as X ray and ultrasound. Both cases were treated by methotolexate and the pain and swelling was relief. [Discussion] The importance of early diagnosis and the benefits of early treatment of PsA are being increasingly recognized. But it is difficult to be diagnosed in cases that have no skin lesion. Ultrasound is especially useful for the diagnosis of PsA without skin lesion in such these cases.

P3-046

Chalamydia Pneumoniae-induced reactive arthritis: radiological features and treatment

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Conflict of interest: None

[Objectives] We retrospectively studied 4 cases of Chlamydia Pneumoniae-induced reactive arthritis. [Methods] The patients were 43, 28, 56 and 38 years old. 3 were female and 1 was male. Radiographs and the results of blood tests were studied. [Results] The patients were introduced to our institution 10~60 months after the onset of arthritis. 3 cases tested positive for IgM antibody. One case tested negative for IgM antibody although both IgA and IgG antibodies were positive. One case showed signs of arthritis in 6 joints although 3 cases presented only monoarthritis. The radiographs of 3 cases showed evident sign of bone atrophy. All the cases were successfully treated with oral intake of minocycline. [Conclusion] In undifferentiated arthritis cases, radiological sign of bone atrophy may suggest presence of Chlamydia Pneumoniae-induced reactive arthiritis. Oral itake of minocycline is an effective treatment.

P3-047

An ultrasound study of metatarsophalangeal joints of gouty arthritis

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Conflict of interest: None

[Objectives and Methods] We investigated the characteristics of gouty arthritis using ultrasonography (US). US was performed in 50 male patients who visited our clinic with gouty arthritis of 1st metatarsophalangeal (MTP) joints(1-MTP). On the right and left joints, vertical scanning (dorsal side) and horizontal scanning (lateral side) were performed.We examined synovial fluid collection, synovial thickening, crystal deposition, powered puller (PD) signal, bone erosion and hypoechoic lesions in or around synobium. [Results] Synovial fluid collection that finds acute gout attack was more frequent in dorsal side (40%) than lateral side (8%). Synovial thickening that finds chronic arthritis was more frequent in lateral side (80%) than dorsal side (32%). Hypoechoic lesions were frequent more in lateral side (80%) than dorsal side (10%). Hypoechoic lesions contain the exudate associated with inflammation. Many of lesions were observed around the uric acid crystals with PD signals. This exudate contains a high concentration of uric acid that reflects the serum uric acid level. [Conclusion] We considered that extravascular uric acid readily crystallizes and tophus increases.

P3-048

The profile of musculoskeletal ultrasonography in patients with adult onset Still disease

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Conflict of interest: None

[Objectives] The clinical course of Adult onset Still disease (AOSD) can be divided into three patterns; monophasic pattern, polycyclic pattern, and chronic articular pattern. We examined the profile of musculoskeletal ultrasonography (MSUS) in patients with AOSD. [Methods] Twenty-seven cases of 20 patients with AOSD were enrolled between 2003 and 2012. Laboratory data, physical findings, and medication were collected. Using MSUS, semi-quantitative evaluation by gray scale and power Doppler were performed. [Results] There are 35 patients with AOSD in our department (M/F;10/25). The proportion of clinical course was as about as follows; monophasic 22.2%, polycyclic 55.6%, and chronic articular 22.2%, respectively. On the background of MSUS, 9 cases were male and 11 cases were female.The positive rate of CRP, ferritin, and LDH was 81.0%, 93.3%, and 29.4%, respectively. In MSUS, the positive rate of GS was 34.8% in MCP, 26.2% in PIP, 50.0% in hand, and 20.7% in knee joints respectively. The positive rate of PD was 19.0%, 5.8%, 42.6%, and 22.4%, respectively. [Conclusion] The positive rate of GS was higher than PD in patients with AOSD. PD signals were frequently observed in hand joints and GS positive rate was high in MCP joints.

P3-049

Usefullness of musculoskeletal ultrasonography of haemophilic arthropathy

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Conflict of interest: None

[Objectives] We investigate the usefulness of musculoskeletal ultrasonography (MSUS) of haemophilic arthropathy. [Methods] We evaluated MSUS of 16 haemophilia patients from July 2010 to November 2012. [Results] In all cases of PD grade2 and grade3, the results of pathohistological examination showed vascularization and the synovium demonstrated hypertrophic appearance in arthroscopy.In target joint, PD signal was weak after joint bleeding, but it became strongwith healing of acute haemarthrosis. [Conclusion] MSUS of haemophilic arthropathy were useful in

evaluation of synovitis in target joint, and it could be promising tools.

P3-050

Retrospective Study on the Crown Den Syndrome: The Importance of Bone-conditional Neck CT

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Conflict of interest: None

[Objectives] It may be difficult to make a clinical difference between acute onset of systemic pseudogout (crystal-induced arthritis) and infectious arthritis. In particular, crown dens syndrome (CDS), one type of pseudogout which occurred in cervical vertebrae may have a diagnosis of meningitis early. We presented one case of CDS and conducted a retrospective study about CDS based on medical data in our hospital. [Case] 79 year-old women was hospitalized because of serious pain of whole body. The patients did not have the meningeal sign and had difficulty with cervical rotation. We gave antibiotics, but her symptom and sign did not improve. X-rays showed calcification in knee and wrist, and CT showed calcification around cervical dens. Furthermore, we found CPPD in knee liquid. Under those data, we diagnosed crystal-induced arthritis and CDS. The patient was restored by PSL and NSAIDs immediately. [Retrospective study] Among database in our institution, there were 49 cases of the pseudogout, and four cases of CDS. Also, two cases showed calcification around dens among 12 cases which performed cervical CT. [Conclusion] We should aware CDS in the patients who presented with systemic pain using cervical CT (bone condition) positively.

P3-051

Detection of muscle inflammatory lesions and malignancy by ^{18}F-fluorodeoxyglucose positron emission tomography/computed tomography in a patient with polymyositis associated with thyroid cancer

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Conflict of interest: None

We report a case of polymyositis associated with thyroid cancer. A 43-year-old man was admitted to our hospital complain of progressive proximal muscle weakness that had initiated one month ago. Physical examination revealed mortar weakness at his upper arms and thighs, but cutaneous lesions were not observed. Laboratory investigations indicated elevated C-reactive protein and high levels of creatine kinase (13,823 U/L). Magnetic resonance imaging revealed increased signal intensity on T2* with fat suppression. Muscle biopsy showed muscle degeneration, necrosis, regeneration of muscle fibers, and inflammatory cell infiltration to the endomysium. ^{18}F-fluorodeoxyglucose positron emission tomography/computed tomography (^{18}F-FDG-PET/CT) indicated intense FDG uptake in proximal upper and lower extremities, and the trunk, indicating inflammatory hypermetabolism in the muscles. Furthermore, a high signal of FDG uptake was also observed in the thyroid. Aspiration needle biopsy from the thyroid revealed follicular thyroid cancer from the both lobes. Thus, ^{18}F-FDG-PET/CT is a useful modality for the screening malignancy in patients with inflammatory myopathy. Furthermore, ^{18}F-FDG-PET/CT can be used for screening the area of muscle inflammation and determining the area of muscle biopsy.

P3-052

Baseline HAQ is the biggest factor to determine patients HAQ after RA treatment even treated with T2T strategy protocol

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Conflict of interest: None

Objectives We have investigated what contributes to patients' individual HAQ. Methods RA treatment with T2T protocol started from August 2010. SDAI and HAQ are collected from every patient. Ninety-two patients have referred to our clinic as a new patient until July 2012, and followed up for more than 6 months with more than 5 times. These patients have been picked up. First time HAQ was defined as Baseline HAQ. Patients were classified according to Baseline HAQ. First, Patients were divided for every 0.125 on scale, and average value of their time average HAQ was calculated for each scale. Relationship between baseline HAQ and the average value was evaluated statistically. Second, patients were divided into two groups with more than 0.5 (Group-F) and no more than 0.5 (Group-R). These two groups were compared statistically. Results Baseline HAQ and time average HAQ demonstrated significantly close relationship (R=0.90865). Group-R demonstrated significantly better value than Group-F in average class distribution, average Baseline HAQ, and patients' time average HAQ (<0.01). Conclusions In our results, only Baseline HAQ demonstrated significant factor that influences time average HAQ. Therefore we conclude that Baseline HAQ is the biggest factor that determines HAQ thereafter.

P3-053

Clinical picture of RA patients with negative anti-cyclic citrullinated peptide antibody

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Conflict of interest: None

[Objectives] Anti-cyclic citrullinated peptide (anti-CCP) antibody is a major diagnostic marker and useful as a predictive indicator for prognosis. The objective of this study is to evaluate the clinical picture of anti-CCP-negative RA patients. [Methods] We investigated the 94 patients with negative anti-CCP antibody (N group), who were followed up for over 1 year, using the 179 patients with high-titer of anti-CCP antibody (>3×ULN) as control. RF factor, disease activity (DAS28-CRP and SDAI), contents of medication and operation, and progression of Sharp score of hands and feet were investigated. [Results] In N group, the rate of RF-negative patients was greater than control (71% vs 26%). DAS28-CRP and SDAI were lower in N group (2.12 vs 2.32, 6.54 vs 8.66, respectively). The rates of patients treated with biologics and MTX were lower in N group (7.5% vs 47%, 25% vs 33%, respectively). The rates of patients operated and patients with joint replacements were lower in N group (33% vs 72%, 15% vs 33%, respectively). Progression of Sharp score was significantly slower in N group. The rate of mutilans type RA patients was lower in N group (1% vs 11%). [Conclusion] This study suggests that anti-CCP antibody might be an efficient predictive indicator for RA progression.

P3-054

The effective factors of change score of HAQ

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Conflict of interest: None

[Objective] To analyze the effective factors of change score of Health Assessment Questionnaire (HAQ). [Patients and methods] We evaluated HAQ in 107 patients with RA in both terms from April to October,2009 and from April to November,2011.We classified it in three groups by the change of the HAQ score after the progress for two years.Three groups were excellent group(39 patients), improvement group (47 patients) and deterioration group (21 patients).There were analyzed multiple comparison authorization (Steel-Dwass) for age, contraction of a disease period, Stage, Class, CRP, MMP-3, ESR and operation. [Results] The mean score of HAQ score was 0.55 in 2009 and 0.45 in 2011. Significant differences were found among excellent group and improvement group, excellent group and deterioration group in Stage and Class, excellent group and deterioration group in age, excellent group and improvement group in ESR (2009) and operation. [Conclusion] The effective factors of change score of HAQ were Stage, Class, age and operation. HAQ showed a tendency to keep better when Stage and Class were excellent. There was suggested that HAQ was influenced by aging. There was a possibility that HAQ was improved by an operation.

P3-055

The change of serum rheumatoid factor in patients with rheumatoid arthritis differs with treatment with methotrexate or tumor necrosis factor inhibitors

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Conflict of interest: None

[Objectives] To clarify whether change in serum level of rheumatoid factor (RF) by treatment with methotrexate (MTX) or tumor necrosis factor inhibitors (TNFIs) relate to disease activity of patients with rheumatoid arthritis (RA). [Methods] MTX-naïve MTX-treated or biologics-naïve TNFIs-treated patients with RF-positive RA were enrolled in this study, in whom serum RF and DAS28 was examined before and after treatment. [Results] DAS28 after treatment was significantly decreased in both MTX- and TNFIs-treated patients. 67.1% and 60.7% of MTX- and TNFIs-treated patients showed clinical remission and low disease activity (CR/LDA). Serum level of RF in MTX- and TNFIs-treated patients was decreased from 271.0 to 204.6 and 224.0 to 143.6 (IU/ml),. Reduction rate of serum RF was significantly higher in TNFIs-treated patients than in MTX-treated ones. Serum level of RF was not decreased in MTX-treated patients with moderate to high disease activity (MDA/HDA), but was significantly decreased in those with CR/LDA. On the other hand, serum RF was significantly decreased in TNFIs-treated patients with both MDA/HDA and CR/LDA. [Conclusion] Serum RF reflects RA disease activity in MTX-treated patients, and the change of serum RF in RA patients differs with treatment with MTX or TNFIs.

P3-056

Effect of Adalimumab on MMP-3 and relationship among other parameters: A survey on 121 patients treated with adalimumab (ADA) in our department

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Conflict of interest: None

[Objectives] In this study, the effect of ADA administration on MMP-3 and chronological relation with other parameters at 52 week were investigated. [Methods] 35 out of 121 RA patients who treated with ADA from May 2009 to Oct 2010 in our hospital were investigated. Correlation between MMP-3 changes and post treatment DAS28-CRP,SDAI,CDAI,CRP,SJC and TJC changes were investigated. [Results] MMP-3 decreased at 4week (mean change: -41.1). In <2 year than ≧2 year group, in Naïve than Switch group and in MTX<10 than MTX≧10mg group, this decrease was more significant and maintained up to 52 week. The MMP-3 changes at 52 week was correlated with DAS28-CRP,SDAI,CRP changes, especially, CRP had a correlation at all-time points. The MMP-3 change at 4 week was correlated with SDAI and CRP changes. [Conclusion] ADA decreased MMP-3 at 4 week, very early post-treatment, more remarkable in early RA and bio-naïve patients. There was a correlation with amount of MMP-3 changes and RA disease activity, which was more prominent with CRP changes. At 4 week and after on, MMP-3 changes was correlated with SDAI amount, therefore, it showed MMP-3 could be a predictor factor for disease activity.

P3-057

The effect of Glucocorticoid on Serum MMP-3 in RA Patient with Biologic Treatment

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Conflict of interest: None

Objectives Serum MMP-3 (MMP) is the one of major index of disease activity for rheumatoid arthritis (RA). We have reported that MMP reflects clinical relevance of biologic agent very sensitively. However, MMP is influenced on glucocorticoid (GCC), that raises MMP, so when GCC is administrated, MMP is thought to be less reliable to evaluate. We have evaluated its effects with our patients' data. Methods 105 patients who are treated with biologic agent (BIO) were analyzed. Patients were classified according to GCC administration. These are group with GCC free from start of BIO (free), with GCC administrated at start but discontinued at last (late free), and GCC is administrated throughout treatment (loaded). Baseline, endpoint (EP), and average (AV) MMP, and MMP improvement ratio (MIR) are calculated and evaluated statistically. Relationship between MIR and DA28 improvement (DI) for each group was evaluated with regression analysis. Results In AV, MIR, and EP, MMP is large in loaded, free, and late free order, however, there was no significant difference between any groups. In every group, MIR demonstrated significant close correlation with DI. As same results were given for each kind of BIO. Conclusions MMP reflects disease activity of RA sensitively even GCC is administrated.

P3-058

The Efficacy and Safety of Tacrolims for the Elderly RA Patients

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Conflict of interest: None

[Objectives] There are increasing usage of MTX and biologics for the treatment of RA. However, there are concerns in terms of

the increasing number of infection in the use of these strong medicines to the elderly patients. The purpose of this study was to identify the efficacy and safety of the Tacrolims treatment for the elderly RA patients. [Methods] Twenty nine patients of older than 65 years old were treated with Tacrolims. Seventeen RA patients (Male:Female=5:12) were included in this study with a least follow up period was 12 months. The average age was 69.8 years old, average periods from the onset were 48.3 months. Biologics were used in the 53% of the patients. Steroids were used an average of 2.9mg/day. Average dosage of Tacrolimus was 1.3mg. MTX was used 29% of the patients and average dosage was 4.8mg/week. The disease activity was evaluated by DAS28-ESR(4) and the response of treatment was evaluated by EULAR improvement criteria. [Results] Twelve patients (70%) showed more than moderate response. One patient was worsened the interstitial pneumonia and ceased the Tcrolimus by 4 months. [Conclusion] Tacrolimus treatment for the elderly RA patients yields generally good results.

P3-059

A Study of Additional Combination Therapy with Bucillamine in Patients with Escape Response to Methotrexate

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Conflict of interest: None

[Objectives] We examined the usefulness of additional combination therapy with bucillamine (Bc) in patients with rheumatoid arthritis (RA) showing inadequate response or escape response to methotrexate (MTX). [Methods] Additional combination therapy with Bc was performed in 32 patients with RA (5 males and 27 females; mean age, 60.7 years) showing inadequate response or escape response to MTX, in order to examine the usefulness of the treatment. [Results] Clinical response evaluation in the 32 patients included in the present study was performed with Disease Activity Score 28 (DAS 28). Because 10 out of the 28 patients responding to the treatment later needed an increase in MTX dose, the dose was not changed. The additional combination therapy with Bc had an efficacy rate of 56.3%. The duration of response to the additional combination therapy was 6 months to 4 years & 6 months with a mean period of 2 years & 5 months. [Conclusion] Bc also has a 50-mg formulation, and is a disease-modifying antirheumatic drug (DMARD) less likely to cause serious side effects at low doses and easy to use. Therefore, when MTX treatment is not as effective as expected, the additional combination therapy with Bc is considered to be useful.

P3-060

The reason for unused methotrexate in patients with rheumatoid arthritis

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Conflict of interest: None

[Objectives] To evaluate the prevalence of the patients with rheumatoid arthritis (RA) who cannot use methotrexate (MTX) and the reason for intolerance of MTX. [Methods] Three hundred and fourteen patients with RA (age 67.1±11.9 years, 82.1% female) were recruited from outpatients visiting to department of rheumatology, Tokyo metropolitan Komagome hospital during October 2012. The prevalence and the reason for unused MTX were investigated from their medical records. [Results] One hundred and thirty eight patients (43.9%, age 70.0±11.3 years,76.8% female) did not use MTX. Twenty-two patients (15.9%) had adequate response to other disease modifying anti rheumatic drugs. Eight patients (5.8%) had no effectiveness of MTX. Fifty-nine patients (42.8%) had complications including interstitial lung disease in 20 (33.9%), infections in 16 (27.1%), malignancies in 12 (20.3%), renal dysfunction in 8 (13.6%) and pleural effusion in 3 (5.1%). Thirty-five patients (25.4%) had adverse reactions including cytopenia in 11 (31.4%), lung injury in 7 (20.0%), fever in 3 (8.6%), liver dysfunction in 2 (5.7%), lymphoproliferative disorder in 2, infection in 2 and nausea in 2. [Conclusion] Thirty percent of the patients with RA were not able to use MTX due to their complications and adverse reactions.

P3-061

Treatment of High Dose Methotrexate in Rhumatoid Arthritis

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Conflict of interest: None

Introduction: The objective of this study was to demonstrate clinical outcome of Methotrexate (MTX) at dose over 10mg/week in Rhumatoid Arthritis. **Materials and Methods:** Twenty five patients who had been treated with high dose MTX from April 2011 to May 2012 were the subject of the study. We estimated DAS28CRP,MMPIII,HAQ at last follow up and the adverse event. **Results:** The significant difference that compared with at beginning of treating of dose 10mg/week was noted in DAS28CRP, MMPIII at 4 weeks, 12 weeks, 26 weeks and 52 weeks($P<0.05$). All patients of HAQ at final follow up were less than 0.5.The common adverse events were 4 hepatic dysfunctions and one interstitial pneumonia. **Discussion and Conclusion:** These results suggest that treatment of high dose MTX can be sufficiently effective for RA.

P3-062

Treatment outcomes in patients with rheumatoid arthritis 24 weeks after high-dose methotrexate therapy

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Conflict of interest: None

[Objectives] In February 2011, methotrexate (MTX) use up to 16 mg/week for patients with rheumatoid arthritis (RA) was approved in Japan. In this study, we evaluated the efficacy and safety of high-dose MTX therapy. [Methods] Subjects were 57 patients with RA who received an increased MTX dose of over 10 mg/week at our hospital (12 men, 45 women). We evaluated the treatment efficacy and safety in 57 patients after 24 weeks. [Results] MTX was administered at 16 mg/week in 2 patients, 12 mg/week in 15 patients, and 10 mg/week in 40 patients. Adverse events occurred in seven patients receiving 10 mg/week of MTX, whereas no adverse events occurred in patients receiving 12 mg or 16 mg/week of MTX. [Conclusion] Observed improvements in symptoms with higher doses indicate that MTX up to 16 mg/week is effective. Adverse events occurred in some patients receiving 10 mg/week but not in those receiving 12 mg or 16 mg/week. The occurrence of adverse events does not necessarily increase in a dose-dependent manner; however, use of high-dose MTX requires attention to side effects.

P3-063

The relationship between tacrolimus use and chronic kidney disease in patients with rheumatoid arthritis

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Conflict of interest: None

[Objectives] To determine the efficacy and correlation with chronic kidney disease of tacrolimus in the patients with rheumatoid arthritis. [Methods] We reviewed DAS28, incidence of CKD more than stage 3, decrement of estimated glomerular filtration rate (eGFR) in the patients with RA treated with tacrolimus during one-year follow-up (TAC group). As negative control, the data of patients treated with methotrexate were used (MTX group). [Results] TAC group had significantly lower eGFR and higher prevalence of CKD than MTX group at baseline (62.3 ml/min/1.73m2 vs. 73.91 ml/min/1.73m2, P = 0.013 and 50.0 % vs. 26.2 %, P = 0.057, respectively). After one year, incidence of CKD more than stage 3 and prevalence of CKD was higher in TAC group than MTX group (20.00 % vs. 4.62 %, P = 0.011 and 65.0 % vs. 27.7 %, P = 0.004, respectively). No significant difference was found in DAS28 in both groups at baseline and one year after. [Conclusion] TAC may raise incidence of CKD in the patient with RA.

P3-064

Safety of Iguratimod in patients with severe chronic kidney disease rheumatoid arthritis

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Conflict of interest: None

[Objectives] Iguratimod is new DMARD that was developped in Japan. We evaluate the safety of Iguratimod in patients with chronic kidney disease rheumatoid arthritis(CKD-RA). [Methods] We prescribed Iguratimod 5 patients with CKD-RA. [Results] No patients were observed in worse kidney disease. [Conclusion] Iguratimod may be used in CKD-RA. We need Iguratimod with CKD-RA more experiences.

P3-065

Study of clinical result of the treatment of rheumatoid arthritis patients

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Conflict of interest: None

[Objectives] To evaluate clinical result of the treatment of rheumatoid arthritis patients. [Methods] We retrospectively studied 54 patients with rheumatoid arthritis who were diagnosed at our hospital from April 2010 to March 2012. [Results] Patients' profile was age 63.4±14.4, male 24 (44.4%), female 30 (55.6%), DAS28-CRP 5.31±1.08. First DMARD was MTX 21 (38.9%), BUC 18 (33.3%), SASP 15 (27.8%). 24 patients (44.4%) intake PSL and the average dose of PSL was 7.4mg/day. At the point of final evaluation, DAS28-CRP decreased to 2.27±1.03. The continuation rate of MTX, BUC and SASP was 95.2%, 72.2% and 60.0%. 19 patients (35.2%) intake PSL and the average dose of PSL was 3.9mg/day at the point of final evaluation. We introduced 24 patients (44.4%) to the doctor who introduced us before, 13 patients to a specialist for rheumatoid arthritis, and 7 patients to a doctor who was not a specialist. The mean treatment period at our hospital was 9.1±7.4 months. [Conclusion] DAS28-CRP was improved from 5.31 to 2.27 significantly. We introduced 80% or more of the rheumatoid arthritis patient who received treatment at our hospital to the local doctor, keenly realized that the cooperation with the local doctor was important.

P3-066

A case of MRA with refractory skin ulcers effectively treated with azathioprine and rituximab

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Conflict of interest: None

A 58-year-old woman was diagnosed as RA in 1977. Skin ulcers in lower extremities first occurred in 2000 and they were controlled with 6mg/week of methotrexate and 3mg/day of prednisolone (PSL). She presented with worsening skin ulcers to our hospital in July 2010. Skin biopsy was performed and it revealed the existence of vasculitis. Infliximab was started in August 2010, but it had an insufficient efficacy. As the ulcers worsened further, PSL was increased to 20mg/day and dermatoplasty was performed. They improved temporary but relapsed as the dose of PSL was tapered to 16mg/day, so we increased it to 20mg/day and conducted dermatoplasty again, however, the ulcer was complicated with infection and the skin graft hardly survived. Mizoribine and etanercept were started respectively, but neither had a sufficient efficacy. Therefore we started azathioprine with 30mg/day of PSL, which could be reduced to 15mg/day, and it successfully controlled skin ulcers. In August 2012, diffuse large B cell lymphoma was diagnosed, and administration of AZP was discontinued as R-CHOP regimen was started. During the courses of R-CHOP, ulcers are controlled successfully with 5mg/day of PSL. It is suggested that azathioprine or rituximab might be alternative therapy to TNF-α inhibitor for MRA.

P3-067

A case of rheumatoid arthritis (RA) diagnosed as non-Hodgkin's lymphoma (NHL) based on pathological findings of ileal perforation after complaint of acute abdomen in outpatient visit to hospital

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Conflict of interest: None

[Case] 64 y.o. female. [Chief complaint] Acute abdominal pain. [Present illness] RA onset at 48 y.o. Joint damage was observed to progress gradually as the patient showed multiple drug resistance to DMARDs. While MTX 6mg/w and PSL 9mg/d generally maintained low disease activity, stomach pain appeared in early June 2012. When upper endoscopy was performed on June 28, a giant ulcer was observed around the anterior wall of the pylorus, so the dose of PPI was raised. At night on July 1, a sharp pain suddenly appeared throughout the abdomen. The next morning she was taken by ambulance to hospital for examination and free air was found on a CT scan. She was diagnosed with acute abdomen due to digestive tract perforation, and rushed to the J University hospital for emergency surgery. Laparotomy showed 2 perforation sites

at not gastric ulcer but the ileum, she was aggressively-treated for endotoxin shock due to sepsis after surgery and recovered. Pathological findings of NHL based on that sites were reported a few days later. [Discussion] ML is known to occur in RA patients taking MTX and perforations can arise from chemotherapy given to fight digestive tract ML. In this case, NHL was found to arise from spontaneous rupturing before treatment. We are reporting this rare, valuable case.

P3-068

Clinical results and disease activity of Golimumab after therapeutic trial

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Conflict of interest: None

[Objectives] We performed mono therapy (Go-Mono study) of Golimumab (GLM) and combination of MTX (Go-Forth study). Total 12 cases (female 9 and male 3 cases) were evaluated about change of clinical results and disease activity after therapeutic trial. [Methods] The average age was 55.6 years and disease duration was 5 years at start of therapeutic trial. Trial duration was 2.5 years and GLM was stopped. 7 cases used GLM 100mg and 5 cases used 50mg at end of trial. Clinical results were evaluated by DAS28, SDAI, and mHAQ. We divided maintained DAS28<3.2 (LDA) and DAS28≧3.2 (non-LDA) group and compared each. [Results] The average follow up was 1.44 years. DAS28 was elevated from 2.87 to 3.35 after 1 year. SDAI and mHAQ showed same results. There were no difference between GLM 100 and 50mg. Restart of biological agents was 4 cases (33%) and all were decrease disease activity. Baseline DAS28 of LDA group was significantly less than that of non-LDA group (2.19 vs 3.09, P=0.046). DAS28 after 12 weeks showed same results. About MTX dosage, LDA group was higher than non-LDA group. [Conclusion] After 1 year stopped GLM, patients maintained LDA showed that baseline DAS28 was low and deep remission, and have kept remission during 12 weeks. These cases are able to keep LDA after stopped GLM.

P3-069

Analyzing of discontinuation of infliximab with clinical remission in rheumatoid arthritis patient

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Conflict of interest: None

Objective: To assess the clinical characteristics of rheumatoid arthritis (RA) patients treated with infliximab (IFX) and achieved clinical remission. Methods: Efficacy was evaluated by DAS28. Results: 55 (8 men, 47 women) of RA patients were treated with IFX and enrolled in this study. Overall remission rate was 52.3%. There were 15 patients (27.2% in whole patients, 51.7% of patients achieved to remission) had achieved discontinuation of infliximab. There were no significant differences in combination therapy with or without MTX, duration of disease before using IFX and initial DAS28 score between RA with discontinuation of IFX with remission and continuation of IFX with remission. DAS28 score was the only marker for the discontinuation of IFX with clinical remission (1.30 vs. 2.54, p=0.016). All patient achieved to discontinuation of infliximab with clinical remission fulfill Boolean remission criteria. Conclusions: Very low score of DAS28 or fulfilling Boolean remission criteria is the marker to achieve discontinuation of IFX with clinical remission.

P3-070

Course of rheumatoid arthritis patients who discontinued biological therapy

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Conflict of interest: None

[Objectives] To investigate the course of rheumatoid arthritis patients who discontinued biological therapy. [Methods] Investigations were duration until discontinued biologics, DAS28CRP at discontinuation the reason of discontinuing biologics and treatment after discontinuation. [Results] The patients who discontinued biological treatment for any reason were 17 cases. DAS28CRP before biological treatment was 5.17. Administration of biologics was etanercept in 10 cases, infliximab 4, tocilizumab 2 and adalimumab one. The duration until discontinued biologics were 21.6 months, DAS28CRP at discontinuation was 4.06. The reason of discontinuing biologics were side effects, including adverse event occurrence can not be denied 10 cases, economic reasons 4 cases and pregnancy 3 cases. After discontinuation, 11 patients increased disease activity of RA. They have required additional medication, increase of methotrexate, prednisolone or addition of tacrolimus. There were two cases who underwent artificial joint surgery and eventually re-administrated biological treatment. [Conclusion] In summary, after discontinuation of the biologics, 64% of the patients increased disease activity and additional medication were necessary.

P3-071

Induction of remission by early administration of methotrexate and adalimumab (ADA), allowing discontinuation of ADA, in a patient with early rheumatoid arthritis: comparison with other patients receiving ADA treatment at our hospital

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Conflict of interest: None

[Patient] A 50-year-old woman. [Present illness] The patient experienced small joint swelling in both hands around March 200X. She developed joint pain in the right hand in February 200X, the rheumatoid factor test was positive, and rheumatoid arthritis (RA) was suspected. In August 200X, she was referred to us with swelling of both the elbows and knees. At presentation, RA was diagnosed, as she fulfilled 6 out of the 7 items of the 1987 ACR criteria. Methotrexate (MTX) therapy was started, at DAS28 (ESR) 6.83. After week 26, the clinical findings were TJC 0, SJC 2, ESR 88, VAS 13, and DAS28 (ESR) 3.71. The MTX dose was then increased to 10 mg/week, and ADA therapy was initiated. At week 42, further improvement of the symptoms was noted, with TJC 0, SJC 1, ESR 34, VAS 0, and DAS28 (ESR) 2.75. Subsequently, the disease was well controlled, and at week 85, the dosing interval of ADA was extended, and at week 125, the drug was discontinued. As of week 162, continuation of MTX 8 mg/week alone has allowed remission to be maintained, with TJC 0, SJC 0,

ESR 26, VAS 0, and DAS28 (ESR) 2.28. [Discussion] We report a patient with early RA, in whom remission was achieved with a combination of MTX and ADA, and maintained even after ADA discontinuation, along with our experience using ADA.

P3-072

On demand injection with maintenance low dose etanercept in patients with rheumatoid arthritis

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Conflict of interest: None

[Objectives] Etanercept (ETN) is very effective in rheumatoid arthritis (RA). It is expensive, and is might not be neccesary to 50mg/week full dose in RA. We evaluate that on demand 25mg ETN injection with 25mg maintenance/week in moderate RA. [Methods] We prospectively treat 12 RA patient(moderate activity, >24 weeks) this therapy. We compare disasease activity from baseline to 24week. [Results] All patients were not changed disease activity from baseline to 24 weeks. Average amount on demand 25mg injection is 0.43/week. [Conclusion] If you have moderate activity RA patients with ETN 50mg, you might give it a try to reduce ETN with on demand ETN 25mg injection.

P3-073

A Case of Rheumatoid Arthritis (RA) with Remission after Methotrexate (MTX) and Etanercept (ETN) Dosing, Followed by Relapse and Subsequent Remission with Re-Treatment with ETN

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Conflict of interest: None

A 34-yo woman w/ left toe arthritis Aug2003; polyarthritis Mar2004; upon RA diagnosis MTX up to 10mg/w was given. Apr2005 ETN50mg/w started due to insufficient improvement (DAS28ESR 4.56); clinical remission(DAS 2.21) was obtained Oct2005 being on 6 mos ETN. Doses reduced to ETN25mg/w and MTX7.5mg/w. After this sustained remission ETN was discontinued Mar2009 and MTX7.5mg/w continued for remission maintenance. About 1yr later, Apr2010 polyarthralgia relapsed(TJC 5; SJC 7; DAS 4.72), MTX increased to 10mg/w. DAS reduced to 3.76 but no remission. Jul2010 ETN50mg/w resumed, resulting remission(DAS 1.52) in Sep. In May2012, MTX was stopped wishing to conceive & ETN + SASP 1g/day started. Under sustained remission she discontinued ETN + SASP due to pregnancy in Sep. Hands/foot X-ray images at follow-up showed no significant bone destruction progression. **Results/Discussion:** Clinical remission sustained about 1yr only w/ MTX7.5mg/w after ETN discontinuation. Re-treatment w/ ETN50mg/w after relapse resulted remission again 2 mos later. ETN resumed after 17-mo Bio-free period with sustained remission w/out side effects. No neutralizing antibody production with ETN has been reported, suggesting its low immunogenicity; this may have allowed re-treatment and good effectiveness/safety profiles.

P3-074

Assessment of patients who underwent infliximab (IFX) administration time reduction

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Conflict of interest: None

[Objectives] IFX admin. time reduction was approved in Apr. 2012. The admin. time has been reduced at various institutions, and there have since been reports about admin. status, adverse effects, etc. This report is about assessment of adverse reaction frequency, clinical efficacy, and drug survival rate, in RA patients with reduced admin. times, and also dose- escalated patients, at our department. [Methods] Since Nov. 2003, admin. times have been reduced with 29 of 51 IFX-treated patients. Background factors, adverse reactions, clinical efficacy, and drug survival rates were compared between Groups A (n = 29) and B (n = 22), which did and did not undergo admin. time reduction, respectively. [Results] Adverse reactions with the following patient numbers were found in Group A: numbness in hand : 1; dizziness: 1; dyspnea: 1; increased blood pressure: 2. In all cases, admin. could be continued by means of admin. time increase, and in some cases repeated admin. time reduction was possible. In Group B, skin flushing and dyspnea each occurred with 1 patient, followed by admin. discontinuation. [Conclusion] Admin.-time reactions sometimes occur with admin. time reduction. However, these are not serious, and admin. time reduction can probably be made safe by careful monitoring.

P3-075

12cases of Rheumatoid arthritis treated by 10mg/kg of infliximab

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Conflict of interest: None

[Background] There is little analysis in Japan about Infliximab (IFX)10 mg/kg. We report the effectiveness, safety of IFX10mg/kg and the relations to human anti-chimeric antibody (HACA). [Methods] We retrospectively analyzed 12 cases that were increased by IFX10mg/kg in our hospital from July, 2011 to August, 2012. [Results] Men:female was 3:9, mean age was 42.3, mean disease duration was 90.5 months at the time of increasing IFX, Stage II:4cases, III:5, IV:3, and Class2:8cases, Class3:4. Mean DAS28CRP was 3.78 before increasing IFX, 3.30 two months after increasing, and 2.68 six months after increasing respectively. The continuation rate was 80% at the time of 6 months. Two cases couldn't continue because one case was by the effect insufficiency, the other was by the side effect. We measured HACA in 7 cases and 3 cases were positive. All HACA-positive cases experienced infusion reaction in the past. At six months after increasing, two cases fell off in five cases that carried out aggressive increasing IFX from 3 mg/kg to 10 mg/kg. 5 switching cases could continue IFX10 mg/kg. [Conclusion] We should adopt a concept of T2T about aggressive increase in the dosage of IFX, and prospectively analyze the effectiveness and safety of IFX10mg/kg and the relations to HACA.

P3-076

Change of the concomitant drug in a RA patient using biological drug and evaluation according to weight of etanercept

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Conflict of interest: None

[Objectives] we investigated change of the concomitant drug in patients of rheumatoid arthritis (RA). Furthermore, we evaluated the effect according to weight of Etanercept (ETN). **[Methods]** We was investigated the concomitant drug of 199 RA patients using biological drug ; 67 patients of ETN, 31 patients of adalimumab (ADA), 28 patients of Tocilizumab (TCZ), 60 patients of infliximab (IFX) and 13 patients of Abatacept (ABT) in JA Shizuoka kousei hospital for two years (however, ABT was carried out one year). As a curative effect according to weight, 22 patients were evaluated with s the high weight group and the low weight group. **[Results]**The amount of MTX was increased with 0.7 mg (9.9%) by IFX, 0.2 mg (2.5%) by ADA, and was reduced 0.1 mg (2.2%) by ETN, 1.1 mg (25.6%) by TCZ and 0.7-mg (9.9%) by ABT in two years. The amount PSL was reduced 2.6 mg (81.3%) by ETN, 1.1mg (78.6%) by ADA, 1.6 mg (84.2%) byTCZ, 1.4 mg (70%) by IFX and ABT 1.4 mg (82.4%) in 2 years. As a curative effect according to weight, PSL was reduced 0.5-mg (16.9%) by the high weight group, it was reduced 2.0mg (67.6%) by the low weight group, and a significant difference was seen. The difference was not seen between MTX, CRP, the number of tender joint counts, the number of swollen joint counts, DAS-28CRP.

P3-077

The influence of the reduced infusion time of Infliximab on patient satisfaction and efficacy

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Conflict of interest: None

[Objectives] Infliximab is one of the most important drugs in rheumatoid arthritis treatment. Since average of two hours was necessary for the administration, patients needed to stay longer at the clinic than the other drugs that can be administered in about an hour, but reduction of Infliximab's infusion time has been approved since April, 2012. Our clinic specializes on rheumatoid arthritis treatment and frequently uses biological drugs, and we have been reducing the infusion time of patients who have been stable with their administrations to 90 minutes and to 60 minutes. Here, we report the influences of reduced infusion time on patient satisfaction through patient surveys and on drug efficacy by clinical data. [Methods] Patient survey [Results] Patients' satisfaction improved, whereas efficacy was maintained. [Conclusion] Even though the patients feel anxious before reducing the infusion time, the advantage of improvement in patient satisfaction by the time reduction is very big, and it was shown that the anxiety disappeared if there was no reduction in efficacy nor adverse event. No efficacy reduction or new adverse event was recognized. It is necessary to explain in advance about the results and remove anxiety, and then provide anxiety-free treatment.

P3-078

Effectiveness of etanercept in our patients, classified by dose, mono or concomitant with DMARDs in evaluable 45 RApts

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Conflict of interest: None

Objective: Etanercept (ETN) treatment may vary from low dose to 50 mg QW, mono therapy and concomitant with DMARDs.We report our retrospective study of ETN effectiveness from the above-mentioned viewpoint. Methods: Effectiveness by dose, mono or concomitant with DMARDs in evaluable 45 RApts on ETN for ≥3 months since Feb/2010; 11 men and 34 women (mean age 56.5 yrs; disease duration 8.2 yrs). Results: DAS28 w/ 25 mg Q2W, QW and 50 mg QW was 3.68, 4.03, 3.37 at baseline and 2.40, 2.77, 2.73 at month 12, respectively. HAQ was 0.73, 1.10, 0.61 at baseline and 0.49, 0.81, 0.30 at month 12. Both showed improving tendencies. In the other side DAS28 single therapy was 3.45, 2.64, at baseline and 3.80, 2.61, at month 12, respectively. Both DAS28 showed improving tendencies. As a background there are many low dose pts.Discssion:Compared to single therapy, concomitant with DMARDs similarly improved effectiveness but using ETN fully lead to low desease activity.

P3-079

Rheumatoid arthritis patient showing excellent response to 100mg golimumab after resistance to 4 prior biologic agents: A case report

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Conflict of interest: None

Case: A female rheumatoid arthritis patient, age 45 with multiple and continuous elapses of allergic urticaria since 1999. Background: In 2005, patient underwent treatment with prednisone (PSL) due to exacerbation of urticaria accompanied by phalangeal joint pain. Symptoms faded and PSL was gradually decreased. In 2009, patient was diagnosed with RA and started methotrexate. At the initial visit, patient was at Steinbrocker stage 2, with major joint-swelling pain, enhanced inflammatory response, and inflammatory signs confirmed by ultrasonic imaging. In 2010, patient started infliximab which was insufficient, switching to etanercept, to adalimumab, and finally abatacept in 2011, and when it failed to respond, it was switched to golimumab in 2012. The first administered dose was 50mg, but when the effect looked dubious after a month, it was increased to 100mg. Within a month, the patient's joint-swelling pain was decreased by half, and blood-tests showed improvement in inflammatory response. It has been 9 months, and there are no swelling or tender joints, and ultrasonic readings have shown a marked decrease in inflammatory signs. Conclusion: In this RA patient, showing resistance to multiple biologics, the optimized treatment of 100mg golimumab proved to be a beneficial choice.

P3-080

Three cases of rheumatoid arthritis patients whose treatment was switched from etanercept to adalimumab achieved good clinical outcome taking concomitant high-dose MTX

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Conflict of interest: None

We report the effective cases with switching from etanercept (ETN) to adalimumab (ADA) plus high dose MTX. Case 1; 30 yrs male had a clinical diagnosis RA in 2003 and started MTX from Sep 2004. Infliximab was switched to ETN due to an allergic reaction in July 2005. Then, ADA was administrated patient with sec-

ondary loss of efficacy from ETN in Mar 2009. Two month after administration with ADA taking concomitant 8mg/wk MTX achieved clinical remission (DAS28-ESR1.6). Because of the secondary failure with ADA, 80mg/eow ADA was administrated and patient got infectious enteritis in Dec 2010. Finally, 40mg/eow ADA plus 16mg/wk MTX restored clinical remission (DAS28-ESR1.9). Case2; 43 yrs male with RA started MTX from Feb 2008, and ETN was added on from Dec 2009 combined together with 16mg/wk MTX. Because of secondary invalidity, ETN was changed to ADA in May 2012 and LDA was achieved. Case3; 39 yrs male with RA who started ETN with the concomitant use of 16mg / week MTX showed primary non-response. ADA started and resulted in prompt clinical response. Discussion; Three cases changed our previous impression about poor clinical response of ADA after ETN failure. These observations indicated the potent clinical effect of ADA in ETN failure patient who is acceptable high-dose MTX.

P3-081

Study of the cases inadequate response in biologics

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Conflict of interest: None

12 patients(15%) in the administration of biological products out of 80 patients with rheumatoid arthritis the agency determines that insufficient effect in this study, we investigated the three cases that we switch to other drugs. Administration of infliximab,it is determined that insufficient effect after bulking addition,two patients who switch to tocilizumab had a good response both. Order to switch to etanercept, tocilizumab, abatacept, golimumab and, after increased to 100mg from 50mg to golimumab,I experienced an example of one that has become a trend intractable remission. Switch of biological products, which is a valid choice to match increased MTX, with changes and additions to other DMARDs, switch to tocilizumab,and increase switch to golimumab is also an effective method in cases of inadequate response I thought to be.

P3-082

Treatment continuation of rheumatoid arthritis patients with four biological agents

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Conflict of interest: None

[Objectives] The objective of this study is to compare the treatment continuation rate of rheumatoid arthritis (RA) patients. [Methods] Comparison is using a log-rank test between Sep. 2003 and Dec. 2011. [Results] A total of 457 RA patients started treatment with biological agents: 130 with infliximab (IFX), 245 with etanercept (ETN), 41 with tocilizumab (TCZ), 41 with adalimumab (ADA). The continuation rate of treatment after one and three years, respectively, was 67.5% and 43.1% for IFX, was 87.5% and 72.7% for ETN, was 68.1% and 52.6% for TCZ and was 73.3% and 66.7% for ADA. Patients treated with ETN were more likely to continue treatment than IFX and TCZ patients. Discontinuation was due to adverse events in 59%(IFX), 59%(ETN), 40%(TCZ), 40%(ADA) of the cases. [Discussion] Despite the relatively high rate of adverse events in IFX and ETN patients, ETN is considered most suitable among the four biological agents because of its high continuation rate.

P3-083

Survey of the Status of Use of Biological Preparations to Treat Rheumatoid Arthritis Patients in our Institution(third 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. [Subjects] Biological preparations were used to treat 121 cases, and consisted of Infliximab (INF) in 63, Etanercept (ETN) in 57, Tocilizumab (TCZ) in 34, Adalimumab (ADA) in 15, Abatacept (ABA) in 6, and Golimumab (GOL) in 11 cases. [Results] Treatment was discontinued in 9 INF cases, 19 ETN, 4 TCZ, 4 ADA, 1 ABA. Treatment was switched to another drug in 30 INF cases, 17 ETN, 8 TCZ, and 7 ADA, 1 ABA, and 2 GOL. Cases in which more than one drug was used because of attenuated or inadequate efficacy or adverse events consisted of 3 cases in which 4 drugs were used, 11 cases in which 3 drugs were used, and 33 cases in which 2 drugs were used. The longest periods of use were: INF, 8 yr 6 mo; ETN, 7 yr 3 mo; TCZ, 4 yr 1 mo; ADA, 3 yr 11 mo. Administration was discontinued because of infection in 12 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.

P3-084

Evaluation of efficacy of Adalimumab (ADA) with high dose MTX inadequate rheumatoid arthritis (RA) patients for 104 weeks

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Conflict of interest: None

[Purpose]We investigated efficacy and drug survival rate of ADA+MTX low dose (<6 mg) combination for the RA patient for 104 weeks. **[Methods]**Total 61 patients were subjected for our analysis and 29 patients were able to be analyzed efficacy using DAS28-ESR and drug survival rate for 104 weeks by LOCF method. **[Results]**The mean of DAS28 (ESR) was significantly improved from 4.61 to 2.92, and 40.7% of patients achieved remission for 104 weeks. MTX mean dose of 17 patients who continued 104 weeks ADA treatment was 5.0±2.0mg. This result indicated that even low dose MTX administration showed long drug survival and two patients discontinued ADA treatment (MTX dose 6mg for 52 weeks and 4mg for 104 weeks respectively). There was significant difference between long term and short term drug survival rate in TJC and SJC improvement. **[Conclusion]**It has been shown that adalimumab shows good efficacy concomitant with high dose MTX. We've shown that adalimumab 80mg monotherapy and adalimumab 40mg with low dose MTX (less than 6mg) show good

efficacy and well tolerability with high dose MTX inadequate RA patients.

P3-085

Efficacy of intravenous injection of high dose steroid for patients with rheumatoid arthritis (RA) who show reduced response to adalimumab (ADA)

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Conflict of interest: None

[Objectives] We report RA patients who restored lower disease activity by high dose steroid after showing reduced response to ADA. [Methods] We investigated 5 RA patients for one year after administration of high dose steroid because of the worsen of the disease condition after ADA treatment.When disease activity got worse,PSL 50mg was injected intravenously.All were female.Average age was 62.6,and disease duration was 12.6 years.MTX and TAC were used for 3 and 2 patients respectively.ADA was the first biological drug for 3 patients.We investigated CRP,ESR,MMP-3,DAS28-CRP,mHAQ,adverse events and continuation rate of ADA. [Results] At start of high dose PSL,and six months after administration of high dose PSL and at final observation,average CRP was 4.10,0.69,0.20,ESR was 75.6,40.4,26,4,MMP-3 was 317,188,189,DAS28-CRP was 5.10,2.13,1.76,and mHAQ was 0.98,0.5,0.5 respectively.4 patients maintained remission at final observation.There was no patient with adverse event and withdrawal of ADA. [Conclusion] It has been suggested that high dose steroid is one of effective therapies for the RA patients who show reduced response to ADA.We suppose that intravenous injection of high dose steroid hold down disease activity temporarily or controll the production of AAA,and recover the effect of ADA.

P3-086

Safety and patient's assessment on rapid infusion of infliximab

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Conflict of interest: None

[Objectives] We have changed administration rate of infliximab from infusion with gradually increasing rate (max 160ml/h) to rapid infusion with constant rate (250ml/h), shortening infusion time. Purpose of this study is to examine safety of the rapid infusion and patient assessment, particularly on satisfaction, on the new protocol. [Methods] This study enrolled 47 patients (RA;22, Crohn's disease 16, Behcets disease who experienced both previous and new methods of infusion. These patients received questionnaire survey on the infusion. [Results] One patients complained headache after rapid infusion, and the others received the infusion without adverse effects. Most patients (87%) were satisfied with rapid infusion. However, patients wish for the infusion were efficacy (82%), and safety (72%), and only 34% of the patients desire shortening of infusion time. [Conclusion] Rapid infusion of infliximab is safe and satisfying patients. However, patients' desires are efficacy and safety of treatment rather than time-saving.

P3-087

Safety and Patient satisfaction of shortened infliximab infusion time in an outpatient clinic of rheumatology

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Conflict of interest: None

[Objectives] Shortened IFX infusion time was approved in April 2012 in Japan. Safety and pt satisfaction was evaluated. [Methods] The IFX infusion time was selected referring to a pre-calculated table for highest speed within 5 mg/kg/hr by every 0.5 mg/kg of IFX. Less than 500 mg of IFX was dissolved in 100 ml of saline whereas 500mg or more was in 250 ml. To avoid volume overload, speed was restricted to 200 ml/hr. Adverse event and questionnaire regarding pt satisfaction were analyzed. [Results] Fifteen pts (14 of RA and one Behcet's disease) met the criteria for shortened infusion in Japan among 19 pts who had been treated with IFX. IFX had been administered for 2 hrs. A number of shortened infusion totaling 42 were performed. Infusion times ranging from 37 min at min to 80 min at max (median: 60 min). Slightly itchy papules appeared on the chest and the back of a RA pt after 3 hrs of infusion and spontaneously disappeared in 3 days. Shortened IFX infusion could be continued in all pts. In the questionnaire, 10 pts chose 'very good', 5 pts chose 'good' and no one chose 'bad' or 'no difference'. [Conclusion] Shortened IFX infusion demonstrated that not only it is safe but also very satisfactory to patients when applied efficiently in the outpatient clinic of rheumatology.

P3-088

The shortening infusion time of Infliximab for rheumatoid arthritis

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Conflict of interest: None

[Objectives] Evaluation of shortening Infliximab (IFX) infusion time for rheumatoid arthritis [Methods] Six individuals who matched our criteia: less than 5mg/kg dosage, no infusion reaction history and more than three times medicated, were procedured shortening IFX infusion time under informed consent. All patients were taken pre-medication. According to our clinical path, body temperature, blood pressure, heart rate and SpO2 were observed every 15 minutes during procedure. [Results] No adversed effect was observed such as infusion reaction. Mean of infusin time was shorten approximately one hour. This shortening time reduced the burden of patients and increased the capacity of our facilities. [Conclusion] So far no adverce events was found under our criteria. This result was suspected due to our proper critreria.

P3-089

Efficacy of golimumab in biologic-naïve patients and switcher with rheumatoid arthritis on TBC registry

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Conflict of interest: None

[Objectives] To assess GLM therapy in biologic-naïve patients and switchers with rheumatoid arthritis [Methods] On our biological study group (TBC), there were 39 cases which were enrolled to have been given GLM and passed 24 weeks after first GLM treatment in all registration cases. We assessed these 39 cases. [Results] There were 19 biologic-naïve patients and 20 switchers. With regard to dosage of GLM, the proportion of patients treated with 50mg in naïve group was 84%(n=16) and significantly more than that in switching (45%(n=9)). At week 24 as an endpoint, drug retention rate in naïve group and in switching were 74% and 65%. There was no significant difference of retention rate between two groups. Baseline data of MTX concomitant rate in naïve group was 95% and significantly more than that in switching (65%).From baseline to week 24, DAS28-ESR in naïve group significantly improved from 5.22 to 3.35, but DAS28-ESR in switching didn't improve. [Conclusion] Improvement of DAS-28-ESR was better in naïve group, but there was no significant difference of drug retention rate between naïve and switching group. In switching group there were more cases treated with 100mg of GLM. That may influence retention rate.

P3-090

Predictive marker for the remission treated with adalimumab in rheumatoid arthritis

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Conflict of interest: None

Objective: To assess the clinical characteristics of rheumatoid arthritis (RA) patients treated with adalimumab (ADA) and achieved clinical remission. Methods: Efficacy was evaluated by DAS28. Results: 24 (5 men, 19 women, average age 52.1 years old) of RA patients were treated with ADA and enrolled in this study. Overall remission rate was 54.1% (average observation period 27.4 weeks). There were no significant differences in the dose of MTX, duration of disease before using ADA and initial CDAI score between RA with remission and without remission. Patient who initially treated with ETN had good response to ADA (73.3%), however no patients achieved to remission treated with both TNF-blocker and TCZ before (p=0.0089). Results: This suggest that ADA is useful for the RA patients, especially failed to ETN therapy.

P3-091

Safety and efficacty of adalimumab and xylocaine mixed injection

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Conflict of interest: None

[Background] Adalimumab (ADA) is effective in patients with rheumatoid arthritis (RA). Some patients feel pain when injection. We evaluate that safety and efficacy of concomitant ADA plus xylocaine. [Methods] We evaluate 62 concomitant injections(ADA plus xylocaine). [Results] No patient has side effects due to this injections. [Conclusion] We recommend that ADA plus xylocaine injections is safty.

P3-092

An Investigation about Biological Switch from Etanercept to Adalimumab in Our Hospital

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Hashima City Hospital

Conflict of interest: None

[Objectives] The definition of treatment for rheumatoid arthritis is treatment goal according to T2T, which is achieving remission. According to the results in patients treated with Etanercept (ETN) who could not achieve remission, we decided to switch a part of these patients to Adalimumab (ADA) and investigated the results. [Methods] We assessed 11 patients who treated with ETN but could not achieve remission and treatment switched to ADA, from September 2009 to September 2011 in our hospital, retrospectively. For missing value, last observation carried forward (LOCF) method applied. [Results] Before ADA administration, MTX combination therapy rate was 63.6% and the average MTX dose was 8.29 mg/week. Before ADA administration, average DAS28 (CRP) was 3.42 which changed to 2.77 (at the end of observation), remission rate was 36.4% (and 54.5% if considered LDA, too), both SDAI and CDAI remission rates were 18.2, and retention rate was 72.7% (average observation period was 15.5 months), respectively. [Conclusion] Both CRP and DAS28-CRP increased 8 weeks prior to ADA administration. If switch to ADA was performed before DAS28-CRP and CRP increased, treatment results after ADA administration would be better. Due to small population of this study, future investigation is needed.

P3-093

Study on Rheumatoid Arthritis Patients That Changed Biologicals at Our Outpatient Clinic

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Conflict of interest: None

[Objectives] In daily clinical practice, treatment failure or adverse events (AEs) often force patients to change biologicals. We examined the current state of biological switching in order to establish the appropriate switching at outpatient clinic. [Methods] Patients that changed biologicals for any reasons at our outpatient clinic were retrospectively analyzed. [Results] A total of 80 rheumatoid arthritis (RA) patients started biological therapies between Dec. 2006 and Jun. 2012, of whom 15 changed their drugs; once in 10 patients, twice in 1 patient, thrice in 3 patients and 4 times in 1 patient due to first- and second-line treatment failures in 4 patients each, AEs in 4 patients and others in 3 patients. After switching, most of patients achieved remission or low disease activity. [Conclusion] In many patients who were unable to continue 1st TNF inhibitor due to treatment failure or AEs, switching to 2nd or later TNF inhibitors or other biologicals was effective. At outpatient clinics, active switching should also be considered as part of a treatment strategy under the concept of T2T. For this purpose, it is important to establish a local RA care system including clinic-clinic network taking advantage of individual expertise, and hospital-clinic network as backup for cases of AEs.

P3-094

Questionnaire-based investigation of infusion time reduction (ITR) in rheumatoid arthritis patients administered infliximab (IFX)

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Conflict of interest: None

[Objectives] IFX infusion took ≥2 hr, burdening patients, but infusion time reduction (ITR) was approved in May 2012. ITR importance was investigated with a questionnaire on 1-hr infusion, with 16 consenting patients without previous infusion reactions (IR). [Methods] By questionnaire, 10 questions were asked about (a) pre- to post-ITR change in in-hospital time; (b) reduced burden due to ITR, use of resulting free time; (c) lifestyle. [Results] With ITR, in-hospital time fell from 5.6 to 3.5 hr, and all parties' burdens decreased. The post-ITR IR rate was 0%. 7 of 16 ITR patients were taken to and from hospital by family, etc. [Conclusion] IFX was the first biologic approved in Japan, and much evidence shows its superiority to other agents, but its chimeric-antibody structure results in IR, anti-IFX antibodies, secondary inefficacy, etc., and thus low long-term admin. continuation rate. These problems are known in relation to MTX and IFX dose increase, and IFX ITR, so responses are possible, but ≥2 hr infusion burdens patients' families, and health-care personnel, as well as patients. This survey showed that ITR was safe, with high patient satisfaction. IFX ITR has benefits such as high anti-inflammatory activity, and rapid action, and facilitates first-line use of TNF-inhibitors.

P3-095

Long-term retention rate of treatment with infliximab in rheumatoid arthritis patients: results from the multi-center TBC registry

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Conflict of interest: None

[Objectives] Concomitant MTX treatment is mandated in treatment with infliximab (IFX) in rheumatoid arthritis (RA). Specifically after high-dose MTX (~16mg/week) was approved, we have been tended to use IFX only in the patients with very sufficient concomitant MTX. However, there have been no data to show the dose-dependent relationship between long-term IFX retention rate and MTX. [Methods] We retrospectively reviewed the clinical data of 440 RA patients treated with IFX in the TBC registry. We compared the IFX retention rate (Kaplan-Meier method) between following two groups divided according to weekly dose of MTX; Low dose (LD, less than 6mg) and Standard dose group (SD, more than 8mg). [Results] Mean weekly dose of MTX was 5.5 mg in LD group (n=180) and 8.5 mg in SD group (n=260). The IFX retention rate was 68/69% (LD/SD group) in one year, 46/44% in 3 years, and 36/32% in 5 years. There was no statistically significant difference between three groups (Log-Rank test). [Conclusion] We found no relationship between IFX long-term retention rate and MTX dose. We could say, at least, that we do not have to hesitate to use IFX in the patients with less than 6mg/week MTX compared to those with 8mg/week.

P3-096

Comparison of the first and second continuous rates and clinical efficacy among infliximab, etanercept, adalimumab and tocilizumab

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Conflict of interest: None

[Objectives] To examine the continuous rates and clinical efficacy of infliximab (IFX), etanercept (ETN), adalimumab (ADA) and tocilizumab (TOC), IFX, ETN, ADA and TOC were administered to 57, 81, 54 and 26 outpatients, respectively with refractory rheumatoid arthritis. [Methods] The average age of patients administered for over one year with IFX, ETN, ADA and TOC were 57.2 years, 56.9 years, 55.6 years and 57.3 years, and the periods until starting IFX, ETN, ADA and TOC were12.9 years, 11.1 years, 13.2 years and 13.0 years, respectively. [Results] DAS28ESR and DAS-28CRP both exhibited a significant improvement for the first three months after their initiation, and these parameters continued to improve through the follow-up periods. Inefficacy of IFX, ETN and ADA was seen in 19, 18 and 20 cases, and their adverse reaction was seen in 11, 9 and 4 cases, respectively. Remission of INF was seen in 7 cases. Continuous rates of the first TNF blockers show ETN>ADA>INF, Those of the second biologics show TOC>ADA. [Conclusion] INF shows the highest remission and ETN shows the highest in the first continuous rates of TNF blockers. Though according to the second continuous rate, TOC shows higher than TNF blockers.

P3-097

Effectiveness and continuation rate of high dosage MTX therapy combined with IFX in RA patients

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Conflict of interest: None

[Objectives] This study compares the effectiveness and continuation rate of low dosage (≦8mg) and high dosage (≧10mg) MTX therapy with IFX in RA patients. While there are numerous reports on the effectiveness of biologics, detailed studies on MTX combined with biologics are still lacking. [Methods] 48 female and 6 male patients with an average medical history of RA of 8.65 years were treated for over 24 months with MTX and IFX. The average dosage of IFX was 261.1 mg (4.71 mg/kg), and the MTX dosage for 41 patients was ≧10mg, whereas 13 patients received a dosage of ≦8 mg. [Results] 5 out of 13 patients who received ≦8mg of MTX stopped the treatment (continuation rate of 61.5%) and their average DASCRP was 2.64. In the group of high dosage MTX (≧10mg), 11 out of 41 patients stopped treatment (continuation rate of 73.1%), the DASCRP being 1.79. [Conclusion] In this study, patients with a high dosage of MTX (≧10mg) were about 11.6 percent more likely to continue treatment than low dosage MTX patients (≦8mg), and the DASCPR score improved by 0.85. Thus, in therapies with MTX and IFX, a higher dosage of MTX (≧10mg) can increase the effectiveness and continuation rate of treatment.

P3-098

Comparison of the effect and the persistence rate of biologics

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pan

Conflict of interest: None

[Objectives] We evaluated therapeutic effect of IFX, ETN and TCZ medication cases in our hospital and compared the persistence rate of them. [Methods] The patients of rheumatoid arthritis treated with IFX (135 cases), ETN(134 cases) and TCZ (54 cases) from July 2003 to August 2012 were analyzed by DAS28-ESR and compared the persistence rate. [Results] IFX group had 105 women and 30 men, average age was 57.5 y. o., disease period was 11.5 years and the average of DAS28-ESR improved from 5.6 to 3.9. ETN group had 104 women and 30 men, average age was 63.8 y. o., disease period was 12.6 years and the average of DAS28-ESR improved from 5.4 to 3.1. TCZ group had 46 women and 8 men, average age was 57.5 y. o., disease period was 14.6 years and the average of DAS28-ESR improved from 5.3 to 2.7. In IFX, ETN and TCZ group, one-year persistence rate was 73.8%, 86.2%, 85.8%, two-year persistence rate was 63.4%, 80.1%, 80.0% and three-year persistence rate was 63.4%, 74.0%, 76.3% respectively. The last persistence rate was 41.5% after 9 years in IFX group, 59.5% in 7.5 years in ETN group. The persistence rate of ETN group was higher than that of IFX group in each period. The persistence rate of TCZ group was 76.3% after 4 years and 4 months and the highest of the three.

P3-099

Results of Long-term Golimumab Treatment on Rheumatoid Arthritis Patients

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Conflict of interest: None

[Objectives] Golimumab (GLM) was launched as the 4th anti-TNF drugs for rheumatoid arthritis (RA) in Japan on September 2011, and as one of its feature it has longer injection interval (4 weeks) than the other subcutaneous anti-TNF drugs. We investigated several effects of long-term GLM treatment on rheumatoid arthritis (RA) patients including efficacy and safety. [Methods] 13 RA patients (all female) who were treated with GLM (50mg) as initial dose for more than 1 year were evaluated on DAS28-CRP, serum MMP-3, continuation rate and safety etc.. [Results] 9 RA patients completed with GLM treatment during 1 year achieved moderate response based on DAS28-CRP. There were no serious adverse events. The level of serum MMP-3 in patients completed with GLM treatment was improved in comparison with baseline. [Conclusion] These data suggested that long-term GLM treatment was well tolerated for RA patients. Furthermore, and the effect on prevention of joint destruction by GLM therapy was well expected though its improvement of serum MMP-3 level.

P3-100

Comparative study of infliximab(INF) and etanercept(ETN) in RA treatment

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Conflict of interest: None

【Objectives】 Both INF and ETN have been indicated in RA patients. We can indicate not only in the amount of one dose but also in the interval of administration individually. This study tries which is better in treatment of RA in our clinic. 【Methods】 The patients treated from 2005 to the end of March in 2012. They were selected who had been administrated continuously until the end of Mar. 2012. For evaluation, the mean value of CRP and MMP titers were selected as the biomarker for comparison. 【Results】 In INF group, 34 (6 male, 28 female) were selected. Fifteen have been treated until the end of Mar. 2012. Total administration was 30 (13-73) months. The mean value of CRP was reduced from 2.98 (ranged 0.11-6.9) to 0.31 (0.03-1.35). MMP was reduced from 308.3 (100.1-728.5) to 99.8(38-406.9). In ETN group,95 (14 male, 81 female) were selected. Forty-nine have been treatedcontinuously. Total administration was 45 (12-80) months. CRP was reduced from 4.34(0.30-12.29) to 1.92(0.00-4.61). MMP was reduced from 320.0(27.0-1712.7) to 148.8(39.9-602.9). Dropping out ratio were 56% in INF group and 48% in ETN group. Not only CRP but also MMP was more reduced in INF group. 【Conclusion】 Without discussion of injection rout, it is better to treat RA patients with INF than ETN.

P3-101

A study of the joint prognosis of the rheumatoid patients continuously treated with methotrexate alone as compared with those treated with adalimumab and methotrexate

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Conflict of interest: None

[Objectives] To compare the joint prognosis of rheumatoid patients treated with methotrexate (MTX) alone and those treated with adalimumab (ADA) and MTX. [Methods] The patients with MTX for more than 6 months (n=143) were compared with those treated with ADA and MTX (n=66). Disease activity was evaluated using DAS28/ESR4, DAS28/CRP4, and EULAR/ACR remission criteria. Radiographic progression was with van der Heijde modified Sharp score. [Results] Disease activity was improved in either groups during 2 years of treatment. Compared with ADA and MTX group, the MTX alone group was inferior in the DAS28/CRP4 improvement, but not DAS28/ESR4 improvement and remission for 2 years. Those who attained EULAR remission were 11% and 37% (p=0.0001) for 1 year and 17% and 29% (n.s.) for 2 years in MTX alone and ADA and MTX groups, respectively. Radiographic progression as was 3.2+6.6 and 3+4.3 (n.s.) for 1 year and 5.6+9.2 and 3+4.8 (n.s.) for 2 years. However, structural remission rate was 41.9% and 62.2% for 2 years (p=0.024). [Conclusion] The extent of radiographic progression of the patients who were successfully treated with MTX alone was almost comparable to those treated with ADA and MTX. Thus, introduction of biologics appears not required for the patients with good response to MTX.

P3-102

Knee condition assessed with MRI in rheumatoid arthritis patients before and after treatment with a TNF-α inhibitor

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Conflict of interest: None

[Objective] The purpose of this study is to evaluate knee conditions before and after treatment with a TNF-α inhibitor in patients with RA using MRI [Method] Twelve patients received infusions of TNF-α inhibitor. We examined the mean DAS28-CRP, CRP and joint effusion, marginal erosion and subchondral cysts by MRI grading system reported in 1996. Effusion was graded as; grade0, no effusion; grade1, small effusion in one or more recesses of the knee; grade2, marked effusion in all parts of the joint. The grading of inflammatory bone destruction was based on following criteria;

grade0, no signs of destruction; grade1, one erosion or cyst (diameter <8mm); grade2, more than one erosion or cyst, or one cyst with diameter >8mm. [Results] Mean treatment period was 22 months. Clinical parameters showed improvements about DAS28-CRP and CRP. Mean DAS28-CRP decreased from 4.77 to 2.19. Mean CRP decreased from 3.15 to 0.64. The result of joint effusion showed that 4 patients become better and 7 patients had no change. On the other hand, the result of marginal erosion and subchondral cysts showed that 5 patients become worse and 5 patients had no change. [Conclusion] Treatment with TNF-α inhibitor does not seem to protect knee joint condition despite improvements in clinical parameters.

P3-103

The effects and limits of conservative therapy for cervical lesions in patients with rheumatoid arthritis— Could the biologics suppress the progress of cervical lesions ? —

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Conflict of interest: None

[Objectives] Recently, surgical operation for upper cervical lesions of RA are decreasing, with the advance of pharmacotherapy for RA. We investigated the effects of pharmacotherapy, especially for biologics, observing progress of conservative cases. [Methods] Subjects were 23 RA patients (2 men, 21 women), with a mean age of 65.9 years, follow-up period was over 2 years. We tried to administer methotrexate for all, but 8 of them were discontinued. The biologics were prescribed for 12 cases, but 3 of them were canceled in a year, 3 of them were changed for other drugs, one of them was led to remission. We evaluated the changes of the Ranawat's criteria for pain and neurological assessment, and ADI and Ranawat's value in x-ray images, and WBC and CRP. [Results] Without regards of kind of drugs, Ranawat's pain evaluation were improved from early stage in well-controlled cases by pharmacotherapy. But, progress of vertical subluxation (VS) or subaxial subluxation in x-ray images were appeared in the cases required to discontinue the biologics or MTX. [Conclusion] Significant improvement of pharmacotherapy for RA has ability of prevention for progress of cervical lesions. But it is difficult to suppress the progress of VS completely, and required to follow-up carefully without pain.

P3-104

The comparison between the clinical efficacy and the dosage of etanercept (ETN) therapy for more than 5 years in patients with rheumatoid arthritis(RA)

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Conflict of interest: None

[Objective] This study aims to compare the clinical efficacy and the mean weekly dose of ETN therapy by every year with RA patients and we can investigate the possibility of the cost-effectiveness for ETN treatment. [Subjects & Methods] 12 RA patients with ETN therapy continuously for more than 5 years were enrolled. Their mean age was 56.4 years old and average disease duration was 12.3 years. We evaluated for clinical effectiveness of ETN and calculated the mean weekly dosage of ETN by each patient every year. [Results] The disease activity parameters resulted in remarkable decreases after one year with ETN treatment. After 5 years, the CRP, DAS28CRP and MMP-3 values had significantly improved (7.1 to 0.4, 5.9 to 2.1 and 649 to 104, respectively). Also, after 3 to 5 years, remission rates (SDAI and Boolean) were increased from 25 to 33% and from 42 to 58%, respectively. And the mean doses of ETN were in turn, 37, 24, 21, 23, 18 and 20mg/week from the first to the sixth year. The running costs in each year were reduced from 30 to 45% after the second to the fifth year with ETN therapy. [Conclusion] The long-term sustained effect in the ETN dose-reduction may be beneficial to RA patients in point of not only clinical maintenance of improvement, but also cost-benefit analysis.

P3-105

Usefulness of ADA from the viewpoint of patient's benefit

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Conflict of interest: None

【Objective】In daily treatment with adalimubab (ADA), gaps of at least 3 weeks where treatment is missed due to various circumstances are seen occasionally. However, continued ADA efficacy has been seen even in such cases. The usefulness in patients that start on a once every 3 weeks ADA treatment from the time the treatment is induced, was investigated.【Method】13 RA patients interval of once every three weeks at the author's institution. DAS28-CRP and MMP-3 were analyzed for at least 24 weeks. The study sample consisted of 12 females and 1 male of mean age 55.6 years. All subjects were Bio-naïve, and on MTX concomitantly. Baseline DAS28-CRP was 3.37 and the mean MTX dose was 6.4mg.【Result】One patient was poor efficacy, and the remaining 12 continued treatment for at least 24 weeks. Mean DAS28-CRP at 24 weeks improved to 2.38, and the remission rate was 58.3%. MMP-3 normalized in 4 patients. Six patients could be assessed up to 52 weeks. Remission was maintained in 5, and MMP-3 normalized in 4 patients. Compared to patients on normal ADA treatment regimen (once every 2 weeks) at this institution, the DAS28-CRP remission rate at 24 weeks (64.5%) was almost similar. In addition, patients bear 30% of the yearly expense of treatment, and that was decreased by 120,000 Yen.

P3-106

Study investigating real values of Biologics in patients with rheumatoid arthritis (RA)– Changes of work productivity after the treatment of Biologics and MTX –

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Conflict of interest: None

Objective: Effect of MTX and biologics (BIO) on work productivity was assessed with RA patients in varied work environments. **Method**: Data was obtained based on the questionnaire of Work Productivity and Activity Impairment (WPAI)-RA from RA patients treated with MTX (n=14) or BIO (n=35) for those who showed inadequate response to DMARD. Correlation between overall work impairment and disease activity among paid workers (PW) and home workers (HW) was investigated. **Result**: Higher mean percentages of absenteeism, presenteeism, overall work impairment and degree of affected regular activities at baseline were shown in PW (3, 39, 40 and 41%, n=20) than in HW (33, 43, 50 and 52%, n=29) with similar DAS28 (>5.5). WPAI remained lower in PW at 12 weeks after the treatments when DAS28 was equally reduced. Effects of regular activities was correlated with DAS28 (p=0.02) and SDAI (p=0.0079) despite no correlation with presenteeism, implying work environment could have an influence on the response to questionnaire. WPAI in ones treated with BIO had higher improvement. **Conclusion**: This study showed both treatments improved WPAI although some environmental factors might

be affected. Further discussion will be made on the difference of work productivity in extended treatments with more subjects.

P3-107

Evaluate the patient recognition on recovery of disability through assessment of individual question of J-HAQ and regional original query with nursing staff

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Conflict of interest: None

Objective: The J-HAQ is an outcome evaluation tools widely used throughout Japan to assess the Rheumatoid Arthritis (RA) patient activity. The disability section of the J-HAQ consists of 8 categories, with 20 questions. To evaluate the functional disability, count the maximum number obtained, in each categories and express as average of the numbers. Here we evaluated each 20 questions independently, compare before and after induction of Etanercept (ETN) administration. Method: We recruited 32 RA patients, average age 58.9, duration 9.9 years, administration of ETN between Feb.2011 to May 2012. The J-HAQ of before and 6 months after administration were compared individually for 20 questions. Result: J-HAQ improved from 0.88 to 0.52 in this 6 months ETN induction period. 68.8% established J-HAQ remission. Individual comparison of 20 questions before and after 6 months, each question showed sign of better performance. The question highly scored at the beginning were reach and get down a 2 litter plastic bottles from above your head 78.1%, Open previously opened jars 56.3%, and Open a new milk carton 56.3%. Each items went down to 53.1%, 37.5% and 28.1% respectively. Conclusion: With induction of ETN, improvement is established even on the most difficulties patient suffered beforehand.

P3-108

Rheumatoid Arthritis Circulatory Regional Collaboration-Pathway for treatment of RA andElectrical Medical Record Reference System

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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 five year summary. [Methods and Results] For 44 hospitals and 73 patients, the RACRC-Path was applied as a tool of biologic and non-biologic DMARDs in convenience for patients and physicians. 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 since 2009. [Conclusion] Critical pathway and electrical connection can be useful for rheumatoid arthritis characteristics.

P3-109

The high wall to be broken in This Bio-Era ~ how can we cover the treatment gap created by patients income

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Conflict of interest: None

[Objectives] We have achieved a weapon which can induce RA patients into remission. Remission is a realistic goal for RA specialist Dr. Although there is a wall in front of [Treat to Target] which is patients economical reason. [Methods] Costs of biologics, blood examination, prescription of MTX and folic acid is calculated and compared. [Results] When patients has fit High-Cost Medical Care of National Health Insurance which is called KOGAKU RYO-YO-HI 3times in recent 12 months, the amounts of the self-load allowance is lowered after the 4th time. Patients payment is 44400yen in a month when the patients has an average income. 3V or more vials of Infliximab use or 8weeks prescription of Etanercept, Adalimumab can be fit the system. Patients will see the Dr 6times in a year and whose payment is lowered as 266400yen per year. [Conclusion] In this time, realistic method to help low-income patients is to fit High-Cost Medical Care with 8week prescription of ETN or ADA, 3V or more vials of IFX. There is TSUBASA fund for leukemia which support patients who is not able to pay high cost medications. We need such system like [BIO-FUND] in the RA world.

P3-110

The effect of the Infliximab(IFX) Infusion Time On Patients' Lifestyles

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Conflict of interest: None

[Objectives] This report describes our investigation into the shortening of the IFX infusion time. Because of the long IFX infusion time, the patient stays a long time at the clinic. We thought that this may affect the patient's working time, and so we wanted to compare this infusion time with the subcutaneous injection time of a biological agent. [Methods] 25 patients were injected with IFX with a 1 hour infusion time. We conducted a questionnaire survey from 20 of these patients. [Results] The average age was 47.8 years old; 13 patients were working, and 7 patients were housewives. The results from the 13 workers surveyed showed that 11 of them were satisfied with the shortening of the IFX injection time. Previously, when these workers were given infusions that took 2 hours, 12 workers were absent from work for either a half or a whole day. On the other hand, with workers that were administered an injection with a 1 hour injection time, 4 workers were able to take less than a half day off, and 6 workers were able to take just a half day off. However, the 7 housewives were not affected by the shortening of the IFX infusion time. [Conclusion] We thought that the shortening of the IFX infusion time is useful for working patients.

P3-111

Evaluation of Quality of Life in patients with Rheumatoid Arthritis by EQ-5D comparing biologics user with non-user - from the analysis of the IORRA cohort-

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Conflict of interest: None

[Objectives] To compare the QOL of patients with RA longitudinally between biologics (BIO) user and biologics non-user using EQ-5D. [Methods] Among the participants in the IORRA study from April 2008 to April 2010, we extracted RA patients who started BIO during the observational period and did not use any BIO for at least 6 months before the initiation of BIO (BIO users group: n=481). We extracted the patients who did not use any BIO during the same observational period by 1:1 propensity score matching method (non-BIO users group: n=481). We compared the EQ-5D longitudinally between the both groups at the endpoint of 6~12 months after the baseline. Furthermore, we analyzed the factors contributing to better EQ-5D by using multiple regression analysis. [Results] EQ-5D (mean [95%CI]) in the BIO users significantly improved from 0.68 [0.67-0.69] at baseline to 0.77 [0.75-0.78] at endpoint. EQ-5D in the non-BIO users also significantly improved from 0.69 [0.68-0.71] to 0.74 [0.73-0.76]. In addition, EQ-5D in the BIO users statistically improved better than that in the non-BIO users ($p<0.001$). Younger age, shorter RA disease duration, better EQ-5D score at baseline, non-use of steroid and use of BIO at baseline were the significant factors contributing to improve EQ-5D score.

P3-113

Clinical evaluation of tocilizumab (TCZ) in patients with rheumatoid arthritis (RA)

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Conflict of interest: None

Objective: To analyze efficacy and safety of TCZ on RA. Methods: Sixteen males and 40 females, with a mean age of 58 years old, were studied. Mean disease duration: 12.56 years. Steinbrocker's stage: I: 7, II: 10, III: 8, IV: 31. Mean ESR 61.5 mm. Mean DAS28 (ESR4) score: 4.27. Methods: The activity and efficacy of TCZ was evaluated by DAS28 (ESR4) score and EULAR improvement criteria. We investigated adverse events and reasons on drop-out cases. Results: Mean DAS28 scores: 2.97 at 24 weeks, 2.84 at 48 weeks and 3.01 at 72 weeks. There was not the significant difference at EULAR Improvement criteria by dosing period of TCZ. Serious adverse events that lead to treatment change were observed that only in three cases. Conclusion: TCZ was effective and may be safe for active RA patients.

P3-114

Factors which Affect Efficacy and Clinical Remission in Tocilizumab Treatment

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Conflict of interest: None

[Objectives] To examine efficacy in patients with rheumatoid arthritis who received tocilizumab (TCZ). [Methods] Clinical remission (DAS, Boolean definition) and factors affecting clinical remission were evaluated by univariate and multivariate analyses of 40 patients at our hospital who could be observed for 52 weeks after introducing TCZ. [Results] DAS and Boolean remission among all patients were 72.5% and 47.5%, DAS remission with and without a previous history of biological agent administration were 41.7% and 86.4%, and Boolean remission with and without a previous history of biological agent administration were 16.7% and 60.7%. The common factor in univariate analysis of factors affecting clinical remission, multivariate analysis of factors affecting clinical remission in patients who attained DAS remission, and multivariate analysis of factors affecting clinical remission in patients who attained Boolean remission was a previous history of biological agent administration. [Conclusion] The use of TCZ can be considered first choice for patients who have not previously used a biological agent.

P3-115

Investigation of availability of Tocilizumab (TCZ) for Rheumatoid arthritis (RA) patients -the difference in treatment efficacy with and without of methotrexate (MTX)-

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Conflict of interest: None

[Objective] We investigate differences in treatment efficacy of between TCZ mono therapy (TCZ-mono) and combination therapy with MTX (TCZ-MTX). [Methods] Subjects were 56 RA patients for whom TCZ was initiated. We investigate the adherence rate and compared the differences in the validity between each group. [Results] The adherences rate were 66.4% in 1-year, 58.4% in 2-year and 54.1% in 3-year. There were 6 invalid cases and 6 cases which presented adverse events. They were discontinued TCZ. Number of TCZ-MTX group was 55.2% of whole subjects, and average dose of MTX was 7.5mg/week in the group. No intergroup difference in absolute values of DAS28 and MMP-3 were observed. However, improvement rates of MMP-3 were significantly improved earlier in TCZ-MTX group. [Conclusion] The adherence rate in 3-year was a favorable 54.1%. TCZ showed high treatment efficacy regardless of TCZ-mono or TCZ/MTX group. We believed that favorable therapeutic effects could be obtained when using TCZ in when MTX cannot be administered.

P3-116

Concomitant use of methotrexate with tocilizumab is necessary in bio-naive rheumatoid arthritis patients

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Conflict of interest: None

[Objectives] The aim of this study is to compare a group of bio-naive RA patients receiving TCZ with concomitant MTX to a group without concomitant MTX in the clinical setting. [Methods] The study was conducted in 39 bio-naive RA patients being treated with TCZ; 22 of these patients were not receiving concomitant MTX (the monotherapy group) and 17 were receiving concomitant MTX (the combination therapy group). At baseline, after 6 and 12 months, the following parameters were investigated: CRP, ESR, swollen joints count (SJC), tender joints count (TJC), MMP-3, DAS28-ESR, DAS28-CRP and adverse events. [Results] In the

baseline, the monotherapy group had significantly higher DAS28-CRP compared to combination therapy group. After 6 months, each of these scores: SJC, TJC, DAS28-ESR and DAS28-CRP, improved significantly more in the combination therapy group than monotherapy group. After 12 months, the combination therapy group exhibited significantly better improvement than the monotherapy group in TJC and DAS28-CRP only. No differences were found between the groups in adverse events. [Conclusion] In this study, the combination therapy group significantly inhibited disease activity at both 6 and 12 months, suggesting that MTX should be used concomitantly with TCZ whenever possible.

P3-117

Tocilizumab is beneficial as 1st biologics as well as 2nd biologics for TNF inhibitor failure in rheumatoid arthritis

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Conflict of interest: None

[Objectives] To compare the result of RA therapy that Tocilizumab (TCZ) was used as 2nd biologics (Bio) for TNF inhibitor failure with those of TNF inhibitor therapy in all patients and in patients whom one TNF inhibitor had used as 1st Bio and another TNF was used as 2nd Bio. **[Methods]** One hundred thirteen patients treated with Infliximab [IFX] (Bio naïve rate 99.1%, age 54.7, disease duration 8.9 y, DAS28 at start 4.8), 117 patients treated with etanercept [ETN] (Bio naïve rate 73.5%, age 61.9, disease duration 11.8 y, DAS28 at start 5.1), 37 patients who failed to a TNF inhibitor as 1st Bio and were switched to another TNF inhibitor as 2nd Bio [TNF/TNF] (age 54.2, disease duration 8.9 y, DAS28 at start of2nd Bio 5.1) and 23 patients who were switched to TCZ as 2nd Bio [TNF/TCZ] (age 60.2, disease duration 10.6 y, DAS28 at start of TCZ 5.1). **[Results]** One year survival rate of each regimen was 69.9% in [IFX], 71.8% in [ETN], 76.7% in [TNF/TNF] and 73.9% in [TNF/TCZ]. Average DAS28 after one year was 2.8 in [IFX], 3.1 in [ETN], 3.1 in [TNF/TNF] and 2.2 in [TNF/TCZ]. DAS28 remission rate was 37.3% in [IFX], 33.6% in [ETN], 47.1% in [TNF/TNF] and 56.5% in [TNF/TCZ]. **[Conclusion]** Tocilizumab is beneficial as 1st Bio as well as 2nd Bio for TNF inhibitor failure in RA.

P3-118

Study of the use of tocilizumab (TCZ) in a cohort of patients in Akita

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Conflict of interest: None

[Objectives] To investigate the use of tocilizumab (TCZ) in a cohort of patients with rheumatoid arthritis (RA) in Akita. [Methods] In 69 patients treated with TCZ registered in the Akita Orthopedic Group on Rheumatoid Arthritis (AORA) database, patient background, continuation rate, and concomitant administration of methotrexate (MTX) were compared between the naive (N) group and switched (S) group. [Results] The mean age was 56 (22-76) years. The mean duration of disease was 134 (3-482) months. The mean duration of administration was 19 (1-42) months, and the continuation rate was 82%. A total of 77% of the patients received concomitant administration of MTX at the mean dose of 7 (2-10) mg/week. In group N (35 patients, 51%) and group S (34 patients, 49%), the mean duration was 22 (3-42) and 16 (2-30) months, and the continuation rate was 78% and 85%, respectively. A total of 77% and 76% of patients received concomitant administration of MTX at the mean dose of 6 (2-10) and 8 (4-10) mg/week, respectively. [Conclusion] Both groups showed a similar tendency in the continuation rate and concomitant administration rate and dose of MTX. Many patients received concomitant administration of MTX, and the continuation rate was high.

P3-119

Efficacy and safety of tocilizumab (TCZ) in patients with rheumatoid arthritis (RA) stratified according to the concomitant use of DMARDs (con-DMARDs) including methotrexate (con-MTX) in our hospital

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Conflict of interest: None

[Objectives] To investigate efficacy and safety of TCZ in patients with RA stratified according to con-DMARDs including con-MTX in our hospital. [Methods] We examined clinical background of RA patients treated with TCZ in our hospital from July, 2008 to October, 2012 and retrospectively evaluated its efficacy and safety. [Results] 43 patients (4 males, 39 females), overall average age at the commencement of TCZ was 65.8 years old, duration of RA 14.6 years, proportion of prior biologics 51%(22 cases), proportion of con-DMARDs (MTX) 79.1% (39.5%), pretreatment mean DAS28-ESR of con-MTX group, no con-MTX were 4.90, 5.12, respectively. After 3 months mean DAS28-ESR fell to 2.81, 3.26, respectively, after 6 months 2.90, 2.90, respectively, and after 12 months 2.99, 2.98, respectively. According to EULAR criteria, at 12 months, 47.1% cases achieved good response, 82.4% cases achieved moderate or more response with 41.2% clinical remission rate in con-MTX group, also 50% cases achieved good response, 83.3% cases achieved moderate or more with 41.7% remission in no con-MTX group, with no significant difference among the groups. Overall, seven ceased TCZ for adverse event by 12 months. [Conclusion] TCZ is efficacious regardless of use of con-DMARDs including con-MTX in our hospital.

P3-120

The effect of Tocilizumab estimated by thickness of both bone hands cortex by X-ray with rheumatoid arthritis

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Conflict of interest: None

Objective:Interleukin6(IL6) is known as one of important cytokine that play a role in bone atrophy and osteoporosis with rheumatoid arthritis (RA). This pathogenesis suspect that at least a part of RA patients that effective anti-IL6 agent has a possibility that has more severe bone atrophy. Methods: 68 patients with RA were estimated by both hands X ray and measured in cortex of both cen-

ter of third proximal finger pharynx and metacarpal bone. The activity of RA were estimated by CDAI before start Tocilizumab (TSM) and after 24 weeks. The rate of improvement was measured by CDAI as followed: no effect;less than 25%, a little effective; from 25% to 50%,effetve; from 50% to 75%,remarkably effective;75% more over. Results: Finger bone cortex thickness were from 1.4mm to 5.8mm and average thickness was 3.2mm. CDAI improvement rate were from 7% to 96% and average improvement rate was 61%. Significantly negative correlation ($P<0.05$) was showed between an improvement rate of CDAI and finger bone cortex thickness. Conclusion: There is a possibility that the RA patients that TSM will be effective has more thin finger bone cortex.

P3-121

The dynamics of the angiogenesis markers in rheumatoid arthritis patients treated with Tocilizumab

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Conflict of interest: None

Objective: Tocilizumab (TCZ), is a humanized monoclonal antibody against human IL-6 receptor, and is used in the treatment of rheumatoid arthritis (RA), due to its effect on suppressing the modification of signal transduction caused by IL-6. However, it is yet unclear as to how the suppression of IL-6 could lead to amelioration of the RA symptoms. On the other hand, IL-6 is already known to play a role in angiogenesis.Hence in this study, our aim was to examine the change in the degree of angiogenesis caused by the administration of TCZ. Methods: We have included patients with RA, who fulfilled criteria of the American College of Rheumatology. The following findings were recorded before TCZ therapy, 1 month, 3 months, and 6 months after the therapy: for the RA activity, SDAI, CDAI, DAS-CRP, DAS-ESR, and Power Doppler Ultrasound (PDUS); for the degrees of angiogenesis, serum VEGF, Ang-1, and Ang-2 were investigated by ELISA. To determine the activity of cytokines, IL-6 and TNF-α were measured. Result: By administration of TCZ, Total Signal Score – a disease activity factor for RA, the PDUS findings, as well as the marker levels of angiogenesis were decreased. Conclusion:we could deduce that one of the pharmacological actions of the drug could be due to suppression of angiogenesis.

P3-122

Successful tocilizumab therapy for 8 patients with refractory adult-onset Still's disease

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Conflict of interest: None

【Objective】 To analyze a feasible plan of tocilizumab (TCZ) therapy to refractory Adult-onset Still's disease (AOSD). **【Methods】** We reviewed hospital records for all 9 patients (Pts) with AOSD (4 women and 5 men at mean age of 37, range 25-60) that received TCZ therapy by 2012. **【Results】 Acute phase therapy**: TCZ was started after stabilizing the inflammation by high-dose steroid therapy. Prior therapy by methotrexate and cyclosporine (CsA) for 4 Pts or TNFα blockers for 2 Pts was ineffective. DIC or MAS in 5 Pts and meningitis in 1 Pt were major complications. On admission, serum level of CRP was 11.1±7.7 mg/dl and ferritin was 13539±16813 (15-45290) ng/ml. TCZ was started at 8 mg/kg dose per week or biweekly, after the CRP level was reduced to 1.6±2.6 (range 0.01-8.55) mg/dl, ferritin level to 1924±2387 (12-7924) ng/ml, and MAS resolved by lipodexamethasone and continuous CsA infusion. Rapid PSL tapering was achieved in the last case of consecutive 8 Pts, and 120 mg/d of PSL was reduced to 20 mg/d in only 35 days. **Maintenance therapy**: During 2 to 52-month-follow-up (median 27), all Pts had remission including one steroid-free-Pt and TCZ-interval was extended up to 8 weeks. **【Conclusion】** TCZ therapy for AOSD may be helpful for rapid steroid tapering and maintaining remission.

P3-123

Tocilizumab is superior to abatacept in ACR/EULAR remission of Japanese patients with rheumatoid arthritis

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Conflict of interest: None

Objectives To compare clinical effectiveness between tocilizumab (TCZ) and abatacept (ABT) for inducing remission in patients with moderate to severe active rheumatoid arthritis. **Methods** We compared the proportions of patients fulfilling the new ACR/EULAR remission criteria at 24 weeks of treatment and those with a score ≤ 1 in each category. **Results** No significant differences were noted in patient background between 21 and 23 patients treated with TCZ and ABT, respectively. The 24-week remission rates were 76% for TCZ and 22% for ABT, indicating a statistically significant difference (P = 0.0007). The proportions of patients with PGA and CRP scores ≤ 1 were significantly higher for TCZ. When patients were stratified by history of previous biological agents administration, no statistically significant difference (P = 0.1357) was detected in the 24-week remission rate of treatment-naive patients between TCZ (78%) and ABT (33%). However, TCZ showed a significantly higher remission rate than ABT for patients switching from other biologics (75% versus 18%, P = 0.0020). **Conclusion** This clinical study based on the new ACR/EULAR criteria showed that TCZ was superior to ABT in achieving remission. In particular, patients switching from other biologics were more responsive to TCZ.

P3-124

Clinical outcomes of tocilizumab therapy in rheumatoid arthritis patients with risk of tuberculosis infection activation

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Conflict of interest: Yes

[Objectives] To investigate tocilizumab (TCZ) treatment outcomes of rheumatoid arthritis (RA) patients with risk of activation of tuberculosis (TB) enrolled in the multi-institutional Tsurumai Biologics Communication Registry. [Methods] Five RA patients with elevated risk of TB infection (history of TB 2, history of tuberculous pleurisy 1, Quantiferon positive 2) were identified, and their 1-year TCZ treatment outcomes were evaluated using DAS28-ESR, MMP-3 and other laboratory parameters. [Results]

Patients had a mean age of 69 years, mean disease duration of 7.5 years, mean MMP-3 334.4 mg/ml and mean DAS28-ESR score of 5.2 at baseline. All patients received isoniazid (INH) prophylaxis in combination with TCZ. At 1 year, the mean MMP-3 and DAS28-ESR were 146.1 and 2.3, respectively, indicating marked improvement in disease activity. One patient showed hyperlipidemia of adverse event. No signs or symptoms suggestive of TB were identified during the study. [Conclusion] In this study serious adverse events associated with the combined use of TCZ and INH were not detected. Despite the fact that post-marketing surveillance of TCZ reported several cases of TB, TCZ plus INH is a plausible option for the treatment of RA patients requiring biologics for disease control.

P3-125

Short term follow-up after phase III clinical trial of tocilizumab s.c

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Conflict of interest: Yes

[Objectives] Short term follow-up after phase III clinical trial of tocilizumab (TCZ) s.c. in RA patients was studied. [Methods] Out of 6 patients who participated in the trial, one requested immediate switch to TCZ i.v., thus 5 patients were included in this study. These patients (1, male; 4, female) had been biologics naïve with mean age and duration of 41.6 and 6.2 years, respectively. We studied clinical data and medication drugs after the trial, comparing those before and during the trial. [Results] The average DAS28-CRP (4) before and 4, 12 and 24 weeks during the trial was 4.74, 3.73, 2.11 and 1.85, respectively, with 4 patients in remission and one in low disease activity at 24 weeks. On the other hand, the average DAS28-CRP (4) at 4-12 after the trial was 2.12 with respective one patient in moderate and high disease activity, which was regarded as recurrence. MTX had been prescribed in all patients before the trial but was stopped during the trial, and was prescribed again in 2 at 4 weeks after the trial and in 3 at 8 weeks. Prednisolone was prescribed in one patient before and during the trial, and in 2 including this case at 8 weeks after the trial. [Conclusion] Recurrence of disease activity was observed in some patients relatively shortly after the cessation of TCZ s.c.

P3-126

Study of cases of seven patients with rheumatoid arthritis that were tried biologics-free remission after tocilizumab therapy

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Conflict of interest: None

[Objectives] To evaluate the possibility of biologics (bio)-free remission for patients with rheumatoid arthritis (RA) after tocilizumab (TCZ) therapy. [Methods] Seven patients who discontinued TCZ after achieving Boolean-based remission were enrolled. We analyzed parameters associated with bio-free remission. [Results] Patients' profiles at the start of TCZ were age 54.0±13.2 yrs, disease duration 5.1±6.3 yrs, class 1.6±0.5, stage 1.5±0.5, tender joint count 2.4±0.6, swollen joint count 4.0±2.9, CRP 3.2±2.7 mg/dl, dose of MTX 4.9±4.6 mg/wk. All cases had no history of biologics use. Remission was achieved at 26.7±30 wks. Duration of remission before stopping TCZ was 36.1±26.2 wks. 4 cases maintained bio-free remission over 1 year. 3 cases relapsed at 22, 25, 40 wks, and achieved remission soon after resuming TCZ. The differences between success and failure of bio-free remission were disease duration(1.3±0.8 vs 8.9±7.4 yrs), duration of remission before stopping TCZ(48.5±3.4 vs 19.5±6.2 wks), and dose of MTX (4.5±3.4 vs 2.7±4.6 mg/wk). [Conclusions] We showed a possibility of bio-free remission after TCZ, and suggested that shorter disease duration, longer duration of remission before stopping TCZ, and higher dose of MTX are important for bio-free remission.

P3-127

Characteristics of RA patients who kept remission 52 weeks after discontinuation of tocilizumab (TCZ) therapy

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Conflict of interest: Yes

[Objectives] We investigated clinical characteristics of RA patients who kept remission 52 weeks after discontinuation of TCZ therapy. [Methods] The subjects were 9 RA patients (2 males, 7 females) to whom TCZ therapy were discontinued 52 weeks before by achievement of clinical remission. The mean age was 48 years. The mean disease duration was 9.2 years. The mean dosing period of TCZ was 2.1 years. Disease duration correlated with dosing period (R^2=0.79). [Results] In 9 patients, remission was kept in 5 patients for 52 weeks, and RA activity relapsed in 4 patients within 52 weeks.In the remission group and relapsed group, the mean age was 46 (1 male, 4 females) and 50 (1 male, 3 females) years old, the mean disease duration was 4.4 and 15.2 years (p=0.05), the mean dosing period of TCZ was 1.6 and 2.6 years, respectively. At the discontinuation of TCZ in remission group and in relapsed group, the mean DAS-28 (ESR) was 1.5 and 1.3, HAQ-DI was 0.2 and 1.3, respectively. Ultrasonographic joint score (a sum of ultrasonographic scores of 26 joints (DAS28 joints - shoulders)) was synovial thickness 3.4/ blood flow 1.8 and 4.3/2.8, respectively. [Conclusion] TCZ was discontinued and kept free more frequently in the early-stage RA patients who promptly achieved deep clinical remission by TCZ.

P3-128

Analyze of the discontinuation of tocilizumab in rheumatoid arthritis with clinical remission

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Conflict of interest: None

Objective: To assess the clinical characteristics of rheumatoid arthritis (RA) patients treated with tocilizumab (TCZ) and achieved clinical remission and TCZ free remission. Methods: Efficacy was evaluated by CDAI. Results: 48 (6men, 42women, average age 50.1 years old) of RA patients were treated with TCZ and enrolled in this study. Overall remission rate was 43.8%. 9 patients were able to decrease the dose of TCZ, and 6 among 9 patients achieved to TCZ free remission. There were no significant differences in combination therapy with or without MTX, duration of disease before using TCZ and using TNF antagonist before TCZ therapy between RA with TCZ free remission and without remission. However 2 patients relapse RA after TCZ free remission, all

these patients achieved to clinical remission within 2 months after restart of TCZ. Results: TCZ is able to achieve TCZ free remission. It is useful to restart TCZ for relapse of RA in patients with TCZ free remission.

P3-129

Clinical features of 3 cases of rheumatoid arthritis who achieved drug-free remission after tocilizumab therapy

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Conflict of interest: None

[Objectives] To investigate clinical features of patients with rheumatoid arthritis (RA) who achieved drug-free remission after tocilizumab (TCZ) therapy. [Methods] and [Results] Case 1: A 67-year-old woman received TCZ monotherapy. She had a disease duration of 1.1 years and DAS28 of 7.51. At week 24, she achieved DAS28 remission which lasted 3.5 years. TCZ was discontinued at a DAS28 of 0.52, and she attained a sustained drug-free remission lasting at least 1.3 years. Case 2: A 56-year-old woman received TCZ monotherapy. She had a disease duration of 1.1 years and DAS28 of 7.33. At week 24, she achieved DAS28 remission, which lasted 2.8 years until TCZ was discontinued at a DAS28 of 2.11. She attained a sustained drug-free remission lasting 1.1 years. Case 3: A 57-year-old woman received TCZ monotherapy. She had a disease duration of 2.6 years and DAS28-CRP of 3.16. At week 72, she achieved DAS28-CRP remission, which lasted 3.1 years until TCZ was discontinued at a DAS28-CRP of 1.98. She attained a sustained drug-free remission lasting 1.1 years. [Conclusion] TCZ monotherapy provided drug-free remission in 3 patients with early RA after long-term sustained remission with TCZ.

P3-130

Remission in Patients with Active Rheumatoid Arthritis by Tocilizumab Treatment in Routine Clinical Practice: Results from 3 Years's Prospectively Registered Data

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Conflict of interest: Yes

Objectives This study aimed to describe remission and it's retention rate in RA patients treated with tocilizumab (TCZ), based on prospectively registered data in routine clinical practice. **Methods** We observed 172 consecutive RA patients treated with TCZ (average age 52.6 years; average disease duration 9.8 years). 112 (71%) had previously received anti-TNF biologics. Remission of RA was evaluated by using the EULAR criteria and the new ACR/EULAR Boolean-based criteria. **Results** Baseline DAS28 of 5.2 improved to 2.4 at 3years. The retention rate was 70.4%. Remission at 1, 2 and 3 years with the EULAR criteria was attained by 54, 75.4, 60.9%, respectively, while 18.5, 25.4, 21.7% with the Boolean criteria. Multivariate analysis revealed that factors significantly influencing the remission were previous usage of anti-TNF biologics and good response at 3 months. Among the patients with achievement of remission at 1 year, 75% of the patients retained within the remission at 3 years. **Conclusions** In patients with RA, TCZ is highly effective, achieving a high remission rate (ACR/EULAR remission: 24.5%) and drug continuation rate (82.4%) in routine clinical practice.

P3-131

Experience in using tocilizumab (TCZ) as the first Biologics in Dogo Spa Hospital

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Conflict of interest: None

[Objectives] There are plenty of patients who receive TCZ as the first biologics, we would like to report our experience with it. **[Methods]** Subjects were 68 RA patients, including those participating in the clinical trial. In order to determine the effect of the treatment, swollen joint count (Sj); tender joint count (Tj); CRP; and SDAI before the treatment, 3, 6,12,24 months after the treatment, and at the last observation period were evaluated. The Kaplan–Meier method was used to evaluate the persistence rate. **[Results]** There were 22 patients who had undergone monotherapy with TCZ. Median duration of TCZ administration was 2.6 years (0–11) The 5-year persistence rate was 88.4%, whereas the 10-year persistence rate was 70.7%. There were 12 patients who stopped the treatment; 5 patients stopped because of a secondary effect ; 3, because of no effect; 1, because of decreased effect; and 3, because of remission. Mean Sj, Tj, CRP, and SDAI before treatment was 7.1, 5.8, 3.0, and 24.6, respectively; the values 3 months after the treatment were 2.5, 1.9, 0.3, and 9.5, whereas those from the last observation were 1.0, 0.7, 0.08, and 5.9. **[Conclusion]** Monotherapy with TCZ as the first Bio treatment yielded a good clinical effect, suggesting a sustainably high persistence rate.

P3-132

Evaluation of dosage adaptation of tocilizumab based on continuation rate

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Conflict of interest: None

【Objectives】 To study the continuation rate of tocilizumab (TCZ) in patients with RA at our facilities. 【Methods】 Subjects included 44 patients administered TCZ. Differences in continuation rate of TCZ were examined, caused by combined administration with MTX and by the order of administration of biological preparations (Bio). 【Results】 At the time of initiating TCZ administration, the mean age of the subjects was 61.2 years, mean disease duration was 12.7 years, and prevalence of usage of MTX combined with TCZ was 40.9%, respectively. In addition, in 50% of patients, TCZ was used as a second line of Bio treatment. The mean administration period of TCZ in the continued cases was 25.5 months, and the 2-year continuation rate was high at 81.4%. When the 2-year continuation rate was compared between treatment with MTX (MTX group) or without MTX (no MTX group), it was significantly higher in MTX group (94.4%; 18 cases) than no MTX group (65.4%, 26 cases).With regard to the order of administration of Bio, we observed a high 2-year continuation rate of 95.5% when TCZ was used as a second line Bio. 【Conclusion】 This study suggests that the continuation rate is higher in combined administra-

tion with MTX. Furthermore, as a second line Bio, TCZ could be used for long-term therapy.

P3-133

Radiographic effectiveness of tocilizumab(TCZ) for rheumatoid arthritis(RA) patients who have poor prognostic factors

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Conflict of interest: None

[Objectives](*a*) the presence of rheumatoid factor (RF) and/or anticitrullinated peptide antibodies (ACPA) (*b*) high disease activity (*c*) early occurrence of erosions are defined as factors believed to predict bad outcome. The radiographic effects of tocilizumab in RA patients who had poor prognostic markers were studied. [Methods] In the Michinoku Tocilizumab Study Group, patients who started TCZ treatment from May 2008 were included. Estimated yearly progression by van der Heijde-modified Sharp method (ΔmTSS) and structural remission rate (ΔmTSS≦0.5) in patients presented prognostically unfavorable factors were evaluated. [Results] Characteristics of 114 patients included mean age of 60.1 years, disease duration of 11.6 years and DAS28ESR of 4.7. ΔmTSS and ΔmTSS≦0.5 were 0.11 and 74.1%, and 1.31 and 75.1% in ACPA-positive and negative patients. ΔmTSS and ΔmTSS≦0.5 were 0.39 and 67.9%, and 0.25 and 78.6% in RF-positive and negative patients. ΔmTSS and ΔmTSS≦0.5 were 0.68 and 56.4%, and 1.31 and 72.6% in patients with high and low disease activity, respectively. No significant differences were found between two groups. [Conclusion] In routine clinical practice, TCZ showed high radiographic effectiveness in RA patients despite of presence of poor prognostic markers.

P3-134

Inhibitory Effect of Tocilizumab on Bone and Joint Destruction in Clinical Practice – Differences Due to Pre-administration MMP-3 Values –

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Conflict of interest: None

Objectives: To examine whether there are differences in inhibitory effect of tocilizumab results due to baseline MMP-3 values in clinical practice. Methods: Joint destruction inhibitory effects were assessed using total sharp score (TSS) in 18 patients. TSS after 52 weeks were compared between 8 patients with MMP-3 (ng/dL) before TCZ administration of 300 ng/ml or more (high MMP-3 group) and 10 patients with less than 300 ng/ml (low MMP-3 group). Results: Patient demographics in all subjects/high MMP-3 group/low MMP-3 group were average age of 62.3/65.5/59.7 years, females 83/62.5/100%, average disease duration of 7.5/8.1/7.0 years, previous use of biological DMARDs was 50/50/50%, concomitant use of MTX was 89/100/80% with average dosage of 7.4/7.5/7.3mg/week, concomitant use of PSL was 83/100/70% with average dosage of 3.5/3.2/3.9mg.Change in ΔTSS/year from before administration to week 52 was 9→0.2 in all subjects, 14.5→-0.5 in the high MMP3 group, and 4.6→0.7 in the low MMP3 group, showing improvement or recovery, and structural remission (ΔTSS/year ≦0.5) was observed in 10 patients (55.6%). showing improvement. Conclusions: Daily clinical use of tocilizumab suggested that baseline MMP-3 values are unrelated to its inhibition of bone and joint destruction.

P3-135

Does Early Decrease of Neutrophil Count in Rheumatoid Arthritis (RA) Patients who Receive Tocilizumab (TCZ) Correlate with Treatment Response?

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Conflict of interest: None

[Objectives] Correlation of changes in neutrophil count after TCZ treatment with treatment response was examined in RA patients. [Methods] Subjects were 72 RA patients receiving TCZ treatment at our hospital to whom administration for at least 24 weeks was possible. Observation period was 24 weeks, and plt, WBC, DAS28 and CDAI were compared before administration and after 4, 8 and 12 weeks. Baseline paired t-test, Wilcoxon rank sum test and Fisher's exact test were used for statistical analysis. [Results] DAS28 and CDAI improved with statistical significance after 4, 8, 12 and 24 weeks. There were 26 patients of CDAI remission, and change rate of neutrophils after 4 weeks was -20.1±25.8% in the CDAI non-remission group and -37.5±27.4% in the CDAI remission group, and statistically significant difference was observed (p=0.005). When -25% was taken as the cutoff for change rate of neutrophils 4 weeks after initiating TCZ, the CDAI remission rate after 24 weeks was 82.61% (vs. 17.39%), and statistical significance was observed (p=0.003). [Conclusion] When change rate of neutrophils 4 weeks after TCZ administration exceeds -25%, remission after 24 weeks is more easily attained, and it may provide significant information on whether or not to continue treatment.

P3-136

Effectiveness of rheumatoid arthritis treatment with tocilizumab according to prior use of biological agents

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Conflict of interest: None

[Objective] To evaluate the efficacy of tocilizumab (TCZ) in patients with rheumatoid arthritis (RA) [Methods] We examined 70 patients (56 female) treated with TCZ for at least 1 year between April 2008 and August 2012. Disease activities were evaluated using DAS28-4 (ESR) and CDAI at 0, 24 and 48 weeks, depending on previous use of biological (Bio) agents. [Results] 36 (51.4%) of the patients had been treated previously with Bio agents. 29 received one Bio agent〔18 infliximab (IFX), 9 etanercept (ETN), 2 adalimumab (ADA)〕, while 5 had 2 and 2 patients received three. Patients who received previous treatment of one Bio agent had low disease activity after induction of TCZ. Patients who had treated IFX was improved greatly. [Discussion] Because TCZ is newer than IFX and ETN, it often is used for patients refractory to two Bio agents. The switch to TCZ was more effective for cases of secondary failure after IFX. Recently, more patients are treated with TCZ as a first-line agent. The number of Bio agents is likely to increase in future. More than before, it is necessary to treat based on evidence and patient education.

P3-137

Efficacy of tocilizumab (TCZ) on initial dosing and its influence on DAS28-ESR at Week 24

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Conflict of interest: None

[Objectives] We compared the efficacy of TCZ on initial dosing with that at Week 24 to examine predictive factors for the efficacy. [Methods] We divided 15 patients with rheumatoid arthritis (RA) in whom TCZ was newly introduced into 2 groups: a group in which target activity parameters (DAS28-ESR (DAS)<3.2, painful joint count (TJC)£1, swollen joint count (SJC)£1, normal ESR, PtVAS£1 cm, and normal MMP-3 level) were achieved after initial dosing, and a group in which they were not achieved. The mean age was 58.0±12.1 years. The subjects consisted of 2 males and 13 females. The mean duration of disease was 13.1±12.1 years. Previous treatment with biological preparations was present in 8 patients, but not in 7. [Results] The correlation between each parameter and DAS at Week 24 in the two groups was examined. In the ESR normalization (n=10) and non-normalization (n=5) groups, the DAS at Week 24 was 2.0 and 3.1, respectively, showing a significant difference (P<0.01). Among the above parameters, there was a significant difference in the ESR alone. [Conclusion] After the initial dosing of TCZ, the DAS at Week 24 in the ESR normalization group was significantly lower than in the non-normalization group. In the future, the long-term efficacy should be further examined.

P3-138

Efficacy of Tocilizumab in Clinical Practice

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Conflict of interest: None

[Objectives] To examine the efficacy of tocilizumab (TCZ) in clinical practice. [Methods] Retrospective analysis of 53 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. [Results] The 24-week DAS28-ESR remission rate was 51.4% and Boolean remission rate was 32.6%, both high rates. CDAI remission rate was also high at 30.0%, and was particularly high in the group with disease duration within 2 years at 55.6%. Long-term continuation rates were 88.6% after 1 year and 73.9% after 2 years, which were better than other biological agents. Combined use of steroids could be decreased or discontinued in 60% of the patients, and in the naïve group, steroids could be significantly discontinued in patients with disease duration < 2 years. [Conclusion] The high efficacy of TCZ was confirmed by a variety of assessment methods, and efficacy was particularly high in naïve patients in the early stage of disease. Sustained remission rate, continued administration rate and dose reduction of steroids were also high for TCZ, which is an effective treatment for rheumatoid arthritis.

P3-139

Examine about the variation of Daily VAS in patients treated with tocilizumab

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Conflict of interest: None

[Objectives]With the advent of biologics, it has become possible to achieving remission in many patients with rheumatoid arthritis (RA). Accordingly, Patient Global Assessment (PGA) has become a large factor prevented achieving new remission criteria. In order to examine in more detail about the biological treatment with the formulation effect on the PGA, we have investigated the variation of PGA per day. **[Methods]**In 16 patients treated with tocilizumab (TCZ), we measured and evaluated PGA by Visual analogue scale (VAS) for 28 days from the administration of TCZ. **[Results]** Patients had a mean age of 65.4 years,disease duration of 7.5 years and a disease activity score in 28 joints of 4.5 atbaseline. The proportion of patients with prior biologics therapy is 63%. VAS was maintained for 28 days. The VAS at Day1 in improved case(n=6) was significant higher than that in exacerbated case(n=10) (p <0.05). **[Conclusion]** In patients treated with TCZ, PGA of 28 days was maintained.The characteristics of improved cases, the high value of the VAS of 1 was shown to date.

P3-140

A patient with acute nephritis and pyogenic diskitis who use tocilizumab : A case report

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Conflict of interest: None

A-66-year old Japanese male was diagnosed with rheumatoid arthritis in 2000. Treatment was started with bucillamine and methotrexate. After then, he was treated with adalimumab in May 2009, but it was discontinued because he had caught. So he was treated with tocilizumab in January 2010 and he went into remission. In April 2011, he had fever and lumbago. He was diagnosed with urinary tract infection and became acute renal failure. He removed to another hospital for treatment. Streptococcus pneumoniae was discovered from blood culture and he was treated with meropenem. He came back to our hospital after 1 month. In May, lumbago continued and he was diagnosed with pyogenic diskitis by magnetic resonance imaging (MRI). But bacterias weren't found from the needle biopsy with Computed Tomography. He was treated with cefazolin sodium for 3 weeks and discharged the hospital. He was followed by MRI and blood tests but there was no recurrence. When we use tocilizumab, the score of C-reactive protein shows low value. So we have to be careful against the infection under the using tocilizumab. In this case, we had to think other diagnosis like pyogenic diskitis when the chief complains was lumbago.

P3-141

Hemophagocytic syndrome in a rheumatoid arthritis (RA) patient treated with tocilizumab: Case report

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Conflict of interest: None

Background: Patient was a male 65 years Stage III Class 2 RA. **Current therapy:** Treatment with tocilizumab (TCZ) 460 mg every 4 weeks was started. CRP became negative after 8 weeks and DAS28ESR was 2.22 at 24 weeks. Concerning concomitant medications, prednisolone doses were reduced to 0 mg at 70 weeks. Methotrexate was discontinued after 2.5 years because of leukopenia.**Clinical course:**Blood tests conducted of the last to TCZ dose (at 4 years and 3 months) reported WBC 2700 Lym 675 AST 35 PLT 81,000. One week after, the patient became ill with anorexia,malaise,fever. Laboratory data showed CRP0.7 AST2412 PLT32,000 WBC1900. The absence of neutrophil left shift suggested viral infection and the patient underwent cytomegalovirus

and Epstein-Barr virus tests which were both positive. The patient started receiving cefepime 2 g/day acyclovir 500 mg/day micafungin sodium 50 mg/day. Next day, 10 units each of platelets and fresh frozen plasma were administered. Liver and bone marrow biopsies confirmed the diagnosis of hemophagocytic syndrome. The patient developed sudden hypotension and died despite cardiopulmonary resuscitation with other treatments.

P3-142

Intra-abdominal abscess in the absence of inflammation reaction in rheumatoid arthritis patient treated with tocilizumab

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Conflict of interest: None

【introduction】GI perforation have been reported 0.2%(n= 6424) in the PMS about TCZ. It is pointed out that the diagnosis is delayed because symptoms of diverticulitis is suppressed by masking of inflammation. we report a case of RA that led to intra-abd abscess caused by diverticulitis with symptoms and inflammatory response being masked by TCZ.【case】A 61-year-old woman. Onset of RA is in 2006. High disease activity was sustained, despite of therapy of SASP 3g, MTX 10mg/wk, TAC 3mg, ETN 50mg/wk. Thus, we began admin of TCZ in January 2010. Then,it became low disease activity, and TCZ continued 80 weeks. The end of May 2011, she got postprandial abd pain, but observed using NSAIDs. No inflammatory reaction at that time. Then, the pain and appetite loss are sustained, and she returned. she revealed tenderness in the left abd, but no rebound and muscular defense. WBC6500/μL, CRP0.05mg/dL. Abd CT showed diverticulum, enhanced lesion in surrounding fat, and the vicinity abscess in left hemi-colon. We diagnosed intra-abd abscess, and started bowel rest, antimicrobial therapy. By 4weeks of therapy, improvement were obtained. Under the masking of inflammation by TCZ, considering that symptoms are suppressed, imaging studies should be performed early if the abd symptoms are persistent.

P3-143

Three cases of rheumatoid arthritis with chronic renal failure treated with biologics

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Conflict of interest: None

Most of DMARDs including methotrexate (MTX) are contraindicated for rheumatoid arthritis (RA) patients with chronic renal failure (CRF). Biologic therapy could be a reasonable choice for such patients. However, there are only a few case reports for the usage of biologics. Here, we report three cases of RA with CRF treated with biologics. Case1: 76 years old woman was treated with maintenance hemodialysis (HD) from 2010. She has been diagnosed with RA for 2 months. Her DAS28CRP was 4.85 and treatment with abatacept was initiated. After 2 months, she is in clinical remission. Case2: 74 years old man received HD therapy from 2007, because of CRF due to diabetic nephropathy. He has been diagnosed with RA for 16 months. He was treated with minocycline with no benificial effect. His DAS28CRP was 7.13 and treatment with abatacept was started. His DAS28CRP was declined to after 3 cycles of therapy. Case3: 63 years old man who has been diagnosed RA for 2 years. And he also had CRF (his serum creatinine is about 1.4 mg/dl). He was treated with salazosulfapyridine but didn't improve. His DAS28CRP was 6.92, and treatment with eternacept was started. After 1 months, he achieved good response. [Conclusion] Abatacept and eternacept, could be a good choice for the treatment of RA patients with CRF.

P3-144

Addition of leflunomide with tocilizumab plus methotrexate inhibits progressive joint destruction in patients with mutilating rheumatoid arthritis

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Conflict of interest: None

Mutilating rheumatoid arthritis (RA) has been reported as one of RA subtype with highly progressive joint destruction and associated poor HAQ activity resistant to any medication including biologics. In this report, we demonstrate addition of leflunomide (LEF) with tocilizumab (TCZ) plus methotrexate (MTX) inhibits progressive joint destruction in patients with mutilating RA. A 41-year-old female had right coxalgia in March 2009. Polyarthritis developed and DAS28-ESR (DAS28) was 4.88 2 months after onset. MTX was administrated for 8 mg per week, however joint destruction progressed. Infliximab (IFX) at 5mg/kg concentration was added from June 2010. Serum CRP level, DAS28 and modified total sharp score (mTSS) increased from 5.5mg/dl to 6.0 mg/dl, from 5.5 to 6.0 and from 21 to 26, respectively 3 months after IFX plus MTX treatment. In September 2010, biological treatment was changed from IFN to TCZ (8mg/kg). Four month later, clinical symptoms improved with 1.47mg/dl of CRP level and 4.95 of DAS28. However, mTSS increased from 26 to 31 (after 4 months) and 54 (after 12 months). LEF (20mg/d) was added in July, 2011. Two months after LEF administration, DAS28 improved to 2.3 and mTSS decreased from 54 to 47.Progression of middle and large joint destruction also has been inhibited.

P3-145

The effect of Tocilizmab(TCZ) on patients with rheumatoid arthritis(RA) in relation to rheumatoid factor(RF) and anti-CCP antibody(ACPA)

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Conflict of interest: None

[Purpose] Both clinical evaluation and the effect of ultrasonography (US) were compared with changes of the titer of ACPA and of RF in 58 patients with RA treated with TCZ. [Methods] ACPA was measured by ELISA method 13 times before and during TCZ treatment in 52 weeks. RF was also measured at the same time. [Results] Mean disease duration was 11.3 years and mean age was 55.0 years. Twenty patients had previous biologics treatment. In patients with the level of ACPA titer less than 20U/ml, the ratio of US level of grade 2/3 was 30% at start changed to 0% at 52 week, and also the level of ACPA titer decreased from 15.4 to 9.1 in 52 weeks. In patients with the level of ACPA titer more than 20U/ml, the ratio of US level of grade 2/3 was 18% at start changed to 0% at 52 week, and also the level of ACPA titer decreased from 160.7 to 120.1($P<0.05$) in 52 weeks. In patients with RF positive group, the ratio of US level of grade 2/3 was 24.1% at start changed to 0% at 52 week, and also the level of ACPA titer decreased from 60 to 40 ($P<0.05$) in 52 weeks. [Conclusion] TCZ treatment in RA patient at 52 week was efficacious, in terms of US improvement in spite of the levels of ACPA and the titer of RF.

P3-146

Multiple Dose, Dose Escalation Study to Evaluate Safety, Tolerability, and Pharmacokinetics (PK) of Subcutaneous (SC) Ixekizumab in Japanese Patients with Rheumatoid Arthritis (RA) on Concomitant Methotrexate (MTX) Treatment

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Conflict of interest: Yes

Objectives: To evaluate the safety, tolerability and PK of multiple SC doses of anti-IL-17 antibody, ixekizumab (LY), in Japanese RA patients (pts). **Methods**: LY was administered SC every 2 weeks (Q2W) at 30, 80, 180 mg, or once weekly (Q1W) at 120 mg for 10 weeks in Japanese RA pts receiving MTX in a randomized, patient/investigator-masked, placebo (PL)-controlled study. **Results**: Total of 32 pts received at least 1 dose of LY (n=24) or PL (n=8); 30 pts (LY=23, PL=7) completed the study. There were 67 adverse events (AEs) reported in 21 pts (LY=15, PL=6); all were mild to moderate, and no dose-related trends were observed. The most common AEs were administration site reaction (8) and injection site erythema (5) in 2 pts each. Infections (9) were observed in 8 pts (LY=4, PL=4). No clinically significant decreases in mean neutrophil, leukocyte, or platelet counts were observed. There were no clinically meaningful changes in clinical laboratory findings, vital signs, or ECGs. C_{max} for LY was achieved by 2 days (Q2W) and 4 days (Q1W), and $t_{1/2}$ was approximately 2 weeks. **Conclusion**: Ixekizumab at doses up to 180 mg Q2W and 120 mg Q1W for 10 weeks was generally well-tolerated in Japanese RA pts on MTX; PK appeared to be slightly less than dose proportional.

P3-147

The relationship between Elbow lengthening and postoperative arc with Coonrad-Morrey TEA : A radiological study

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Conflict of interest: None

[Objectives] This radiological study determines the effect on limb lengthening across the joint after Total Elbow Arthroplasty (TEA) using the Coonrad-Morrey(C-M) prosthesis on patients with Rheumatoid Arthritis. The clinical results were analyzed, focusing on mean arc. [Methods] This is a retrospective study of a consecutive series of patients, who received a C-M total elbow prosthesis, between June 1998 and February 2002. A total of 13 TEA were carried out. The mean age is 62.2±2.0years at the time of operation. Pre and post-operative Mayo Elbow Performance Score (MEPS) of the arc of motion and restricted extension, along with radiographs were taken. The radiographs were taken anterior-posterior (AP) and lateral. The postoperative reference value was then subtracted from the preoperative value to determine absolute elbow lengthening. Overall lengthening after TER was then calculated and, we reviewed between the elbow lengthening and MEPS, arc, restricted extension. [Results] The lengthening of distance is correlate with restricted extension and arc, and low score of MEPS. [Conclusion] Our clinical findings suggest that there is a relationship between lengthening after C-M TEA and clinical results of restricted extension, a decrease of arc motion, or low score of MEPS.

P3-148

Clinical results of NRE type total elbow arthroplasty for rheumatoid arthritis

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Conflict of interest: Yes

【Objectives】We reviewed clinical results of total elbow arthroplasty for rheumatoid arthritis.【Methods】The subjects were 16 elbows of 15 RA patients treated by NRE type TEA over 1-year period. We evaluated them by means of the JOA score for clinical results and radiographic analysis.【Results】The mean preoperative JOA score was 48.4 points, and it had improved to 83.8 points at the time of the final follow-up evaluation. The average preoperative range of motion was 105.7°in flexion, -46.8°in extension, 55.7°in pronation, and 29.7°in supination, contrasted against 135.8°, -26.7°,75.8°, and 57.9°at the last follow-up. 2 ulnar nerve palsy and 1 delayed wound healing occurred, but no intraoperative fracture, dislocation, deep infection occurred.【Conclusion】Our findings suggest that NRE type TEA can produce satisfactory results in the short term.

P3-149

Radiological changes of ulnar drift angle after metacarpophalangeal joints arthroplasty with silicone implant in patients with rheumatoid arthritis

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Conflict of interest: None

[Objectives] The purpose of this study was to investigate the radiological changes of ulnar drift in RA patients underwent metacarpophalangeal (MCP) joint arthroplasty using silicone implants. [Methods] A total of 18 RA patients underwent MCP arthroplasty of all 4 fingers. Ulnar drift angle, correction of ulnar drift angle, and loss of correction angle of 6 months after surgery from angle of immediate postoperatively were examined. We also examined every data divided into two groups of radial fingers and ulnar fingers. [Results] Mean ulnar drift angle was corrected significantly from 43.1°preoperatively to 9.5° immediate postoperatively; however, ulnar drift angle was progressed to 13.7° at 6 months after surgery. Mean correction angle of immediate postoperatively was 33.6°, and loss of correction angle at 6 months after surgery from immediate postoperatively was 4.2°. At 6 months after surgery, mean ulnar drift angle in radial fingers was 18.3° significantly higher than that was 9.2° in ulnar fingers ($p<0.01$). [Conclusion] Ulnar drift in radial fingers might caused by pinch movement having become possible with thumb and radial fingers postoperatively. Therefore, it was thought that soft tissue reconstruction for radial fingers had to perform particularly strongly.

P3-150

Three cases of RA who were able to improve disease activity by hand surgery without changing medicine

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Conflict of interest: None

(Case1: 52-year-old woman) She has been treated with 6 mg of MTX per week but showed moderate disease activity. Arthroplasies of the wrist, thumb MP and fingers (2-5) MP were performed. (Case2: 35-year-old woman) She has been treated with 8 mg of MTX per week but showed moderate disease activity. Arthroplasies of the wrist, index finger MP and middle finger PIP were performed. (Case3: 38-year-old woman) She has been treated with 8 mg of MTX per week but showed moderate disease activity. Synovectomy of the wrist was performed. Over 1-year after surgery, all cases got low disease activity with same dose of MTX, and were satisfied with no symptom and functioning of hand. In RA patients whose arthritis is relatively localized at hand, hand surgery (synovectomy or arthroplasty) seems to be useful to improve disease activity without changing dose of DMARDs or receiving biologics.

P3-151

Limited wrist arthrodesis using strut bone graft for a patient with marked bone resorption resulting from rheumatoid arthritis of bilateral carpal joints

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Conflict of interest: None

Introduction Since the report by Taleisnik (1987), limited wrist arthrodesis has widely been performed as the purpose of maintaining an acceptable range of motion (ROM) and stability. However, for patients with marked bone resorption and palmar dislocation of the carpal bone, total wrist arthrodesis has been unavoidably selected since limited wrist arthrodesis is difficult to complete in those patients. We grafted the strut bone from the ilium into the marrow cavity of the radius and successfully restored the stable carpal joints with a satisfactory ROM. Case Report A 65-year-old woman had noticed bilateral arthralgia for about 10 years, but RA was not diagnosed and she had been left untreated. Plain X-ray revealed the grade IV according to the Larsen classification and stage IV and class III according to the Steinbrocker classification. We grafted her strut bone, fixed the radius with the scaphoid and the lunate to retain a good purchase of wires, followed by post-operative casting and K-wire fixation for about 10 weeks.Painless limited wrist arthrodesis was achieved.Her ROM was 45 degrees for palmar flexion,35 degrees for dorsal flexion. Discussion Insertion of the strut bone into the radial marrow cavity resulted in adequate K-wire fixation and satisfactory limited wrist arthrodesis.

P3-152

Retrospective study of ankle arthrodesis in severe hind foot deformity in patients with rheumatoid arthritis using an intramedullary nail with fin

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Conflict of interest: None

[Objectives] The aim of ankle arthrodesis are the relief of pain and deformity and the development of a solid fusion. We retrospectively reviewed 12 patients(13 ankles) with rheumatoid arthritis (RA) who had undergone ankle arthrodesis using intramedullary nail with fin, from 2001 to 2012. [Methods] The surgical treatment, post-operative management and clinical evaluation are described. They were 10 female and 2 male, and followed from 2001 to 2012 (mean 61 months). The mean duration of RA was 17.8 years. We used intramedullary nail with fin for 13 ankles. Solid fusion was achieved in all patients. Mean time to bone union was 15 weeks. [Results] The patients were able to bear weight fully in an average of three weeks after operation. Nonunion was not observed and no remarkable change of the Chopart joint was recognized between preoperation and the follow-up period. In our series, delayed wound healing was recognized in 2 of 13 ankles, infection was recognized in 1 of 13 ankles,and neuropathy was recognized in 2 of 13 ankles. [Conclusion] IN conclusion, the intramedullary nail with fin was effective for the treatment of severe RA deformity of hind foot, because of high rate union and relatively few complications.

P3-153

Cementless primary total hip arthroplasty in rheumatoid arthritis

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Conflict of interest: None

[Objectives] This study was performed to analyze clinical and radiographic results of a group of RA patients after primary cementless THA. [Methods] Between 2004 and 2011, fifteen RA patients had a cementless prosthssis implanted. Eleven women and 4 men, a mean age of 65.9 years (49 - 75), participated. A mean follow up period was 15 months. The endpoints for survival analysis were failure of one or both components due to radiographic loosening or revision. [Results] Five Trident (Stryker), 8 Trilogy and 2 trabecular metal cup (Zimmer) were used. Five Ominifit (Stryker), 6 Versys and 4 Kinectiv (Zimmer) stem were implanted. One cup needed revision due to aseptic loosening. A Stem had to be exchanged in an early stage. No SSI was seen. All patients were able to walk independently. Allogenic blood transfusions were needed in two patients. Two patients were dead due to hepatic abscess and pulmonary embolism. Two patients were treated with etanercept, and one used tocilizmab. [Conclusion] Cemented total hip arthroplasty has traditionally been considered the gold standard for the treatment of end-stage joint destruction in RA patients. Recently, good results have been reported for cementless total hip replacements. The cementless prosthesis seems to be useful in RA patients.

P3-154

Evaluation of Synovitis among Patients with Rheumatoid Arthritis Undergoing Total Hip Arthroplasty

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Conflict of interest: None

[Objectives] Drug therapy using methotrexate and biologics in patients with rheumatoid arthritis has enabled powerful suppression of inflammation. The present study was undertaken to investigate patients having undergone total hip arthroplasty (THA) with focus set on local disease activity of the hip joint. [Methods] The study involved 17 patients (21 joints) in whose histological evaluation of hip joint synovium was possible among all patients having undergone THA for rheumatoid arthritis. [Results] All of the 17 patients were female, with the mean age being 64.5 years. Mean CRP was 2.74 mg/dL. Median Larsen grade was 5. Using the operative specimens, the severity of inflammation of hip joint synovium was almost slightly and sever for no joint. It was suggested that the severity of synovial inflammation does not correlate with preoperative CRP level. [Conclusion] The hip joint is the depths and has characteristics that it is difficult to detect joint swelling. Therefore, we tend to overlook early inflammation that joint destruction

does not progress. If the appropriate treatment could not be performed at that time, the joint destruction would progress and it results in THA. It is important that we detect local inflammation by ultrasonography and treat joint inflammation in early phase.

P3-155

A case of being able to diagnosis RA oppotunity starting hip contracture

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Conflict of interest: None

[Case] 66Y female [Subjective] right hip contrucure [medical history] A few weeks ago, she felt right hip contracture, and she was consultated from other clinic. [observation] right hip flexion 110° extension -40° WBC 5.200 /ul Hb 12.6g/dl Plt 262 10^3/ul TP 7.5g/dl Alb 3.8 g/dl GOT 23IU/L GPT 35 IU/L LDH 215 IU/L CK 106 IU/L BUN 20.1mg/dl Cr 0.51mg/dl CRP0.10mg/dl RF5.7 U/ml C3 93.8mg/dl C4 12.9mg/dl HBsAg>2000C.O.I HBsAb-HbeAg- HbeAb+ MRI :Although there were not evidence of hemtoma and infection at iliopsoas but inflammation was considerated in synovial membrane. [Post admission] After 2 weeks, we operated synovectomy.Hip contracture was recovered slowly.This case was suspected RA in pathology. It is rare diagnosis RA in opprtunity of starting hip contracture. It is necessary to investigate her care plan consderating fulminant hepatitis.

P3-156

The effect of glucocorticoid on osteoclast differentiation and FK506 binding protein 5 (FKBP5) expression in RAW264.7 murine macrophage cell line

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Conflict of interest: None

[Objectives] Previous studies have disclosed the enhanced expression of FKBP5 mRNA in bone marrow CD34+ cells in rheumatoid arthritis (RA). We have also demonstrated that stable FKBP5 overexpression in RAW264.7 cells resulted in the enhancement of osteoclast differentiation. Of note, RA itself is regarded as a risk factor for osteoporosis. The current studies explore the influence of glucocorticoid on the differentiation of osteoclasts and the expression of FKBP5 mRNA in RAW264.7 cells. [Methods] RAW264.7 cells were incubated with RANKL (30 ng/mL) in the presence of various concentrations of prednisolone for 5 days followed by TRAP staining. RAW264.7 cells were treated with various concentrations of prednisolone for overnight and FKBP5 mRNA was examined by real-time PCR. [Results] Prednisolone enhanced the differentiation of TRAP-positive multinucleated cells from RAW264.7 cells and also upregulated the expression of mRNA for FKBP5 in RAW264.7 cells in a dose-response manner. [Conclusion] The dose-response effect on FKBP5 expression was almost identical to that on TRAP-positive multinucleated cells. The results therefore strongly suggested that glucocorticoid increases osteoclast differentiation from RANKL-stimulated RAW264.7 cells through upregulation of FKBP5 expression.

P3-157

Efficacy and safety of minodronate in the treatment of glucocorticoid-induced osteoporosis

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Conflict of interest: Yes

[Objectives] Minodronate (MIN) is the most potent inhibitor of bone resorption among oral bisphosphonates (BP) used for the treatment of osteoporosis (OP). However, no reports are available so far, which examined the effects of MIN on Glucocorticoid (GC)-induced OP. [Methods] We prospectively investigated the efficacy and safety of MIN on OP patients receiving GC for the treatment of rheumatic (connective tissue) diseases. Methods: Patients (n=25) were treated with MIN (1 mg/day) for 6 months, and bone turnover markers, and lumbar spine (LS) and femoral neck (FN) BMD were measured every three months by DXA. [Results] Anteroposterior and lateral LS BMD, and FN BMD at both sides significantly increased by 4.4%, 7.0%, 5.9% (right FN), and 4.7% (left FN), respectively. Urinary NTx, serum CTx, and TRACP-5b significantly decreased at 3 months and after, and BAP significantly decreased at 6 months after treatment. No incident fracture was observed during the study. One patients developed toothache, which disappeared after withdrawal. [Conclusion] These data demonstrated for the first time that MIN is effective and well tolerated on GC-induced OP. Further studies are of interest to compare the usefulness of MIN with other BPs.

P3-158

The implementation rate of recommendations for prevention and treatment forglucocorticoid-induced osteoporosis in each speciality

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Conflict of interest: None

[Objectives] In 2004,Japanese society for Bone and Mineral Research had published the recommendations for prevention and treatment of glucocorticoid-induced osteoporosis (GIOP). In 2010, ACR (American College of Rheumatology) also revised the recommendations for GIOP and suggested that patients on prednisolone as low as 7.5 mg daily or equivalent for more than 3 months should take anti-osteoporosis drugs.We analyzed the implementation rate of ACR recommendations in our hospital and each specialty. [Methods] A retrospective review of medical records from January to October in 2012 was performed. We evaluated the total rate of minimal standard of care in three group, female patients over 50 years old who were recommended to take bisphosphonates with vitamin D analogue, female patients less than 50 year-old recommended to take vitamin D analogue and, male patients recommended to take bisphosphonates with vitamin D analogue. [Results] 1921 patients were included and the results were 53 .8 % in total, 54.1% in general internal medicine, 52.0% in dermatology, 37.8% in gastroenterology, 34.2% in hematology, 17.7% in ophthalmology, 16.7% in hematology and oncology,11.1% in endocrinology, 1.2% in neurology. [Conclusion] The implementation rates are differ according to each specialty.

P3-159

Effects of bisphosphonate on bone quality in patients with rheumatoid arthritis

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Conflict of interest: None

[Objectives] We prospectively evaluated biochemical markers of bone in rheumatoid arthritis (RA) patients administered bisphosphonate (BP) for the first time. [Methods] A total of 10 RA patients were evaluated. The serum levels of pentosidine, homocysteine, intact P1NP and TRACP-5b before the first dose of BP, then three and six months after starting BP treatment were assessed. The bone mineral density (BMD) was also measured before and six months after starting BP treatment. [Results] The mean serum pentosidine levels changed from 0.036188 (mean level before treatment) to 0.039750 (three months after starting treatment) and 0.053320 (six month after starting treatment), and the mean serum homocysteine levels changed from 8.588 (mean level before treatment) to 9.088 and 8.140(three and six months after starting treatment, respectively). The intact P1NP levels were significantly lower three and six months after starting BP treatment compared to the baseline level. There were no significant differences in the serum TRACP-5b level or the BMD. [Conclusion] There was a trend toward higher serum pentosidine levels six months after initiating BP treatment compared to the baseline level. This study suggests that the serum pentosidine levels in RA patients are increased by BP treatment.

P3-161

Bilateral atypical femoral fracture in a rheumatoid arthritis patient on long-term oral bisphosphonate therapy

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Conflict of interest: None

[objectives] We report a case of bilateral atypical femoral fracture in a rheumatoid arthritis (RA) patient on long-term bisphosphonate therapy. [Case] The patient was a 61-year-old woman who was daignosised with RA(steinbrocker stage III)10 years Ago. She had been prescribed steroids, MTX, and tocilizumab her RA was under control.And she had a 5 year-history of bisphosphonate use. [Elapse] She susutained a subtrochanteric fracture of the left femur when she tumbled on the uneven of her home staircase her home staircase, subsequently invasive osteosynthesis was performed. However,she tumbled again on the same day of her discharge following surgery;this time diaphyseal fracture of the right femur occurred and invasive osteosynthesis was performed again. [conclusion] The relative risk of atypical bone fractures in patients using steroids and active RA patients is 5.2 times and 16.5 times respectively,wiyh long-term usu of bisphosphonates,it is important to exercise extra caution to avoid atypical bone fractures in such patients. There are many cases of RA patients on oral steroids, additionally many of them have been taking these steroids in combination with bisphosphonates for a long period. Hence, more precautions needs to be taken when dealing with atypical fractures.

P3-162

Bone mineral density in female patients of connective tissue diseases

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Conflict of interest: None

[Objectives] Osteoporosis under steroid therapy is yet elucidated.To study influence of steroid on bone mineral density (BMD) in connective tissue disease (CTD) patients. [Methods] Female CTD patients who underwent BMD measure were retrospectively studied for menopause (mp), steroid use, T-score and % age-matched of BMD, anti-osteoporosis and Vit D3 drugs use. [Results] 69 patients aged 57.5±17.0 were included. 25 were pre-mp and 44 were post-mp, 25 had steroid at a dose of 24.9±18.2 mg of PSL and 44 had never. Anti-osteoporosis and Vit D3 use were in 1 and 7 among pre-mp patients, and in 13 and 14 among post-mp patients, respectively. T-score was 0.0±1.2 vs. -1.5±1.2($p<0.05$), and % age-matched was 100.0±12.7 vs. 114.0±22.0%(ns), in pre-mp and post-mp patients. When dividing patients into those with and without steroid, they were -1.5±1.2 vs. -0.7±1.5(ns), and 111.7±24.3 vs. 106.3±18.5%(ns). As for post-mp patients, they were -1.6±1.3 vs. -1.4±1.2 (ns), and 114.7±24.2 vs. 113.3±19.9%(ns). [Conclusion] In spite of a scant use of anti-osteoporotic and Vit D drugs in pre-mp, and its frequent use in post-mp patients, T-score was higher in the former. On the other hand, BMD did not differ between patients without and with steroid.

P3-163

Prospective examination of clinical efficacy of minodronate which is administrated prophylactically in glucocorticoid-induced osteoporosis

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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, and at 6 months after glucocorticoid treatment. Bone mineral density values are measured at the lumbar spine and femoral neck on day 0 and at 6 months 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. [Conclusion] We speculate that minodronate might be good response to bone turnover.

P3-164

A case of osteonecrosis of the jaw treated with teriparatide therapy

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Conflict of interest: None

Osteonecrosis of the jaw (ONJ) is rare but crucial disease because the recommended treatment still remains suboptimal. Recently, a few case reports were published, but no large study was seen. Case: 85 y.o male who had history of RA treated with prednisolone, mizoribine and methotrexate and osteoporosis treated with risedronate for 5 years presented to our clinic in December 2011. He had persistent pain at right mandibular socket after tooth extraction, at which it was surrounded by swollen gingiva with suppuration. We diagnosed as ONJ, so we stopped risedronate and treated only by cleaning cavities and keeping good oral hygiene

without surgical intervention. But there was no improvement in spite of oral care. Five months later, We found the ONJ worse at that time of admission of concomitant acute prostatitis in April 2012. We treated acute prostatitis with ampicillin-sulbactam for 4 weeks. Besides we started teriparatide therapy for osteoporosis at the same time. After treatment of 1 month, ONJ was rapidly improved and severe mandibular pain was dramatically relieved, even though we use antibiotics unintentionally for ONJ. Teriparatide could be optimal treatment for ONJ.

P3-165

Three cases of insufficiency fracture of the ankle and forefoot in rheumatoid arthritis patients

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Conflict of interest: None

We report 3 patients who had 3 insufficiency fracture of the forefoot,lower fibula and tibia. <case1>62y.o.female valgus deformity of the ankle joint was present. fracture of the left lower fibula was diagnosed at 4 month after increasing pain of the ankle <case2>57y.o.female. fracture of the left lower fibula and tibia was diagnosed at 5weeks after increasing pain and swelling of the ankle joint <case3>35y.o.female valgus deformity of the ankle region was present. fracture of the metatarsal(III) was diagnosed at few days after increasing pain of the forefoot. <discussion>foot and ankle symptoms are common in patients with longstanding rheumatoid arthritsis.It is the riskfactors for insufficiency fracture of ankle and forefoot to malaligment of the ankle and hindfoot, long disease histories, joint reconstructive surgery, osteoporosis and corticosteroid therapy.The fractures of distal fibula and medial metatarsal were associated with valgus deformity of the ankle. <conclusion> It was reports that insufficiency fractures had about 70% of all fractures of rheumatoid arthritis patients. Without obvious injuries if such patients experience sudden pain,tenderness,or swelling in the ankle region,insufficiency fractures should be suspected.

P3-166

The evaluation of bone mineral density in rheumatoid arthritis patients undergoing total knee arthroplasty

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Conflict of interest: None

[Objectives] To examine the bone mineral density of rheumatoid arthritis (RA) patients who underwent total knee arthroplasty (TKA). [Methods] 16 RA patients and 29 osteoarthritis (OA) patients who underwent TKA were included. We measured bone mineral density of the lumbar spine and the femoral neck by the methods of dual energy X-ray absorptiometry (DEXA) preoperatively. [Results] Mean Z score of lumbar spine in the front, in the profile and femoral neck in RA patients was 0.4, -0.12 and -0.575, respectively. On the other hand, in OA patients, mean Z score of lumbar spine in the front, in the profile and femoral neck was 1.1, 1.64 and 0.51, respectively. [Conclusion] We verify the deteriorating of bone mineral density, especially in femoral neck in RA patients who undergo TKA, preoperatively.

P3-167

A case of femoral fracture in a patient on bisphosphonate therapy

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Conflict of interest: None

Bisphosphonates have been used in many patients for the prevention of osteoporotic fractures, reports of atypical femoral fractures in patients on long-term is occasionally seen in recent years. We experienced a patient caused subtrochanteric femoral fracture while taking bisphosphonates long term. The patient was a 73-year-old woman admitted thigh pain from a few weeks ago. Cause of the fracture was falling from a standing. She has been rheumatoid arthritis treated with oral prednisolone 7.5mg /day more than twenty years, and osteoporosis with oral alendronate more than 10 years. It showed atypical fractures associated with thickening of the lateral cortical bone and transverse fracture with the spikes medially. Emergency operation (Intramedullary nailing) was performed. Oral alendronate discontinued immediately after the injury, and ultrasound therapy was initiated. Because of steroid osteoporosis, we began human parathyroid hormone therapy 6 months later. Current of 11 months after surgery, bone union is delayed, and considering the autologous bone grafting.

P3-168

Is Glucocorticoid-induced Osteoporosis Recommendation Enough to Determine Anti-osteoporotic Treatment for Rheumatoid Arthritis Patients?

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Conflict of interest: None

[Objectives] We investigated to verify treatment guidelines of osteoporosis applied rheumatoid arthritis (RA) patients and to identify the impact of screening vertebral fractures (VFs) on deciding anti-osteoporotic treatment for these patients [Methods] We investigated to verify treatment guidelines of osteoporosis applied rheumatoid arthritis (RA) patients and to identify the impact of screening vertebral fractures (VFs) on deciding anti-osteoporotic treatment for these patients [Results] We investigated to verify treatment guidelines of osteoporosis applied rheumatoid arthritis (RA) patients and to identify the impact of screening vertebral fractures (VFs) on deciding anti-osteoporotic treatment for these patients [Conclusion] For the decision of anti-osteoporotic treatment for RA patients, screening for VFs and application for NOF guideline in patients not eligible or classified as low risk group according to GIOP recommendation might be required. Is Glucocorticoid-Induced Osteoporosis Recommendation Enough to Determine Anti-osteoporotic Treatment for Rheumatoid Arthritis (RA) Patients?

P3-169

The usefulness of measuring of femoral quadriceps muscle strength using bathroom scale for patients with osteoarthritis of the knee

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Conflict of interest: None

[Objectives] We assessed the reliability of the measuring technique of quadriceps muscle strength using a bathroom scale.

[Methods] The 202 Japanese aged 50-90 years, including participants with knee OA (n=103), and age -matched healthy controls (n=99), were enrolled in the study. Isometric strength of quadriceps was carried out by squashing a cylindrical paper on bathroom scale at his/her popliteal fossa. The control group was classified into the following sub-groups: 1) men with athletic habit, 2) men without athletic habit, 3) women with athletic habit, 4) women without athletic habit. **[Results]** In the men, the muscle strength was significantly lower in the knee OA participants (n=43) compared with controls ($p<0.0001$). In the control group, the muscle strength was significantly higher in the men with athletic habit than men without athletic habit ($p=0.048$). In the women, the muscle strength was significantly lower in the knee OA participants (n=60) compared with controls ($p=0.036$). In the control group, the muscle strength was significantly higher in the women with athletic habit than women without athletic habit ($p=0.016$). **[Conclusion]** The technique might be useful for patients with knee OA in a program of home quadriceps exercises to keep their motivation for the exercise.

P3-170

Does chemically cross-linked hyaluronic acid increase the risk of severe acute inflammatory reactions among Japanese patients with osteoarthritis of the knee?

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Conflict of interest: None

[Objectives] To determine the frequency of severe acute inflammatory reactions (SAIRs) after hylan G-F 20 (Synvisc) intra-articular injections among Japanese patients with osteoarthritis (OA) of the knee. [Methods] Adult patients suffering from knee OA were injected with one syringe (2 ml) of hylan G-F 20 three times, one week apart (one course). If knee pain was repeated, one or two more courses of injection were administered, three months apart. We recorded the cases of SAIRs and sent the questionnaire to all the patients who were treated in our hospital. [Results] In 286 cases, 22 patients had swelling or pain of the knee; 18 cases (6.3%) with hydrarthrosis were diagnosed as SAIRs. Arthrocentesis revealed leukocytosis, no crystals, negative Gram stain and cultures. [Conclusion] We should alert ourselves that 6.3% of SAIRs is unignorable as compared with the rate reported in other countries: 5-23%. We must recognise and inform the patients how often SAIRs occur after hylan G-F 20 intra-articular injections.

P3-171

Two cases of primary osteoarthritis of the tarsometatarsal joints with rotational malalignment of the lower extrtemity

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Conflict of interest: None

【Introduction】 Primary degenerative osteoarthritis of the tarsometatarsal joints is a relatively rare disorder and its pathogenesis is still unkown. Here we report two cases of primary osteoarthritis of the tarsometatarsal joints associated with rotational malalignment of the lower extremity. 【Case reports】 Case 1. A seventy-one-year-old woman presented with left foot pain. She had had an ipsilateral total hip arthroplasty five years before, and the decrease of the femoral neck anteversion was detected on CT images. Case 2. A sixty-two-year-old man presented with left foot pain following a light ankle sprain. The patient had malunited fractures of tibia and fibula with internal rotation. The foot radiographs showed severe degenerative changes and forefoot abduction at the tarsometatarsal joints in both patients. The tarsometatarsal arthrodesis was performed, and the JSSF score improved from 72 preoperatively to 92 postoperatively in case 1, 57 to 91 in case 2, respectively. 【Discussion】 In our cases, internal rotation malalignment of the lower extremity was considered to increase the abductional stress in the tarsometatarsal joints resulting in degenerative osteoarthritis. 【Conclusions】 We must examine the whole leg alignment when we treat the deformity or degenerative change.

P3-172

Relevance of cervical and lumbar spinal instabilities and the degree of progress of hand lesion in patients with rheumatoid arthritis

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Conflict of interest: None

[Objectives] The objectives of this study are to examine relevance of cervical and lumbar spinal instabilities and hand lesion in patients with rheumatoid arthritis (RA). [Methods] Thirty-one patients (4 men and 27 women, mean age 63 (42-83) years), who were examined with radiograph, were included in this study. In cervical spine, we defined the instabilities as atlantodental interval (ADI) > 3 mm, Ranawat-value < 13 mm and anteroposterior translation at middle to lower cervical spine > 3 mm by plain radiograph. In lumbar spine, the instability was defined as anteroposterior translation > 3 mm. We used Steinbrocker's classification to hand lesion. [Results] Six cases (19%) exhibited cervical spinal instability in ADI, 3 cases (10%) were revealed in Ranawat-value and in anteroposterior translation, respectively. Ten cases (32%) exhibited lumbar spinal instability. Hand lesions were classified into stage I in 8 cases (26%), stage II and III in 9 cases (29%) respectively, and stage IV in 5 cases (16%). Instabilities of cervical and lumbar spine were observed significantly higher in stage III and IV compared to stage I and II ($P<0.05$). [Conclusion] A progression of hand lesion was associated with spinal instabilities in lumbar spine as well as cervical spine in patients with RA.

P3-173

Mesurments of cartilage thickness of femoral condyle and epicondylar axis in osteoarthritic knee using 3D-MRI

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Conflict of interest: None

[Objectivese] We measured the effect of cartilage thickness of femoral condyle to the change of the posterior condylar axis (PCA) in varus osteoarthritic knees using 3D-MRI. [Methods] Seventeen patients 18 knees waiting for total or unilateral knee arthroplasty were obtained MRI. MRI was performed at 3T with 3D-VIBE for T1 by one-side 0.6mm cube. PCA and the surgical epicondylar axis (SEA), and the cartilage thickness of posterior condyles were measured. PCA were measured as the cartilage PCA included cartilage and as the bone PCA excluded cartilage. The Hip-Knee-Ankle Angle (HKAA) was measured at the standing position leg full

length Xp. [Results] The average cartilage thickness of medial and lateral posterior condyles were 0.8 mm (0 - 1.1 mm) and 2.2 mm (1.1 - 3.5 mm). The average difference in SEA on the basis of of the bone PCA and the cartilage PCA was 1.8 °(SD=0.9,range-0.4 °to 2.8 °). As for neither, the correlation with HKAA was seen. [Conclusion] The range of the influence of cartilage wear in PCA is 0 to about 3°, and cautions are required when referring to PCA in total knee arthroplasty.

P3-174

Successful management of systemic lupus erythematosus (SLE) with calcineurin inhibitor (CIN) during pregnancy. Compared ofTacrolimus and Ciclosporin

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Conflict of interest: None

[Objectives] We report cases of successful management of systemic lupus erythematosus (SLE) and lupus nephritis with calcineurin inhibitor (CIN) during pregnancy. [Methods] Case 1 was treated with prednisolone (PSL) and tacrolimus (Tac) during pregnancy and trough level of Tac was kept around 2ng/ml.She resulted in the induction of remission during pregnancy and delivered at 36 weeks by cesarean delivery a healthy baby with a birth weight of 2,008 g. She had done breast feeding and the levels of Tac in the blood of the cord and infant were 1/5 of that of mother. Case2 was received PSL and ciclosporine (CsA) combination therapy during pregnancy. She had twice successful pregnancies. The first baby was weighed 2652g and the second baby was weighed 2716g. CsA was effective in controlling SLE activity, but she was advised to avoid breast feeding. [Results & [Conclusion] The success of pregnancy and childbirth in our 2 cases, without any side effects, shows the possibility that CsA and Tac therapy may be considered safe to control a pregnant lupus patients. From the view point of breastfeeding, Tac is more advantageous than a CsA for female planning to become pregnant and breast feeding.

P3-175

Efficacy of tacrolimus for non-renal systemic lupus erythematosus

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Conflict of interest: None

[Objectives] To examine the efficacy of Tacrolimus (TAC) for non-renal systemic lupus erythematosus (SLE) [Methods] We initiated TAC treatment for steroid reduction in SLE patients who satisfy the ACR criteria and have non-renal SLE activity. We evaluated their SLE activity and steroid dose during administration of TAC. [Results] 11patients were recruited and all were female. Average age was 34.1y.o.(22-58), mean disease duration 12.1 years(1-26), and the mean dose of predonisolone was 13.9mg/day(8-20). 16 manifestations including overlap in 11patients were examined. They were consisted of 4 general symptoms, 5 skin symptoms, 4 arthritic symptoms 2 muscular symptoms, and 1 peripheral neuropathy. Improvement of non-renal symptoms was observed in 10 manifestations at 24 week after starting TAC, 13 at 48 week. Average predonisolone dose was 13.9mg/day on initiation, 10.7mg at 24 week, and 9.6mg at 48 week. There were significant differences between the steroid doses of 0week, 24week, and 48week. [Conclusion] These results suggested that TAC was effective for non-renal lupus manifestations and had a steroid sparing effect.

P3-176

Remission of systemic lupus erythematosus after treating coincidental cytomegalovirus septicemia

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Conflict of interest: None

A 42-year-old woman developed arthritis in June 2007. She had been given a diagnosis of idiopathic thrombocytopenic purpura (ITP), and predonisolone (PSL) had been prescribed. Then she had her spleen removed later due to inefficacy on her ITP. In December 2009, she developed a high fever of 39°C, arthritis and skin rash. She was referred to our hospital on the basis of existence of antinuclear antibody of x1280. Positive for antinuclear antibody, presence of immunological abnormalities, serological abnormality, renal failure and erythema, a diagnosis of systemic lupus erythematosus (SLE), complicated with interstitial pneumonia (IP) and autoimmune hepatitis was made. Initially, we could not rule out the possibility of miliary tuberculosis, her condition was worsened. So, we had started PSL treatment (30mg/ day). Her IP and pleural effusion were worsened, despite the use of PSL treatment. Further, she developed MRSA and cytomegalovirus septicemia. To manage the exacerbation of SLE, we treated her cytomegalovirus septicemia with ganciclovir thoroughly. Then gradually her SLE was improving. It has been discussed the association between viral infections and exacerbation of autoimmune disease.

P3-177

In-Hospital outcomes of Methylprednisolone Pulse Therapy in the Treatment of Systemic Lupus Erythematosus

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Conflict of interest: None

Objective: To determine the in-hospital outcomes of patients with systemic lupus erythematosus (SLE) treated with methylprednisolone pulse therapy (MPPT). **Design:** Data of 30 adults with SLE, admitted at Philippine General Hospital from 2008 to 2011, who underwent MPPT, were reviewed. Demographics, disease characteristics, indications for MPPT, and in-hospital outcomes were obtained. Chi-square test and Fisher's exact test were used to elicit association of population characteristics to outcomes. **Results:** Most are females (97%), on their 1st year of illness (70%), and with high disease activity (83%). Infection was seen in 97%. Anemia and hypoalbuminemia were the most common laboratory abnormalities. The top MPPT indication was nephritis (86.7%). Majority (73%) received the standard dose of 1 g methylprednisolone per day for 3 days. Majority (77%) improved, even among those given a lower MPPT dose. Complication rate was 63% while mortality rate was 20%. The most common complications were infection, neuropsychiatric symptoms and hypertension. Standard-dose MPPT was associated with increased complication (p=0.01), but not mortality. **Conclusion:** MPPT is useful in high SLE activity even at a lower dose. The standard MPPT dose may be associated with increased in-hospital complications.

P3-178

A case of purpura fulminans due to *Salmonella* Enteritidis in a patient with systemic lupus erythematosus

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Conflict of interest: None

A 38-year-old woman revealed that she had suffered from lupus nephritis and antiphospholipid syndrome for more than 20 years. She had obtained remission by taking low dose of prednisolone and mizoribine for a while. But she was introduced our hospital because of decline in renal function. As a result of renal biopsy, lupus nephritis (WHO VI) was diagnosed. Two months later, she was conveyed to our hospital by an ambulance due to disturbance of consciousness and dysstasia. She presented with purpura in the limbs end. Labolatory findings showed severe pancytopenia, no thrombus, elevation of procalcitonin and endotoxin. Symmetrical purpura at lower limbs expanded rapidly. She was treated with antibiotics and steroid pulse therapy and underlyed an intensive care, but died after seven hours. The next day, *Salmonella* Enteritidis was isolated on blood culture. Thus, we diagnosed purpura fulminans due to *Salmonella*. Patients with SLE are susceptible to infections, notably salmonellosis, mainly by cellular immunodeficiency and immunosuppressive therapy. Although there are several reports showing the association between SLE and *Salmonella*, purpura fulminans caused by *Salmonella* in SLE is extremely rare. Therefore, we report it with a review of the literature.

P3-179

A case of systemic lupus erythematosus(SLE) in which anaphylactic shock caused by azathioprine(AZP) was suspected

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Conflict of interest: None

Case: A 32-year-old woman. **Chief complaints:** Fever and costovertebral angle (CVA) tenderness on the left side. **Present illness:** The patient had been diagnosed in 200X-1 with SLE. Prednisolone had been administered at 20 mg/day. On June 15,200X, combined use of 50 mg/day AZP was initiated due to persistent serological activity.On June 25, the patient developed a fever of >38°C and CVA tenderness on the left side, and was admitted to our department with suspected pyelonephritis. AZP was discontinued, and an antimicrobial drug was administered. On July 4, administration of 50 mg/day AZP was resumed after confirming that the patient no longer had an infection.Four hours after administration, however, the patient developed a fever of >39°C, reductions in blood pressure and SpO_2, generalized erythema, and edematous changes on the face. No clear signs of infection were seen,and anaphylactic shock caused by AZP was suspected. Systemic condition improved following administration of Bosmin and steroids and so on. **Discussion:** AZP has been shown to be effective not only for rejection after transplantation, but also for autoimmune diseases, and is considered highly safe compared to other treatments. Side effects are observed in rare cases, however, and we report this case as an example of a serious complication.

P3-180

Usefulness of cyclosporine for systemic lupus erythematosus-associated blood cell disorders

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Conflict of interest: None

[Objective] The usefulness of cyclosporine (CSA) for SLE-associated blood cell disorders was investigated. [Subjects] Six patients at the Division of Clinical Immunology and Rheumatology, Osaka Medical College [Results] The blood cell disorder was hemophagocytic syndrome (HPS) in 2 patients, pure red cell aplasia in 1, thrombocytopenia in 2, and thrombocytopenia and leukopenia in 1. 4 patients were female, and the median values were as follows: age, 30.5 years; C3, 54.4 mg/dl; anti-ds-DNA antibody, 9.6 IU/ml; SLEDAI-2K, 15.5; prednisolone, 37.5 mg/day; and CSA, 187.5 mg/day. Anti-Sm antibody was positive in 3 patients, anti-RNP antibody was positive in 3, anti-SS-A antibody was positive in 4, and anti-phospholipid antibody was positive in 3. Regarding organ lesions other than blood cell disorders, 1, 1, and 2 patients were complicated by nephritis, serositis, and arthritis, respectively. CSA improved blood cell disorders with improvement of clinical findings of SLE in 4 patients. CSA was ineffective for the 2 HPS patients, and the disorder was improved after switch to rituximab and VP-16. [Conclusion] CSA was useful for blood cell disorders other than HPS in the SLE patients at our department, and strengthening of treatment was necessary for the HPS cases.

P3-181

A case of systemic lupus erythematosus with generalized lymphadenopathy and elevated serum IgG4

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Conflict of interest: None

59 year-old man was admitted for systemic lupus erythematosus (SLE). He was found to have morning stiffness and arthralgia for 1 month prior to admission. He was diagnosed as SLE according to the ACR criteria (arthralgia, lymphopenia, ANA and anti-double stranded DNA antibody positivity). He had no family history of rheumatic diseases. Computed tomography and FDG-PET showed generalized lymphadenopathy. The elevation of soluble interleukin-2 receptor and serum IgG4 were found. Renal biopsy demonstrated lymphoplasmacytic infiltration in the intertitium. Lymph node biopsy revealed follicular hyperplasia without malignant lymphoma. Few IgG4-positive plasma cells were detected in renal interstitium and lymph node (IgG4 positive/IgG positive plasma cell ratio: 10%). Systemic lymphadenopathy was considered to be secondary to SLE. SLE should be remembered as the cause of systemic lymphadenopathy along with malignant lymphoma and IgG4-related disorder. As the role of IgG4 in SLE has remained to be elucidated, we present this case with some discussion and literature review.

P3-182

A case of SLE developing SLE manifestations 19 years after the onset of myasthenia-gravis

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Conflict of interest: None

[Background] The coexistence of myasthenia gravis (MG) and systemic lupus erythematosus (SLE) has been reported. [Case] A 58-year-old female patient; 23 years before admission, she developed diplopia. Anti-AchR antibody was detected and Tensilon test was positive. The electromyogram showed the wanning phenomenon. She was diagnosed with MG. Thymectomy was performed in the same year and oral corticosteroid was started, then stopped 15 years ago. 7 years before admission, decreased white blood cell counts and anemia with a positive direct Coombs' test were noted. Four years before admission, pleural effusion and patchy infiltrates of the right lung developed. Increased numbers of inflammatory cells consisting mainly of lymphocytes were observed in the effusion. Pathology of the infiltrate showed foreign-body granuloma, accompanying the infiltration of mononuclear cells and polynuclear histiocytes with phagocytosis of foreign bodies. ANA and anti Sm antibody were positive and marked hypocomplementemia was noted. Collectively, she was diagnosed with SLE. With methylprednisolone pulse therapy and oral 30mg of corticosteroid, the pleural effusion decreased promptly and hypocomplementemia gradually improved. [Conclusion] MG patients should undergo evaluation for the coexistence of SLE.

P3-183

A case of lupus pleuritis required the differentiation from malignant mesothelioma

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Conflict of interest: None

A 63-year-old man with systematic lupus erythematosus (SLE) developed chest pain on inspiration, and pleural thickening was confirmed. There was no evident sign of abnormality except for increasing figures of antinuclear antibody and anti-dsDNA antibody examined by a blood test, nor was sign of other serositis found. The thoracoscopy biopsy of pleura was conducted while the patient was hospitalized because the pleural thickening had been advanced. It showed evidence of edematous thickenning of pleural tissue accompanied by proliferation of blood vessels, with fibrin infiltrate on the surface, and minor inflammatory cell. Since indication of malignant mesothelioma or other disorders was negative, the case was diagnosed with lupus pleuritis, and continued 10mg/day PSL administration. Subsequently the pleural thickening was worsening, therefore raised PSL dose to 40mg/day. As a result, the thickening pleural was significantly improved, the figures of anti-dsDNA antibody and CRP improved as well. In this case, pleural thickening was only disorder associated with SLE pleuritis, unaccompanied by pleural effusion in the course, and responsive to PSL administration reflecting the extent of SLE. We report this as an informative case of SLE which succeeded to conduct biopsy.

P3-184

Successful management of fulminant lupus myocarditis with mechanical circulatory support: report of a severe case

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Conflict of interest: None

A 36 years old woman was diagnosed as systemic lupus erythematosus(antinuclear antibody 5,120 times (Sp), anti ds-DNA antibody 42IU/mL, anti Sm antibody 452 U/mL, C3 65 mg/dL, C4 10 mg/dL, WBC2560/μl, joint pains). But she didn't receive the medication. One years later she came to the hospoital with fulminant lupus myocarditis undergoing percutaneous cardiopulmonary support (PCPS) and intra-aortic balloon pumping (IABP). Immediately we started the steroid therapy including mPSL pulse therapy (0.5g/day for 3days) for three times biweekly. One week later we wean this patient off the PCPS and IABP. At first her left ventricular ejection fraction was about 10% by echocardiogram. Finally her EF was recovered about 60%. We could successfully manage the patient with fulminant lupus myocarditis with mechanical circulatory support.

P3-185

A case of SLE complicated with gait disturbance caused by a giant rheumatoid nodule of the right inguinal region

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Conflict of interest: None

We reported a 38-year-old female of SLE associated with giant rheumatoid nodule. She had been diagnosed with SLE in 1992, and was successfully treated with prednisolone. In winter of 2010, subcutaneous nodules with mild tenderness developed mainly on fibular head, heel, malleolus medialis, lateral malleolus, which was pathologically diagnosed of rheumatoid nodule by the biopsy of the left calcaneal region. In spite of combination treatment of PSL and CyclosporinA, subcutaneous nodules newly-developed in the right back, a right inguinal region, the sacral region in October, 2011. She felt difficulty in walking due to right coxalgia and numbness of right leg caused by giant rheumatoid nodules of right inguinal region, and was admitted to our hospital in January 2012. Laboratory data showed that inflammatory markers of ESR and CRP were normal, and serological test of RF and ACPA were both negative. We resected the cystic nodule of the right inguinal region surgically, which was 6cmX6cm in size, and pathological findings showed rheumatoid nodule. But the subcutaneous nodules were resistant to even IV-CY therapy. We carefully treat her nodules with a steroid local administration now. We here discuss about the association of SLE and rheumatoid nodule, and review related literatures.

P3-186

Carpal tunnel syndrome associated with tenosynovitis in a man with SLE: use of ultrasonographic study in diagnosing the involvement

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Conflict of interest: None

A 43 years old man had appeared proteinuria, leg edema. The numbness of both hands and a grip fall got worse gradually. The pathologic study of the kidney revealed membranous nephropathy. An antinuclear antibody positivity and lymphocyte reduction were accepted. The pain fall was in agreement with the median nerve domain, Tinel signs, and Phalen test positivity, and the conduction-rate fall of the median nerve was accepted.It found the swelling of

extensor/flexor tendon of both hands joint, and a power doppler (PD) positivity, and the median nerve was also PD positivity by ultrasonography. The contrast-enhanced effect was accepted in canalis carpi, and it was proved that it is the carpal tunnel syndrome by tenosynovitis. It was diagnosed as SLE, he started to take the amount of steroid middle classes, and tacrolimus 3mg/day. The subjective symptoms and the laboratory findings such as ultrasonography was gradually improved. Most examples of a detailed report about the carpal tunnel syndrome accompanying this disease cannot be found. In this case, the carpal tunnel syndrome by tenosynovitis has improved by treatment for SLE, and the ultrasonographic test was useful to the diagnosis and curative effect judging. Bibliographic consideration is added and reported.

P3-187

The efficacy and safety of tacrolimus to SLE patients with cytopenia

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Conflict of interest: None

[Objectives] To evaluate the efficacy and safety of tacrolimus (TAC) in SLE patients with flare-up of cytopenia. [Methods] Cytopenia was defined as < 3000/μl of WBC or < 10×10^3/μl of PLT. Fourteen SLE patients (1 man and 13 women) with flare-up of cytopenia were treated with TAC in addition to prednisolone (PSL). [Results] Mean PSL dose before TAC therapy was 12.7±8.1 mg/day. WBC, PLT, and the serum C3 level were 2966 ± 1222/μl, $20.5\times10^3 \pm 10^3$ /μl, and 65.1 ± 16.4 mg/dl, respectively. TAC in addition to PSL was 2.1±1.4 mg/day. WBC, PLT, and the serum C3 level 1 year after TAC therapy were significantly increased 6150 ± 1741/μl, $26.2\times10^3 \pm 8.9\times10^3$/μl, and 77.9 ± 18.6 mg/dl (P=0.0002, 0.0134, 0.0027), respectively. PSL dose 1 year after TAC therapy was reduced to 8.9±4.9 mg/day. Nausea, and elevated serum creatinine were observed in a patient each, and improved by the reduction of TAC dose. [Conclusion] TAC is efficient and well tolerated in SLE patients with cytopenia.

P3-188

Combination therapy with azathioprine(AZP) and tacrolimus (Tac) in refractory systemic lupus erythematosus(SLE)

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Conflict of interest: None

[Objectives] To evaluate the efficacy and safety of the combination therapy with AZP and Tac in SLE refractory to steroids. [Methods] Nineteen SLE patients (4 men and 15 women) were enrolled. AZP dose ranged from 25 mg to 125 mg/day and Tac dose ranged from 0.5 to 5 mg/day. [Results] Prednisolone dose and serum C3 level before the combination therapy were 22.3±12.3mg/day and 65.3±18.2mg/dl respectively. Serum C3 level at one year after the combination therapy was 75±14.5mg/day. SLE had improved 18 patients, and had failed to respond to treatment in one. [Conclusion] The combination therapy with AZP and Tac is efficient and well torelated in refractory SLE.

P3-189

Severe dysphasia in Polymyositis and Dermatomyositis : Clinical characteristics, Treatment, and Outcome

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Conflict of interest: None

【Objective】 To asses the clinical characteristics, treatment, and outcome of patients with Polymyositis (PM)/Dermatomyositis (DM) associated severe dysphasia ; required tube-feeding or Percutaneous endoscopic gastrostomy (PEG). 【Method】 We retrospectively reviewed the medical record of all patients with PM/DM seen at the National Tokyo medical center, between April 1 2010 and August 31 2012. 【Result】 A total 35 patients (10 men and 15 women; mean age 60.2 years) with PM/DM were Visited National Tokyo Medical Center. Of these, 5 patient with severe dysphasia (2 men, 3 women; 1 PM-patient, 4 DM-patients, average duration of disease 4.4 years.), and 30 patient without severe dysphasia (8 men, 22 women; 14 PM-patient, 16 DM-patients, average duration of disease 10.4 years.) 【conclusion】 Dysphasia is a serious and at times presenting problem in patients with PM/DM. It may appears to be more frequency in patient with DM, with carcinoma.

P3-190

Three cases of polymyositis/dermatomyositis with anti PM-Scl antibody

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Conflict of interest: None

We described clinical profiles and courses of 3 patients with polymyositis /dermatomyositis(PM/DM) with anti PM-Scl antibody. First case was 77-year-old female with amyopathic clinical course. She was also positive for MPO-ANCA. The chest CT showed interstitial pneumonia and her clinical course was rapidly progressive. We started intensive immunosuppressive therapy with prednisolone (PSL) and cyclosporine-A (CyA), and the pneumonia had gradually improved. Second case was 72-year-old male, who had interstitial pneumonia with clinically amyopathic DM. In spite of the intensive immunosuppressive therapy with intravenous cyclophosphamide and intravenous immunoglobulin, the pneumonia did not improve. The last case was 76-year-old male with hypomyopathic DM. After the initiation of PSL and CyA, his dermatomyositis started to improve. We have reviewed few cases reported in the Japanese literature of polymyositis/dermatomyositis with anti PM-Scl antibody, and we make this report to broaden knowledge available on this topic.

P3-191

A case of overlap syndrome successfully treated with tocilizumab

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Conflict of interest: None

[Case] A 40 years-old woman. She noticed Raynaud Phenomenon, ulceration of the fingertip, myalgia, and heliotrope rash from 2002. Chest CT scan revealed interstitial pneumonia (IP). She was diagnosed as overlap syndrome, and treated with PSL (60mg) from 2003. It was difficult to taper PSL to lower dosage in spite of the

combination of CyA or cyclophosphamide because of elevation of CK. In 2009, She noticed arthralgia at her right wrist. Anti-CCP Ab (≧100 U/ml) and RF (28 IU/ml) were positive. MRI revealed active synovitis, bone erosion and bone marrow edema at the wrist joint. Therefore we diagnosed her as RA complicated with overlap syndrome. MTX worsen interstitial shadow of IP. Adalimumab improved her arthritis but worsened myositis. So adalimumab was discontinued, and treated with IVIG. The effect of IVIG was temporally and insufficient. Therefore we decided to prepare tocilizumab on July 2012. Her symptom improved quickly and CK improved gradually from two month after the induction of tocilizumab. **[Discussion]**In this case tocilizumab improved not only arthritis but also myositis. Only a few cases are reported about the efficacy of tocilizumab for myositis. Tocilizumab may be effective therapy for refractory myositis.

P3-192

A case of interstitial lung disease associated with dermatomyositis with posterior reversible encephalopathy syndorome (PRES) and thrombotic microangiopathy (TMA) induced by cyclosporine

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Conflict of interest: None

A 49 years old woman developed dyspnea on exertion in April 2012. After a month, she was diagnosed as interstitial pneumonia associated with dermatomyositis because of Gottron's sign, muscle weakness, myopathic changes on electromyography, elevated serum levels of CK and KL-6, and ground-glass opacity in the chest CT. She was treated with steroid therapy with unfavorable response, and was referred to our hospital. The combination of intravenous pulse cyclophosphamide, cyclosporine, and prednisolone were initiated. Thrombocytopenia, hemolytic anemia, schizocytes, and renal insufficiency were observed 27 days after the combination therapy. She was diagnosed with TMA. Plasma exchange (PE) was performed, but convulsion and consciousness disturbance were appeared. T2WI and flair images of brain MRI showed high intensity in occipital white matter. She was diagnosed as PRES and cyclosporine was discontinued, resulting in the improvement of her consciousness. TMA and interstitial pneumonia were improved by treating with repeated PE, mycophenolate mofetil, and prednisolone.

P3-193

A case of anti-aminoacyl transfer RNA synthetase antibody syndrome associated with psoriasis vulgaris

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Conflict of interest: None

A 31 - year old woman had been aware of skin lesion in elbow and knee for 10 years and dry cough for 2 years. After she visited dermatologist in our hospital, skin biopsy was conducted from red eruption with hyperkeratosis in knee and she was diagnosed with psoriasis vulgaris. As she complained of deformity of finger joints with and chest CT showed interstitial pneumonia, she was consultated to our department for further investigation. On physical examination, Gottron's papule was confirmed on dorsal side of finger joints and mechanic's hand was confirmed on lateral side of index finger. Laboratory data showed elevated CRP and KL-6, and anti-Jo-1 antibody was positive. Hand X-ray showed subluxation of right 2nd and 3rd distal interphalangeal joints. She was diagnosed as having anti-aminoacyl transfer RNA synthetase (ARS) antibody syndrome. After administration of 60mg of prednisolone for interstitial pneumonea, dry cough was improved and the level of CRP, anti-Jo-1 antibody and KL-6 were decreased. But, interstitial pneumonia was not improved on CT. It seems careful follow-up of this patient will be needed. Anti-ARS antibody syndrome with psoriasis vulgaris is rare and we discuss this case with previous reports.

P3-194

A case of inflammatory myositis accompanying Campylobacter enteritis

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Conflict of interest: None

The patient was a 78-year-old male in whom systemic myalgia, weakness of the four limbs, watery diarrhea, and nausea developed on July 29, 2012. Since weakness of the four limbs progressed, the patient visited our hospital on July 31. Fever,myalgia and reduced muscle strength dominant in the proximal muscles of the four limbs were noted. CPK was 40,860 U/ℓ and aldolase was 195.6 U/ℓ, showing marked elevations of myogenic enzymes. CRP was 13.7 mg/dl. Anti-nuclear, Jo-1, ds-DNA, SS-A, and RNP antibodies were negative, and the C3 level was 102 mg/dl. Thyroid function was normal. On abdominal CT, hypertrophy of the wall was noted in the ileocecal region over the ascending colon. When the left shoulder, in which myalgia was the severest, was examined by MRI, a diffusely high intensity was noted in an extensive muscular region, and this region was enhanced on contrast imaging. Thermophilic Campylobacter was detected in fecal culture. After admission, diarrhea and nausea were remitted by fluid replacement and antibiotic administration, myalgia and weakness were improved within the 10-day course, myogenic enzymelevels decreased. To our knowledge, only one case of inflammatory myositis accompanying Campylobacter enteritis has previously been reported, and this was a rare case.

P3-195

A case of polymyositis with cancer of unknown primary lesion

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Conflict of interest: None

The patient was 84-year-old man. He was admitted to our hospital complaining of severe proximal muscle weakness and tenderness. He displayed no skin changes suggestive dermatomyositis (DM). We diagnosed it as polymyositis (PM) because of high titer creatine kinase (CK) and histological findings of lymphocytic infiltration in the muscle biopsy specimen. At the same time, we recognized lymph nodes swelling in lower portion of abdominal aorta and left inguinal lesion. Poorly differential adenocarcinoma was detected by biopsy specimen of left inguinal lymph node. Although gastrointestinal endoscopies, enhanced CT and PET were performed, primary lesion could not be identified. His general condition was gradually worsened by muscle weakness and dysphagia, so we started to treatment with prednisolone (PSL) 50mg/day. Al-

though his CK titer was improved after treatment, symptoms of myositis did not improve. The risk of cancer is increased in DM and PM, but there is a greater risk with DM when compared to those with PM. Although some cases of DM associated with cancer of unknown primary lesion are reported, PM associated with cancer of primary lesion is extremely rare.

P3-196

A rare case of polymyositis (PM) with the Signal recognition particle(SRP) antibody complicated with Adult onset still disease

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Conflict of interest: None

A 55-year-old female was admitted to our hospital with myalgia and weakness in her limbs and swallowing difficulty. The levels of Creatinine kinase (CK) and Aldolase (ALD) were 5185 IU/l and 62.4 U/l respectively. She was diagnosed as polymyositis (PM) and 50 mg/day of prednisolone (PSL) and 150 mg/day of Azatioprine (AZP) were initiated on her 2nd hospital day. On the 8th hospital day, she complicated adult onset still disese (AOSD) with high fever, arthralgia, salmon pink rash and elevations of serum CRP and Ferritin levels. High-dose mPSL pulse was initiated 3 days and changed from azathioprine to 150 mg/day of cyclosporine (CSA). But a few days later, CSA was changed to 3 mg/day of tacrorimus for drug-induced liver injury. Though her fever and arthralgia had improved, serum inflammatory appearance had continued. In addition it revealed the Signal recognition particle (SRP) antibody was positive, 500 mg/body of intravenous cyclophosphamide (IVCY) was initiated. Her clinical and laboratory findings of PM and AOSD gradually improved.

P3-197

A case of dermatomyositis associated with interstitial pneumonia accompanied by persistent pneumomediastinum and pneumoderma

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Conflict of interest: None

[Introduction] Interstitial pneumonia (IP) as a complication of dermatomyositis (DM) generally shows poor prognoses in patients developing pneumomediastinum (PMD). [A case report] A 42-year-old man complained of limb myalgia, erythema in eyelid, finger and knee regions, and dyspnea. His local doctor found lung lesion with CT and introduce him to us. Based on skin and muscle biopsy results, we diagnosed DM associated with IP. DM was cured with a steroid therapy. Rehabilitation exercise caused the rupture of his left external iliac artery developing a large hematoma, which healed conservatively. We added an IVCY therapy for IP accompanied by PMD. Although IP and PMD once ameliorated, dose reduction of steroid worsened them again along with skin lesions and induced pneumoderma (PD) additionally. While dose increase of steroid and addition of cyclosporine cured skin lesions soon, they brought about only slow improvement of IP and PMD/PD. [Discussion] Several factors are thought to contribute the pathogenesis of PMD in DM; IP-related one, steroid-related one, vasculitis-related one, etc. In this case, the steroid-related factor seemed to take the best part, because of the persistency of PMD and the tissue fragility reasoned by the arterial rupture during initial steroid treatment.

P3-198

Efficacy of IVIG therapy for refractory polymiositis

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Conflict of interest: None

[Objectives] In October, 2010, IVIG was approved as drug for Steroid-resistant polymyositis / dermatomyositis(PM/DM) with muscle weakness.We experienced two cases that enforced an IVIG and reviewed efficacy and availability of IVIG therapy for refractory PM. [Methods] Case report of two refractory polymiositis cases in our hospital. [Results] [Case 1] 31 years old woman. After abortion, it showed elevation of CK (3,029IU/L), and she showed muscle weakness of proximal muscle, and it was diagnosed as PM by muscle biopsy, and was performed steroid therapy and twice steroid pulse therapy, but because CK high level, muscle weakness remained, we performed IVIG therapy. [Case 2] 57 years old woman did follow-up in 300-400 CK IU/L a few years ago, but it increased to 1,834 CK IU/L in August, 2012, and it was diagnosed as PM by muscle biopsy, and was performed steroid large therapy, but cytomegalovirus infection was suspected six weeks later and performed IVIG therapy.In two cases recovered with enforced an IVIG therapy, the level of CK decreased, showed normalization of CK, amelioration of subjective symptom. [Conclusion] We performed IVIG therapy for 2 refractory PM cases and succeeded. We are investigating all cases registration now, and evidence to proper use of IVIG is waited for.

P3-199

Clinical characteristics of Takayasu arteritis

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Conflict of interest: None

[Objectives] To clarify clinical manifestations, laboratory data, images and treatment of Takayasu arteritis. [Methods] I retrospectively investigated 25 cases who were diagnosed Takayasu arteritis in our department since January, 2003 to September, 2012. [Results] The average age was 44.6±18.3 years old, and the sex ratio was 2:23. Onset age was 33.6±18.5 years old, and 15 cases was 10-20 years old. Common signs and symptoms were fever, headache, general malaise, easy fatigability of upper extremities, arthralgia, neck pain, dizziness and lack of pulse. White blood-cell count was 9238 ± 3838/mm^3, CRP 5.80±5.91 mg/dL, IgG 1,603±520 mg/dL, fibrinogen 506±129 mg/dL. Antinuclear antibody and rheumatoid factor were positive in two cases, respectively. HLA - B52 allele was positive in eight of 13 cases. Type I was 11 cases and type V was eight cases. A macaroni signature was detected in four of seven cases in carotid ultrasound examination. Nineteen patients was treated with glucocorticoids. Immunosuppressive agents were prescribed together in 12 cases. [Conclusion] Most patients with Takayasu arteritis were women, and the HLA-B52 allele was frequently positive. The disease activities were high, and there were many cases to need the combination of glucocorticoids and immunosuppressants.

P3-200

A rare case of HLA typing in a patient of Takayasu's arteritis associated with ulcerative colitis

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Conflict of interest: None

A 26-year-old man consulted our hospital due to fever and nausea.Infectious disease was suspected with high C-reactive protein (CRP) level,but obvious focus could not be detected.As antibiotic therapy was ineffective,computed tomography (CT) was performed.That showed wall thickening of aorta and its proximal branches. Then Takayasu's arteritis (TA) was diagnosed,and steroid therapy was started.In the course of treatment,clinical remission had been kept.After three years exacerbation of TA was suspected because of elevation of CRP level.Though steroid dose was increased,improvement was insufficient.Thereafter the patient complained of dull pain around hip and persistent diarrhea.CT revealed wall thickening of colon,and colonoscopy revealed hemorrhagic mucosa and multiple erosions.Biopsy study showed infiltlation of inflammatory cells and crypt abscess.Ulcerative colitis (UC) was diagnosed and steroid dose was increased in accompanied with mesalazine.There are some case reports about association of TA and UC.These two disease are strongly related in the basis of genetic factors.Significant high frequencies of the haplotype of HLA-A24,B52,DR2 was demonstrated in coexistence of TA and UC.Our case showed A11,31,B-35,54,DR-4,15 and none of generally reported typing.

P3-201

Case report and review of patients diagnosed as aortitis syndrome and ulcerative colitis

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Conflict of interest: None

We present a rare case diagnosed with aortitis syndrome and ulcerative colitis (UC). The patient was diagnosed as ulcerative colitis at the age of 14 and was in clinical remission by treatments with mesalazine. At the age of 19, he noticed continueous pain in neck and was referred to ENT clinic. Neck contrast computed tomography revealed narrowing of the left carotid artery. At the initial referral, examination showed weak radial pulsation, >20 mmHg systolic blood pressure difference, and bruit on the left side of the neck. Laboratory examination showed elevated serum C-reactive protein level. Excercebation of UC was not present. In our department, we experienced 2 additional cases of aortitis syndrome and UC, which led us to speculate that the disease may be independant disease entity. Literature search revealed that the most of the cases are reported from Japan, relatively higher incidence in male, precedence of UC, and many of them were *HLA-B*52* carrier. We compare our 3 cases with aortitis syndrome and ulcerative colitis with previously reported 40 cases in past 80 years.

P3-202

A case of takayasu arteritis coexisting coronary artery aneurysm

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Conflict of interest: None

Forty seven-year-old women, she has no particular family history and past history with arteriosclerosis. Since December 2011, exertional chest pain and dyspnea were noticed. On January 2012, neck pain over the back and left precordia pain were appeared without trigger. Body temperature was 37.9°C, blood pressure were 138/72mmHg (right) and 118/90mmHg (left), feeble pulse of the left radial artery and tenderness and the bruit of the right neck artery. No vasculitis findings were found in the funduscopy. Serum level of CRP was 1.88 mg/dl, erythrocyte sedimentation rate was 43 mm/h and HLA typing B52 was positive. Contrast enhanced CT showed diffuse wall thickening from aortic arch to the iliac artery, subclavian artery and common artery, and stenosis of superior mesenteric artery and left renal artery. The coronary angiography revealed left coronary artery aneurysm and 90% of stenosis of the left coronary arteries and the right coronary artery. For active takayasu arteritis, prednisolone (1 mg/kg) was started and adds to azathioprine (2 mg/kg). Fever, tenderness, angina attack and blood examination were improved. Although the frequency of the takayasu arteritis coexisting coronary artery disease was reported about 10%, coexisting coronary artery aneurysm was rare.

P3-203

A rare case of 28-year-old woman with peripheral artery disease and coronary aneurysm due to Takayasu arteritis

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Conflict of interest: None

The case is a 28-year-old woman with no smoking history. Two years ago, Raynaud's phenomenon on her left fingers and sudden left visual loss emerged. She was diagnosed with hypertensive retinopathy and the treatment with antihypertensive drugs ameliorated her symptoms. One and a half years later, she was referred to our hospital for further examination of coldness and numbness of her right foot. The contrast enhanced CT revealed occlusion of left radial artery and remarkable stenosis of bilateral tibial arteries. Because she had neither the evidence of large vessel vasculitis nor positive laboratory findings except for the acceleration of ESR, we could not provide a definite diagnosis. Thus, she was followed by the medication with antiplatelet drugs and vasodilators. Thereafter, a left coronary artery aneurysm was found and she developed right hand coldness and pain, left visual loss caused by papilledema. While FDG-PET showed no abnormal findings and typical HLA-B27, B51, B57 were negative, the diagnosis of Takayasu arteritis with coronary aneurysm was made by exclusion of other possible diseases. The treatment with PSL 40 mg/day has just initiated at present. To the best of our knowledge, this is the first case of Takayasu arteritis with peripheral artery disease.

P3-204

A case of aortic aneurysm with anti Chlamydophilia pneumoniae antibody continuous positive

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Conflict of interest: None

A 78-year-old woman with urine occult blood since 1985 was diagnosed as interstitial nephritis by kidney biopsy in 1998. Corti-

costeroid treatment was performed because of a finding of vasculitis by biopsy. In 2002, multiple erythemas with pain were seen in left lower leg and diagnosed as erythema nodosum by biopsy. The erythema decreased by corticosteroid and cyclophosphamide treatment. In 2004, she felt chest pain and diagnosed as aortic aneurysm. In 2005 and 2006, graft replacement surgery was performed. Histopathologically, aorta showed atherosclerosis and infiltration of inflammatory cells around vasa vasorum in adventitia and media. Cystic medial necrosis with degeneration of elastic fiber in the media was also seen. We diagnosed as inflammatory aortic aneurysm with cystic medial necrosis. Chlamydia was proved in aortic tissue immunohistochemically, and there was persistent high level of IgM antibody for Chlamydophila pneumoniae in blood. It suggested Chlamydia might be the cause of inflammatory aortic aneurysm.

P3-205

Successful treatment with tocilizumab (TCZ) in patient with Takayasu's arteritis (TA)

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Conflict of interest: None

A 28-year-old female was admitted to our hospital on 7 February 2007,because of high fever, left neck pain.She had bruits in her left neck. The laboratory data revealed high CRP. Computed tomography (CT) showed wall thickening and luminal narrowing of the both common carotid artery, the left internal carotid artery and the left subclavian artery. She was diagnosed with TA. Administration of daily 30mg PSL was started. Although clinical symptoms improved temporary, she repeated relapse when the PSL dose was reduced. The treatment of CsA was added in May 2009. But she couldn't reduce to below daily15mg PSL because continuous of high disease activity. MTX and IFX were started in January 2012. She was able to get improvement for a while, but high fever and abdominal pain revealed in June. CT showed wall thickening of abdominal aorta, she was diagnosed with TA relapse. Increased daily 30mg PSL and TCZ (8mg/kg/4wks) were administered. After these treatments, she maintains remission. In TA inflammatory cytokines such as TNFα and IL-6 increases as well as rheumatoid arthritis. The present case, a treatment-resistant of PSL, CsA and IFX, was able to inhibit relapse of TA with TCZ. Because IL-6 promote the production of endothelial cell growth factor, TCZ may be an effective drug for TA.

P3-206

Two Cases of Refractory Aortitis Syndrome successfully treated with Infliximab

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Conflict of interest: None

Recently, the effectiveness of biological products for refractory aortitis syndrome has been reported. We reported that two cases of aortitis syndrome that did not make a response to conventional therapy and successfully treated with infliximab (IFX). Case1: 33-year-old woman, chief complain were fever and headache. This case was treated with prednisolone (PSL) and immunosuppressants such as azathioprine (AZP) and methotrexate (MTX), cyclosporine A (CsA), cyclophosphamide (CY). However, this case was required high dose PSL to achieve clinical remission of aortitis and was not effective to immunosuppressants. Therefore, IFX therapy was started at 37 years old, Ischemic symptoms and laboratory findings were improved immediately. this case was enabled to finish IFX treatment because of long-term remission after a total of 18 doses over a period of two and a half years, and has been maintained a clinical remission during about two year follow-up period. Case2: 23-year-old man, chief complain were fever and chest pain. This case was treated with PSL and AZP, MTX, CsA, CY, although was not effective to conventional therapy. IFX therapy was started at 24 years old, similar to case1, ischemic symptoms and laboratory findings were improved immediately.

P3-207

A case of Takayasu's Arteritis concomitant with Crohn's disease during Infliximab therapy

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Conflict of interest: None

A 29-year old man developed abdominal pain and nausea in February 2011, and Crohn's disease (CD) was diagnosed by colonoscopy findings. He was treated with 5-aminosalicylic acid (5-ASA) and infliximab 5mg/kg. 6 months later, he presented abdominal pain and elevated inflammatory markers. The dose of infliximab was increased to 10mg/kg. In March 2012, he was admitted to our hospital because of back pain, headache and persisting elevated inflammatory markers. From the colonoscopy examination, the activity of CD seemed to be well controlled. CT scanning showed the thickening of the wall of SMA suggesting aortitis. PET-CT showed the accumulation in bilateral internal carotid artery and descending aorta. In addition, HLA-B52 was positive. From these findings Takayasu's Arteritis (TA) was diagnosed. He was treated with corticosteroids, the symptoms and elevated inflammatory markers were improved. Follow up CT demonstrated the improvement of the arterial wall thickening. There are some case reports about the co-existence of TA and CD. On the other hand, the development of autoimmune diseases (including vasculitis) related to TNF-targeted therapies has been reported. We report a case of Takayasu's Arteritis concomitant with Crohn's disease during Infliximab therapy.

P3-208

A case of Takayasu disease developing under treatment with Adalimumab for Ulcerative colitis

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Conflict of interest: None

A 24-year-old woman who had been treated ulcerative colitis (UC) with adalimumab, was admitted to the hospital because of spike fever and neck pain. Her laboratory data showed high inflammatory reaction (CRP 25mg/dl), and contrast CT image of body revealed wall thickness of internal carotid arteries, subclavian artery, and the aortic arch. Positron Emission Tomography (PET) showed high uptake in the aortic arch. She was diagnose with Takayasu disease complicated with UC, and treated with high dose corticosteroid, methotrexate, resulting in improvement of arteritis. The pathogenesis of Takayasu disease is largely unknown. TNF-alufa inhibitor have been reported as key drug for steroid-resistant patients of Takayasu disease. However, interestingly in this case, she developed arteritis under treatment with Adalimumab, suggesting

the complexity of immune-pathogenesis of Takayasu arteritis.

P3-209

Japanese patients with biopsy-proven giant cell arteritis: Report of eleven cases

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Conflict of interest: None

[Objectives] To clarify the characteristics and imaging results of Japanese patients with giant cell arteritis (GCA). [Methods] Eleven patients with biopsy proven GCA were enrolled. Their clinical data and imaging results were retrospectively examined from their medical records. [Results] All the patients met the Criteria for the classification of GCA by the ACR. Although the clinical manifestations are similar to those previously reported, none of 11 patients presented ocular symptoms. US of temporal artery showed the halo sign in all the patients. FDG-PET was performed in six patients and indicated the presence of aortitis of the patients. [Conclusion] US is a quick and non-invasive test to detect the inflammation of temporal artery and FDG-PET is very helpful for the early diagnosis of aortitis in GCA. Awareness of the disease and appropriate imaging tests will result in a diagnosis of GCA.

P3-210

Juvenile temporal arteritis: A case report

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Conflict of interest: None

A 30-year-old woman presented to our hospital with a painful slow-growing nodule on the right temporal area. The nodule, which she had first noticed 6 month previously, was well demarcated and had a diamater of 2.5cm. There was no evidence of systemic diseases, history of trauma or surgery in the area. Laboratory data showed slight eosinophilia (600/ μL). C-reactive protein was 0.27mg / ml. MPO/PR3-ANCA were negative. The histological examination of the nodule revealed temporal arteritis with lymphoeosinophilic granulomatous infiltrate and perivascular extension of inflammatory infiltrate of eosinophils. A diagnosis of Juvenile temporal arthritis (JTA) was made. The patient was well with no evidence of recurrence at 3 month after surgery. JTA is a rare disease of unknown etiology, however, has a benign clinical course and it is curable by surgical excision.

P3-211

A case of central retinal artery occlusion(CRAO) and posterior ischemic optic neuropathy(PION) associated with temporal arteritis

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Conflict of interest: None

The patient was a 89-year-old man, who treated with steroids for polymyalgia rheumatica two years ago, had tapered off predonisolone a year ago. He aware of the blurred vision of the right eye, leading to blindness after 5 days. Central retinal artery obstruction (CRAO) was diagnosed in his right eye. Because of the cerebral CT lack of evidence of cerebral infarct, antiplatelet therapy was continued. One month after onset of CRAO, he felt blurred vision in the left eye. As left eye had been exhibit of inferior horizontal hemianopia, and ocular fundus in his left eye was normal, he diagnosed as posterior ischemic optic neuritis (PION). He hospitalized to department of neurology. Afterthen gradually jaw claudication appeared, he reffered to department of rheumatology. Temporal arteritis was suspected because of the elevation of ESR and CRP and the tenderness of temporal artery. On the diagnosed day, methylpredonisolone pulse therapy was administrated. Left field has been restored completely despite steroid pulse therapy was started on the eighth day from onset.

P3-212

Successful high-dose IVIg therapy in a patient with polyarteritis nodosa

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Conflict of interest: None

We report successful intravenous immunoglobulin (IVIg) use in a patient with refractory polyarteritis nodosa (PAN). Treatments with prednisolone (PSL) and various types of immunosuppressants including methotrexate and intravenous cyclophosphamide (IVCY) were unsuccessful. High-dose IVIg therapy was then started. By IVIg treatment, high fever, arthralgia, mononeuritis multiplex and eruption (erythema) with induration improved. Moreover, Normalization of inflammatory markers was confirmed. High dose IVIg is an excellent treatment for refractory PAN. We demonstrated and considered this case with some literature.

P3-213

A case report of sever cryoglobulinemic vasculitis

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Conflict of interest: None

We report the clinical course of one patient with sever cryoglobulinemic vasculitis (CV) who had HCV infection, treatment of the HCV infection with antiviral agents was not indicated. A 43-year-old man presented with 2 months history of multiple ulcers, edema in his extremities. His condition worsened rapidly with acute cardiac failure and severe anemia. And he was referaled to our hospital. At admission, the cryoglobulin test was positive for type II mixed cryoglobulinemia. Serological test for HCV was positive. A skin biopsy revealed leukocytoclastic vasculitis. The diagnosis was HCV-related CV with acute cardiac failure, skin lesions, peripheral neuropathy, glomerulonephritis and anemia. The patient received three times cryofiltrations, followed by two infusions of rituximab (1000mg/body, biweekly) and oral prednisone (1mg/kg/day). C-reactive protein improved, but HCV-viral load and hyperviscosity syndrome worsened. Then, we performed several cryofiltrations and DFPPs. The improvement was noted with resolution of the leg ulcers, anemia and recovery of cardiac and renal function. In the result, pegylated interferon alfa was induced and decreased the HCV load and cryoglobuline to undetectable levels. In the 6months that followed, he have achieved lasting remission.

P3-214

Primary central nervous system vasculitis with subcortical cerebral hemorrhage :A report of three cases

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Conflict of interest: None

Primary central nervous system vasculitis with subcortical cerebral hemorrhage :A report of three cases Case1: A patient was 64-old female complicating headache. CT scan revealed recurrent subcortical cerebral hemorrhage on July, and Dec in 2011 and Feb in 2012. Angiography was normal. Serum CRP levels were normal. Autoantibodies were negative. Cerebral biopsy samples obtained at removal of hematoma revealed granulomatous vasculitis in leptomeningium and leukoklastic angitis in white matter. The patient was diagnosed as having primary central nervous vasculitis (PCNSV) and treated with glucocorticoid and IVCY, preventing recurrence of hemorrhage. Case 2: 71-year old male with lt. hemiplegia. CT scan revealed right subcortical hemorrhage. Cerebral biopsy samples at hematoma removal revealed vasulitis. Angiography was normal. Autonatibodies were negative and CRP levels were not elevated. Case 3: 73-year old male with rt. hemiplegia. CT scan revealed subcortical cerebral hemorrhage at left frontal and right temporal lobes. Biopsy samples showed vasculitis. Implication: PCNSV should be suspected and biopsy should be considered, when a patients showed recurrent subcortical hemorrhage.

P3-215

The rapid efficacy of Tocilizumab in a patient with refractory rheumatoid vasculitis - The usefulness of immunohistochemical staining for IL-6 of skin tissues

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Conflict of interest: None

The patient was a 69-year-old male with rheumatoid arthritis. He received predonisolon (PSL) 20 mg/day and tacrolimus 3 mg/day. The patient suffered rupture of the right Achilles tendon and first visited this department. He underwent Achilles tendon reconstruction surgery. Antibiotic therapy and two surgical debridements were provided to control postoperative wound infection and the dose of PSL was tapered to 12.5 mg, although that did not close. One month later, periungual infarction on the hands and purpura, multiple ulcers and peripheral neuropathy developed in the lower extremities. Laboratory tests revealed hypocomplementemia, elevated C1q immune complex and elevated RAPA. The skin biopsy specimen revealed leukocytoclastic vasculitis. After administration of PSL at a dose of 1 mg/kg and oral cyclophosphamide at a dose of 100 mg/day, CRP became negative and the dermatological findings tended to reduce. However, because the steroid dose could not taper in 20mg or less, Tocilizumab was administered. After introduction of this therapy, marked improvement in the skin ulcers. Furthermore, the endotherial cells of skin tissues were relatively strongly positive for IL-6. Interleukin (IL)-6 blockade could be a new therapeutical choice in rheumatoid cutaneous vasculitis.

P3-216

Small intestinal perforation in primary Sjögren's syndrome with necrotizing vasculitis: a case report

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Conflict of interest: None

We report a case of small intestinal perforation association with vasculitis in a 69-year-old female patient in which a subsequent diagnosis of primary Sjogren's syndrome was made. She was admitted due to high fever, anorexia. On the second hospital day, abdominal pain developed suddenly. Contrast enhanced computerized tomography scan showed intra abdominal free air and fluid consistent with gastrointestinal tract perforation. She underwent an emergency operation. The surgically resected small intestine measured 70 cm in length. The mucosal surface of the small intestine showed multiple transversely oriented shallow ulcers. One of the ulcerations was perforated. Histological examination of the surgically resected specimen demonstrated evidence for necrotizing vasculitis of medium-sized arteries. After steroid therapy was initiated, her symptoms improved. We encountered a SS patient complicated by vasculitis who achieved clinical remission due to steroid therapy following enterectomy.

P3-217

Multiple Infections in a Filipino with Polyangiitis Overlap Syndrome (POS)

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Conflict of interest: None

BACKGROUND: POS rarely has features of 2 ANCA-associated vasculitis (AAVs). Infections may be etiologic in primary syndromes. **OBJECTIVE:** To present a case of POS with features of 2 AAVs and infections. **CASE:** A 25-year-old Filipina had 6 years of recurrent purpura and debilitating arthralgia, hemoptysis, epistaxis, eye redness, dyspnea. She had cachexia, oral ulcers, rhinorrhea, crackles, and polyarthritis. She had anemia, elevated ESR and CRP, positive c-ANCA and anti-proteinase 3, chronic sinusitis on rhinoscopy and lung vasculitis on chest CT. Skin biopsy showed leukocytoclastic vasculitis. There was eosinophilia without parasitism, but negative p-ANCA and anti-myeloperoxidase. ANA and anti-dsDNA were negative. She had high ASO titers, chronic hepatitis B, bronchial *P. aeruginosa* and sinus MRSA infections. HIV infection was ruled out. There were incomplete features of limited granulomatosis with polyangiitis and Churg Strauss syndrome with multiple infections. She was given naproxen and culture-guided antibiotics with partial symptom resolution. Prednisone was initiated after lamivudine, which led to complete symptom and inflammatory marker improvement after 12 weeks. **CONCLUSION:** This is the first reported case of POS with 2 AAVs and multiple infections in Southeast Asia.

P3-218

Comparative proteomic analysis of neutrophils from patients with microscopic polyangiitis and granulomatosis with polyangiitis

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Conflict of interest: None

[Objectives] Both MPA and GPA belong to ANCA-associated vasculitis (AAV), in which neutrophils are thought to be involved in their pathology. In this study, to find the difference of the neutrophil function between MPA and GPA, proteomic profiles of polymorphonuclear cells (PMNs) were analyzed using two-dimensional difference gel electrophoresis (2D-DIGE). [Methods] Proteins extracted from PMNs of 11 MPA patients, 9 GPA patients, and 10 HC were separated by 2D-DIGE. Differentially expressed protein spots were identified by mass spectrometry analysis. [Results] In all the 864 protein spots detected, intensity of 55 spots was found to be significantly different ($p < 0.05$) among the three groups by an analysis of variance (ANOVA). 31 out of the 55 spots were identified by mass spectrometry. 13 out of the 31 protein spots were considered as biomarker candidates to distinguish between MPA and GPA using SIMCA-P+ (multivariate data analysis). In those spots, whose intensity was higher in MPA than in GPA included cytokeratin proteins, whose intensity was higher in GPA than in MPA were proteins related with the activity of neutrophils. [Conclusion] These results indicated that the profile of PMN proteins may be used as a biomarker that can discriminate AAV from HC, and MPA from GPA.

P3-219

Mast cells are involved in fibrosis of lip salivary gland in Sjögren's Syndrome

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Conflict of interest: None

Objectives: Sjögren's syndrome (SS) is characterized by the salivary gland with autoreactive lymphocyte infiltration. We have investigated the role of mast cells (MCs) in SS. ***Methods:*** Salivary glands were biopsied in 184 SS patients and 6 Sicca syndrome (Sicca) patients. Histological scoring was performed for cell infiltration, acinar atrophy and intralobular fibrosis and MCs were detected by toluidine blue staining. ***Result:*** Tissue MCs in SS vs Sicca was analyzed for degree (mild/moderate/severe) of cell infiltration (42/112/30 vs 4/2/0), acinar atrophy (13/66/105 vs 3/3/0) and intralobular fibrosis (11/83/90 vs 4/2/0) resulting in higher degree of gland destruction in SS. There was no difference in number of MCs between primary and secondary SS. Number of MCs and serological measurements reflecting the activity of SS did not correlate. Of note, positive correlation between number of MCs and intralobular fibrosis was observed in primary SS, without association with inflammatory cell infiltration and acinar atrophy. ***Conclusion:*** Our data suggest that not only lymphocyte but MCs also contribute to the pathogenesis of SS. In particular, MCs contribute to the development of intralobular fibrosis in primary SS.

P3-220

Analysis of M3R reactive T cell epitopes in M3R induced autoimmune sialoadenitis

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Conflict of interest: None

[Objectives] To clarify the major T cell epitopes of M3 muscarinic acetylcoline receptor (M3R) reactive T cells in M3R induced autoimmune sialoadenitis (MIS). [Methods] 1) Splenocytes of C57BL/6 immunized with M3R peptides mixture (N-terminal region, 1st, 2nd and 3rd extracellular loops) were cultured with each M3R peptide. The cytokines (IFN-g, IL-17 and IL-4) production were measured by ELISA. 2) Splenocytes of C57BL/6 mice immunized with each N1 and 1st loop peptide, which was the candidate for the dominant T cell epitopes, were cultured with each M3R peptide. The cytokines (IFN-g, IL-17 and IL-4) production were measured by ELISA. [Results] 1) M3R reactive T cells produced IL-17 and IFN-g against N1 and 1st loop significantly more highly than controls and other extracellular domains of M3R. IL-4 production could not be detected. 2) Both M3R N1 reactive T cells and M3R 1st loop reactive T cells produced IL-17 and IFN- g significantly more highly than controls and other extracellular domains of M3R. IL-4 production could not be detected. [Conclusion] We concluded that the major T cell epitopes in MIS might be both N1 and 1st extracellular loops of M3R.

P3-221

Efficacy of pilocarpine hydrochloride for dry mouth in the morning with Sjogren's syndrome

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Conflict of interest: None

[Objectives] Sjogren's syndrome is characterized by xerostomia (dry mouth) and xerophthalmia (dry eyes). Especially xerostomia of waking with night diminished saliva secretion may lead to oral pain, sticky mouth feeling and sleep disruption. Pilocarpine hydrochloride stimulates saliva secretion and improves xerostomia, but the efficacy of morning xerostomia is not clear. We investigated the effect of pilocarpine hydrochloride against the morning xerostomia with sjogren's syndrome patients. [Methods] 12 female patients with Sjogren's syndrome (mean age 61-year-old) received oral pilocarpine hydrochloride 5-15 mg/ day. We evaluated sleep disruption to count the waking times due to water intake, morning xerostomia, oral pain and sticky mouth feeling using the VAS scale on days 1 and 28. [Results] Xerostomia and oral pain of waking were significantly improved by administration of pilocarpine hydrochloride in patients with Sjogren's syndrome. 5 patients who has improved oral pain received each dose of pilocarpine hydrochloride, 15 mg3X (2 cases), 10 mg2x (1 cases), and 5 mg1x A or vds (2 cases). [Conclusion] The results suggest that administration of pilocarpine hydrochloride after supper or at bedtime improve xerostomia and oral pain of waking in patients with Sjogren's syndrome.

P3-222

Anti-aquaporin 4 antibody was positive in the case of myelitis associated with Sjogren's syndrome

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Conflict of interest: None

<Case> A 38-year old woman <History> In 2002, she noted paresthesia and muscle weakness in both legs and abdominal symptoms. She was diagnosed with multiple sclerosis and treated with three courses of methyl-prednisolone (mPSL) pulse therapy. In 2003, she had a similar episode. At another hospital, she was diagnosed with Sjogren's syndrome (SS), and her symptoms were ascribed to myelitis due to SS. She received three courses of mPSL pulse therapy followed by oral steroid therapy. When her steroids were tapered, she repeatedly had myelitis. In 2012, she had another relapse and was admitted to our hospital. The number of cells in the CSF and IgG index were only slightly elevated, but IL-6 in the CSF was 818pg/ml. Serum anti-aquaporin4 (anti-AQP4) antibody tested at this time was positive. After three courses of mPSL pulse therapy, her symptoms improved, and the CSF IL-6 was 3.0pg/ml. <Discussion> Many reports have shown that anti-AQP4 antibody is specific for neuromyelitis optica. A few reports showed that anti-AQP4 antibody may also be positive in some cases of myelitis associated with SS, and in this case of myelitis associated with SS, anti-AQP4 antibody was positive. This case also shows that CSF IL-6 may be useful in monitoring disease activity of myelitis associated with SS.

P3-223

Malignant lymphoma occurred in a patient with Sjögren's syndome complicated with pulmonary aterial hypertension, treated with R-CHOP

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Conflict of interest: None

〔Case〕 A 54-years-old woman was referred to our hospital due to short of breath and Raynaud's phenomenon. According to ultracardiography, her right ventricular pressure revealed 60 mmHg. Serologically, anti SS-A antibody and anti SS-B antibody were positive. Lip biopsy showed chronic sialoadenitis, consistent with Sjögren's syndrome (SjS). Diagnosis of primary SjS complicated with Pulmonary arterial hypertension (PAH) were made. She was given beraprost sodium, bosentan hydrate, sildenafil citrate and predonisolone. In April 2012, she developed low grade fever and increasing C-reactive protein (CRP) level, were noted. Cervical lymph nodes were swollen and multiple nodular shadows were noted in both lungs, according to chest CT. Lymph node tissue noted Diffuse large B cell lymphoma. She was treated with R-CHOP. Her lymphoadenopathy and PAH improved gradually. We herein discuss about effects of R-CHOP on Sjs and PAH.

P3-225

A case of Sjögren syndrome complicated with microscopic polyangiitis presenting severe alveolar hemorrhage

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Conflict of interest: None

The case is 76-year-old female who referred to our hospital because of lung lesions in 2008. High resolution CT (HRCT) of her chest showed slight bronchiectasia and respiratory tract infection. We diagnosed her as having Sjögren syndrome on basis of presence of anti-SS-A/B antibody and salivary gland biopsy in 2009. Her condition was stable. She had suffered from fever and cough since August,2011. Antibiotics did not ameliorate her condition, and she was admitted to our hospital due to acute dyspnea and hemo sputum. She fell into acute respiratory failure, and HRCT showed diffuse air space consolidation and grand glass opacities in the bilateral lung fields. She was diagnosed with microscopic polyangiitis based on positive MPO-ANCA,and alveolar hemorrhage. She was treated with steroid pulse therapy, cyclophosphamide pulse therapy, and plasmapheresis with favorable response.

P3-226

Successful discontinuation of plasmapheresis by alternative-day steroid treatment in patients with hyper viscosity syndrome due to Sjogren syndrome

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Conflict of interest: None

A 69 years old woman had suffered from dry mouth and conjunctivitis for 5 years. On June 2012, she complained of vertigo, palpitation and dyspnea and consulted the general practitioner. Physical examination revealed that dysfunctions of lacrimal and salivary gland. She also showed purpura in her extremities. Laboratory studies showed serum IgG 2340 mg/dl, IgA 2030 mg/dl, IgM 44 mg/dl, RF 3880 IU/ml. Antinuclear antibody and anti-SSA antibody were positive. Serum immunoelectrophoretic study showed M-bow in IgA-κ type. Cryoglobulins were positive mixed with IgA-κ type M protein and polyclonal IgG. Lip biopsy showed lymphoplasmacytic infiitration. She was diagnosed as type II cryoglobulinaemia and hyperviscosity syndrome due to Sjogren syndrome. She was treated with weekly plasmapheresis for hyperviscosity syndrome. On September, she visited our hospital for further treatment. She was treated with 50 mg alternate-day of prednisone (PSL) and her symptoms and laboratory data improved. In this case, alternate-day of PSL therapy made it possible to discontinue plasmapheresis promptly.

P3-227

A case of Sjögren syndrome with acute renal failure and various autoimmune disorders complicating angioimmunoblastic T cell lymphoma

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Conflict of interest: None

A 63-year-old man with Sjögren syndrome (SS) suffered from multiple purpura on lower legs and acute renal failure (Scr 3.7 mg/dl) and liver dysfunction (AST 317 IU/l, ALT 213 IU/l). On admission, his temperature was 37.7°C. On physical examination, spleen was palpable in his left subcostal area, and widespread cervical, axillary and inguinal lymphadenopathies were detected. He also tested positive for antinuclear antibody, anti-DNA antibody, anti-liver kidney microsome (LKM) antibody, and cryoglobulin. Skin biopsy of purpura showed leukoclastic vasculitis. Renal biopsy showed diffuse infiltration of inflammatory cells, which are mainly

plasma and lymphocyte cells, and diffuse fibrosis. Tubuli were almost destroyed, which was compatible with tubulo-interstitial nephritis (TIN). In addition, a few lymphoid nodules were seen in the interstitium, and most of these nodules consist of clear cells with middle-sized irregular nuclei, in which CD21 positive follicular dendritic cells were observed. Then, he was diagnosed with SS complicating angioimmunobastic T cell lymphoma (AITL) on pathological evidence of renal biopsy specimen. This is the intriguing case of SS who complicated AITL, which led to exacerbate tubulo-interstitial nephritis of SS and various autoimmune disorders.

P3-228

Study in Fibromyalgia(FM), over the value of glutamic acid, serotonin, noradrenaline and GABA, in serum

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Conflict of interest: None

[Objectives] In cognition of pain in FM patients, the aggravation of pain can be considered as the results of bizarreness of ascending pain path and descending pain suppression path in spinal cord.In ascending pain path in the cord, glutamic acid participation can be considered. In the descending pain suppression path, serotonin and noradrenaline participation can be considered. Also, in superior nerve system, GABA participation can be considered. Therefore,these four substances were examindes. [Results] Glutamic acid; the mean value of it in FM is 73.2 nmol/ml, that of health subjects is 47.6 nmol/ ml. t=4.8, α=0.001.Serotonin; the mean value of FM is 73.8 ng/ml, that of healthy subjects is 145 ng/ml. t= 8.22 p<0.01%.Noradrenaline; the mean value of FM is 0.55 ng/ml and that of healthy subjects is 0.29 ng/ml. t=2.95, α=0.01. GABA; this is considered to work in suppression at the supral portion of central nerve system. The mean value of FM is 145 pmol/ml, that of healthy subjects is 163 pmol/ml.This demostrates that the mean value of GABA in FM is significantly lower value than that of healthy person. t=1.74, α=1.0. [Conciusion] In FM patients, Glutamic acid is significantly high, serotonin is significantly low, NR is significantly high, and GABA is significantly low.

P3-229

Development of a linguistically validated Japanese version of the Revised Fibromyalgia Impact Questionnaire (JFIQR)

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Conflict of interest: None

[Objectives] The Revised Fibromyalgia Impact Questionnaire (FIQR) was developed to address the limitations of the Fibromyalgia Impact Questionnaire. In order to use the FIQR with Japanese patients, we developed a Japanese version of the FIQR (JFIQR). [Methods] After obtaining permission for translation, a Japanese version of the FIQR was developed and linguistically validated, according to the general cross-cultural adaptation process: 1) forward-translation (English to Japanese), 2) back-translation (Japanese to English), and 3) cognitive debriefing. [Results] Two independent Japanese-native bilinguals translated the original FIQR into Japanese, then a single forward-translation was produced after reconciling differences between the two translations. Next, backward-translation was performed by an English-native bilingual. Finally, cognitive debriefing interviews were conducted with 6 Japanese fibromyalgia patients (5 females, average age 51.7 years old), to assess respondents' comprehension of the questions and response scales. Overall, the patients had no difficulties with the wording and correctly interpreted each item's meaning. [Conclusion] Through the translation and adaptation process, a linguistically-validated JFIQR was successfully developed.

P3-230

Overlapping rate analysis between Fibromyalgia and Sjogren syndrome in Japan. A single center study

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Conflict of interest: Yes

[Objectives] Fibromyalgia (FM) and Sjogren syndrome (SS) have similar clinical symptom, so we examined overlapping rate between FM and SS in Japan. [Methods] We examined number of FM (ACR criteria 1990) and SS (Japanese criteria 1999) by over viewing clinical record since April 2011 to October 2012, retrospectively. [Results] FM patients were 70 (11 male, 59 female, average age 44 years old) and SS patients were 44 (2 male, 42 female, average age 60 years old). FM with xerosis (dry eye or dry mouth) were 55 (78.0%) and SS with general myalgia were 10 (22.7%). However, the number of patients who met both criteria FM and SS were only 4 (5.7%). [Conclusion] FM with xerosis was common clinical symptoms due to mental status or therapy such as anti-depressants, but overlapping rate was not so high.

P3-231

Efficacy of Go-sha-jinki-gan (GJG) for pain disorder using chronic constriction injury (CCI) model mice

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Conflict of interest: None

[Objectives] Fibromyalgia have been classified as (CCS) central sensitization syndrome, owing to involvement of central sensitization. The effect of herbal medicine for CCS was sometimes reported, but the mechanism of its efficacy is still unclear. We examined the effect of herbal medicine in CCI model mice that is a representative model of central sensitization. [Methods] C57/BL male mice underwent CCI model (ligated left sciatic nerve) or sham model, and administered four kinds of herbal medicine (GJG, Keishi-ka-jutsu-bu-To, Mao-bushi-saishin-To, Juzen-daiho-To). We evaluated the analgesic effect by nociceptive tests (Von Frey Test, Cold Plate Test, Hot Plate Test). [Results] GJG only suppressed the pain behavior in all tests. After 3 weeks administration, GJG improved pain behavior significantly compared with sham (Von Frey p <0.0001, Cold Plate p <0.0001, Hot Plate p <0.05, t-test). Additionally, the effect of GJG showed the dose dependent manner. High concentrations of GJG showed a potent analgesic effect in early phase of CCI model mice. [Conclusion] GJG inhibited pain behavior through the intermediary of the superior CNS as well as spinal reflex. These results suggest that adjusting the dosage of GJG have more analgesic effects in severe fibromyalgia patients.

P3-232

Consultation Status and Follow-up Survey of Fibromyalgia (FM) Patients at a Rheumatism Clinic

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Conflict of interest: None

Purpose: To determine the medical consultation behaviors and treatment methods of FM patients **Subjects and Methodology:** (1) Review of consultation records – The diagnostic records of all the patients who visited our clinic as FM-suspects over the past seven years were reviewed to identify FM patients. (2) Follow-up survey – A questionnaire survey was conducted to determine the medical consultation behaviors of the identified FM patients both at and outside of our clinic. The survey topics included the types of medical departments they consulted, their symptoms, and the methods of treatment they received. **Results:** (1) Of the total 156 FM-suspected patients who were examined at our clinic over the past seven years, 96 were diagnosed as FM patients. (2) Of those 96 confirmed FM patients, 16 were currently under the care of our clinic. The current statuses of the other 80 FM patients were: a) outpatients at other clinics, b) no longer going to any hospital, c) convalescing at their homes, d) being hospitalized. The overall findings on the 96 confirmed FM patients were: They were referred to multiple departments, as they manifested diverse clinical symptoms and courses. The methods of treatment they received were also diverse.

P3-233

Characterization of IgG4-related disease in 6 patients

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Conflict of interest: None

[Objectives] IgG4-related lymphoproliferative disease (IgG4-RD) was first reported in Japan in 1990s, and showed elevated-serum IgG4 and infiltration of IgG4 positive plasmacytes in various organs. IgG4-RD was also thought to favorably respond to steroid. In this report, we analyzed the clinical features and prognosis of patients (pts) with IgG4-RD treated in our hopsital. [Methods] We analyzed the data of 6 pts with IgG4-related disease, who were admitted to our hospital from April 2011 to October 2012. [Results] Pts included 2 males and 4 females. Mean age was 58.7±9.2 years old. Nine tumor lesions were detected in 6 pts. Two pts had tumors within the orbit, 2 in submaxillary glands, 1 lower eyelid, 1 parotid gland, 1 lung, 1 as whole body lymphoadenopathy, and 1 intravenously. Mean serum IgG levels were 2397.2±1287.7 mg/dL, mean serum IgG4 1093.0±1144.3 mg/dL, mean count of lymphocyte was 1306.3±317.5 /uL, and mean CRP 0.09±0.06 mg/dL. Mean dose of prednisolone administered at induction therapy was 0.7±0.2 mg/kg/day. All 6 pts favorably responded to the treatment. [Conclusion] We experienced 6 pts with IgG4-RD. Tumors were detected in various organs and beyond typical sites. We should consider this disease as a differential diagnosis of lymphoproliferative disease.

P3-234

A case of multicentric Castleman's disease mimicking IgG4-related disease

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Conflict of interest: None

A 68-year-old man was referred to our hospital due to elevation of CRP (≧4mg/dL) for several years. He noted brown nodules on the right malar and left axilla. Laboratory findings revealed elevation of IgG (5497 mg/dL), IgG4 (671.0 mg/dL), anemia (Hb:9.7 g/dL), and mild renal dysfunction. Computed tomography showed multiple lymphadenopathy and lung involvement including diffuse ground-glass opacities, infiltrates, and cysts. Histopathological findings of the specimens obtained from the left inguinal lymph node showed marked plasma cell infiltration in the interfollicular area, and numerous plasma cells were IgG4(+) (IgG4(+)/IgG(+) plasma cell ratio:30~40%). We diagnosed this patient as multicentric Castleman's disease rather than IgG4-related disease because of high level of IL-6 (22.4 pg/mL) and poor IgG4(+) plasma cell infiltraion of the biopsy specimens from kidney and lung. Radiological and serological findings and skin lesions improved after the initiation of high dose oral corticosteroid treatment. It may be important to know the similarities and differences between Castleman's disease and IgG4-related disease. We will discuss it through the present case.

P3-235

Clinical examination in a case of IgG4-related prostatitis

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Conflict of interest: None

[Objective] To introduce interesting case of IgG4-related prostatitis [Case] A 34 year-old-male complained of the right lower abdominal pain in February 2012. In the abdominal contrasting CT, significant prostatic swelling involved right ureter that resulted in slight hydronephrosis. The blood test findings was CRP 0.23 mg/dl, IgG 1,438 mg/dl, IgG4 157 mg/dl, ANA (-), RF (-), sIL-2R 677 U/ml. In FDG-PET, the prostate swelled in irregularity and SUV level of it was 4.8, but salivary gland, pancreas, retroperitoneum did not have the abnormality. Histopathologic examination of the prostate showed marked lymphocyte and plasmacyte infiltration and fiblosis. Almost all of the plasma cells were positive for IgG4 by immunostaining. At this point in time, we diagnosed it with IgG4-related prostatitis in reference to Comprehensive diagnostic criteria for IgG4-related disease, 2011. Initiated oral prednisone at the dose of 15mg daily, CRP became negative immediately, and serum IgG4 was normalized. [Consideration] When we diagnose an IgG4-related disease, we must consider many factors and we should make a new judgment rule for a diagnosis guidance.

P3-236

The present state of diagnosis and therapy for IgG4-related diseases in our hospital

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Conflict of interest: None

[Objectives] IgG-related disease (IgG4RD) is a systemic lymphoproliferative disorder characterized by tissue infiltration with IgG4-secreting plasma cells, occasionally leading to organ dysfunction. We underwent a clinical study in order to clarify the diagnosis and course of treatment IgG4RD. [Methods] To determine the state of diagnosis and therapy for IgG4RD in our hospital,

since April 2011, we have prospectively followed up patients with IgG4RD who were diagnosed mostly by the physical and image findings highly specific for IgG4RD and serum IgG4 levels of >135mg/dL. [Results] Of 15 patients enrolled in the study at present, 7 patients have been treated with glucocorticoids (GC) therapy for their retroperitoneal lesions, renal dysfunction, pancreatitis, periaortitis, and others, and in 5 of them, azathioprine (AZA) was added later because of insufficient GC efficacy and/or its adverse effects. They responded well to the treatment, and 8 other untreated patients have not yet developed any organ dysfunction. [Conclusion] These results indicate that IgG4RD principally shows a benign clinical course and GC therapy thus should be indicated for patients with progression or risk of organ damage. In our experience, AZA may be useful for patients GC-resistant or intolerant patients.

P3-237

A Case of hypereosinophilic syndrome with elevated IgG4, presenting eosinophilic myocarditis and intracardiac thrombus

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Conflict of interest: None

A 51-year-old male was referred to our hospital because of hypereosinophilia in August 2012. In May 2012, he had been diagnosed with hypereosinophilia and treated by corticosteroid. At the same time, atrial fibrillation had been detected and anti-coagulant agent was administered. He also had been diagnosed with asthma at 46 years of age. Laboratory data at the first visit were as follows: eosinophils 23400/μl, IgG 2463mg/dl, IgE 2653 IU/ml, IgG4 457mg/dl. The echocardiography showed akinesia at cardiac apex and thrombus in left ventricular cavity. We initiated 1mg/kg/day of prednisolone (PSL), which leaded to the normalization of eosinophil count and IgG4. The coronary angiography revealed no significant coronary stenosis. Hence we concluded that the cardiac disease was caused by hypereosinophilia. Bone marrow biopsy and gastroduodenal mucosa biopsy showed increased eosinophils and few IgG4-positive cells. We diagnosed him as hypereosinophilic syndrome showing elevated IgG4. IgG4 is thought to be associated with allergic disease, because some patients with IgG4-related disease have a history of allergic disease and some patients with allergy disease show elevated IgG4. We discuss the pathophysiology of the patients with elevated IgG4 and eosinophilia.

P3-238

A case of IgG4-Mikulicz's disease with multiple nodules-forming hypertrophic pericardium

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Conflict of interest: None

IgG4 Mikulicz's disease (IgG4-MD) characterized by bilateral symmetrical lacrimal and salivary glands swelling. This is one of the IgG4-ralated diseases (IgG4-RD). This case report describes a middle-aged woman having IgG4-MD with multiple nodules-forming hypertrophic pericardium and hypertrophic neck of uterus, and then corticosteroid treatment was remarkably effective. A 69-years old woman having allergic rhinitis developed enlargement of the bilateral submandibular and lacrimal glands. She became aware of xerostomia. ANA, Anti-SS-A antibody, Anti-SS-B antibody were every negative. Serum IgG, IgG4, IgE were elevated and biopsy of the submandibular glands showed an expansion of heavily infiltrating plasma cells. Immunohistochemical analysis revealed that the IgG4-positive/IgG-positive plasma cell ratio was 60%, which led us to diagnose IgG4-RD. Oral prednisolone treatment resulted in prompt resolution of the physical, serological, and imaging. FDG-PET/CT revealed accumulation of lacrimal glands, submandibular glands, pericardium and cervix uteri severally. Cancer of cervix uteri was denied by biopsy. 0.6mg/kg prednisolone promptly took effect to every lesion, and never flare up again with reducing the quantity of PSL.

P3-239

Two cases of mikulicz disease with pulmonary lesion

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Conflict of interest: None

Case 1. A 52-year-old man presented with cough and bilateral swelling of the sabmandibular glands. He also had swelling of the mediastinal lymphnodes, pulmonary lesion, and high inflammatory biomarker level. A pathologic examination of a sabmandibular gland biopsy specimen revealed infiltration of IgG4-positive cells, and on this basis we diagnosed Mikulicz disease and IgG4 related lymphoproliferative syndrome. The pulmonary lesion turned worse afterwards. In process of time, it improved with no treatment. Case2. A 62-year-old man presented with weight loss and bilateral swelling of the sabmandibular glands. He also had pulmonary lesion and high inflammatory biomarker level. A pathologic examination of a lip biopsy specimen revealed infiltration of IgG4-positive cells, and on this basis we diagnosed Mikulicz disease. The pulmonary lesion turned worse afterwards. He was judged that medical treatment was required. He did medication of the corticosteroids. And the pulmonary lesion improved. The features of Mikulicz disease are swelling of the salivary and lacrimal glands, high serum IgG4 level and infiltration of IgG4-positive cells in salivary glands. This disease contains various organ disorders. In case of pulmonary lesion, there are various pathological types and clinical courses.

P3-240

A case of IgG4-related disease with multiple pulmonary nodules

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Conflict of interest: None

A 38-year-old man had radical surgery of the maxillary sinus due to mass lesion of right maxillary sinus with fever. Pathological findings of specimens revealed lymphocyte and IgG4+ plasma cell infiltration with tissue fibrosis indicating IgG4-related disease. Several months later, chest CT scan revealed multiple pulmonary nodules. Although the diagnosis of the nodules was not obtained by the transbronchial biopsy, it was supposed to be the pulmonary involvement of IgG4-related disease. Then, we administrated prednisolone (PSL) 0.6mg/kg/day to treat pulmonary lesion and fever with elevation of CRP. However, the treatment was ineffective, so PSL was tapered, and video-assisted thoracoscopic surgery was

performed. Although histologic examination of the lung specimens showed infiltration of the lymphocytes and plasma cells with fibrosis, IgG4+ plasma cells ware not detected at all. According to the possibility of chronic bacterial infection, Meropenem and Clarithromycin ware administrated for one month. There was a partial response, but it was not sufficient. Therefore, the pulmonary lesion was supposed to be the involvement of IgG4-related disease resistant to PSL 0.6mg/kg/day, so we administrated PSL 1mg/kg/day. It induced improvement of the remaining signs and pulmonary lesions.

P3-241

Polyarthritis and erythema nodosum as a complication of granulomatous mastitis

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Conflict of interest: None

[Introduction] Granulomatous mastitis is an inflammatory disease of the breast. It typically presents in parous woman of childbearing age. Although extramammary manifestations of this disease are extremely rare, arthritis and erythema nodosum have been reported. We report here another case of granulomatous mastitis which developed polyarthritis and erythema nodosum. [Case report] A 35-years-old woman presented in June 2012 with the complaint of a painful large mass in her right breast. Computed tomographic scan showed an abscess in the breast. She was initially treated with incision for drainage and administration of antibiotics. A few days later, the patient complained of painful erythema nodosum affecting both legs and arthritis involving both ankles. Serum CRP was elevated at 5.61 mg/dl, and WBC was 11,260/μl. Gadolinium-enhanced MRI showed active tenosynovitis of the left ankle. A breast biopsy was performed, and she was diagnosed as having a granulomatous mastitis. Treatment with prednisolone at a dose of 30 mg/day was initiated. Such treatment resulted in the improvement of arthritis, erythema nodosum and granulomatous mastitis. [Summary] Rheumatologists who treat patients with arthritis and erythema nodosum should be aware of granulomatous mastitis as the underlying disease.

P3-242

Rheumatoid Arthritis patient with palindromic rheumatism manifestation might be exist in early phase, but after this period, very few cases contaminated to palindromic rheumatism in Japanese population

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Conflict of interest: None

Objective: Palindromic rheumatism (PR) has inflamation within 3 days and intermittent elevation of CRP. It is easy to distinguish PR to rheumatoid arthritis (RA), since the clinical futures are so apart. But 1/3 of PR may develop RA in future, or anti-CPA antibody(anti-CPA) may exist in PR. Method: We observed 42 patients with joint inflammation within 3 days, intermittent CRP elevation, in our first visit, and further assessments were performed. Result: Following 6 months observation, 6 patients diagnosed as other diseases, 12 patients as RA. No additional case reported to have RA after this period. PR patients were observed for average of 11 years, no chronic inflammation found in all 24 cases. The anti-CPA was positive (average 216) in 14 patients, and any rheumatoid factors in 19 cases. For the 12 patients diagnosed as having RA in first 6 months observation, anti-CPA was positive for all cases, average117.7, and the joint inflammation persist, thus fulfilled the criteria with 1987 ACR RA classification. Coclusion: RA patients with PR manifestation might be exist in early phase, but after that, very few cases turn to PR. The serological examination of PR, 19 out of 24 patients showed positive for anti-CPA, or IgM-RF, for the titer of anti-CPA, 14 cases above three times higher.

P3-243

Refractory eosionphilic fascitis successfully treated with infliximab: A case report

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Conflict of interest: None

Six months before admission, 32-year-old male developed myalgia in his left forehand without obvious trigger. One month before admission, his myalgia spread to his both bilateral upper and lower extremities with disabled daily life. After admission, he was diagnosed of having an eosinophilic fasciitis (EF) from peripheral eosinophilia, normal CK, MRI findings and muscle biopsy findings. He received high dose prednisolone (PSL) of 60mg/day and tacrolimus of 2mg/day with dramatic improvement of signs and symptoms. Six months after starting the treatment, he complained of stiffness in his trunk and difficulty in flexing and extending his trunk with enhanced thickened fascia of his erector spinae and iliopsoas muscles on MRI at the PSL dose of 10mg/day during gradual tapering of PSL. He received steroid pulse therapy with transient improvement of his symptoms at the diagnosis of exacerbation of EF. Therefore, infliximab (IFX) of 3mg/kg was incorporated with methotrexate of 8mg/week instead of tacrolimus, which resulted in dramatic improvement of his symptoms and MRI findings. Because there are limited reports to treat EF with IFX, we will herein review and discuss treatments of refractory EF through the case reports.

P3-244

Successful use of adalimumab for the treatment of refractory Crohn's disease that developed in a patient with systemic lupus erythematosus

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Conflict of interest: None

We report on a 35-year-old Japanese man who developed abdominal pain with diarrhea when he was on the maintenance therapy of systemic lupus erythematosus (SLE) with low-dose corticosteroids, tacrolimus, and mizoribine. He was diagnosed as having SLE with autoimmune hemophagocytic syndrome at his age of 27. Abdominal symptoms had got worse over 2 months and thereafter melena emerged, and then he admitted to our hospital. Computed tomography showed an enteric wall thickening from the distal ileum to the colon. Colonoscopy showed inflamed edematous mucosa with erosions and ulcers in the entire length of the colon. No infectious pathogens were observed in blood, stool, and biopsied specimens of colonic mucosa. Pathology of the colonic mucosa showed non-caseous granulomas. These findings led us to the diagnosis of CD. No deteriorations of SLE-related serological activity and other organ damage were observed. Add-on adalimumab dramatically

improved clinical signs and symptoms related to CD that was refractory to conventional therapy without any detrimental effects. [Conclusion] There have been only 8 cases of CD associated with SLE in the literature so far. Here we present this case as the first case report of CD developed in a patient with SLE that was treated by adalimumab.

P3-245

A case of subarachnoid hemorrhage and airway involvement associated with the exacerbation of ulcerative colitis

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Conflict of interest: None

A 42-year-old man with ulcerative colitis (UC) admitted to the hospital because of the exacerbation of UC. He also had high fever, cough, bloody sputum and purulent nasal discharge. He was diagnosed as acute sinusitis and was treated with antibiotics. However, they were ineffective. He began to complain of progressive hoarseness, wheezing and dyspnea one week after his admission. The chest CT showed the wall thickness of the trachea and main bronchi. Then he was treated by the mPSL pulse therapy, followed by high dose mPSL. There was an immediate improvement after this treatment. Fiberoptic bronchoscopy revealed that mucosa of trachea were edematous and small ulcers scattered mainly in membranous portion of trachea. Additional blood analysis showed that PR3-ANCA was positive. Although we suspected airway involvement of UC or granulomatosis with polyangiitis (GPA),the biopsy of tracheal mucosa demonstrated atypical inflammation and failed to reveal the diagnosis. Several days later he had a sudden loss of consciousness and was diagnosed as subarachnoid hemorrhage. Airway involvement is a rare complication of UC, and vasculitis, such as GPA, could be suspected because of the involvement of cerebral artery. We will report this case along with a review of the literature.

P3-246

Late-onset sarcoidosis presenting with multiple subcutaneous nodules and polyarthralgia in an 85-year-old female

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Conflict of interest: None

Sarcoidosis is a multisystem granulomatous disorder of unknown etiology characterized by the formation of non-caseating granulomas in various organs or tissues. Although sarcoidosis is not uncommon in patients over 65 years of age, the clinical features are different than in younger patients. Here we report a case of an 85-year-old woman that is the second oldest biopsy-proven case of sarcoidosis, in which subcutaneous sarcoidosis and polyarthralgia were presenting features. She was referred for further examination of arthralgia. On physical examination, multiple subcutaneous nodules in the upper extremities and buttock were observed. Routine examinations were almost normal without hypercalcemia. elavation of C-reactive protein and angiotensin-converting enzyme. Ocular examination findings were normal and chest radiographs were normal except for bilateral hilar lymphadenopathy. Gallium-67 scintigraphy revealed increased uptake in both hila, bilateral elbow and knee joints, and the multiple subcutaneous lesions of the upper extremities. Biopsy specimens from the subcutaneous nodules revealed non-caseating granulomas. The diagnosis was systemic sarcoidosis and she was treated with oral prednisolone at a daily dosage of 10 mg and the nodules and arthralgia subsequently resolved.

P3-247

A case of CD73 deficiency by *NT5E* mutations who presents crystal-induced arthropathy

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Conflict of interest: None

[Background] The pathogenesis of basic calcium phosphate (BCP) deposition remains unknown about. In 2011, St. Hilaire et al identified mutations in *NT5E* (the ecto-5'-nucleotidase gene encodes CD73) in members of three families with symptomatic arterial and joint calcifications. Here, we report a case of *NT5E* deficiency presented crystal-induced arthropathy. [Case] A 54-year-old woman with history of intermittent arthritis of finger and toe from 18-year-old visited our hospital in 1991. A diagnosis of BCP crystal deposition arthropathy was made based on the intermittent monoarthritis and juxta-articular calcification in radiographs of hands and feet. She had intermittent claudication and numbness of toes during a follow up examination. Plain radiographs showed calcified arterial walls in lower extremities. [Methods] We performed targeted gene sequencing using genomic DNA. We investigated CD73 expression in peripheral lymphocyte by flow cytemetry. [Results] We identified a mutation at the start codon in Exon 1 and a nonsense mutation in Exon 2 in *NT5E*. The expression of CD73 proteins was not detected in both B cell and T cell from the patient by flow cytometry. [Conclusion] This is the first case report of CD73 deficiency by *NT5E* mutations in Japan.

P3-248

Acute pseudogouty lumbar discitis resembling acute pyelonephritis: a case report

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Conflict of interest: None

[Objectives] Calcium pyrophosphate dehydrate (CPPD) deposition disease, including pseudogout, is a relatively common disease affecting the major joints, especially the knee. However, this disease in the vertebral column is rare. I describe a case of acute CPPD-induced (pseudogouty) lumbar discitis. [Case report] An 89-year-old woman presented with a 1-day history of acute low back pain with fever. Since laboratory findings revealed inflammation and bacilluria, a diagnosis of acute pyelonephritis was made. Though bacilluria disappeared by initial treatment with antibiotics, her low back pain and spike fever reached the 39°C mark was not improved 1 week later. MRI showed a left paravertebral cyst connecting L5/S disc space and septic discitis was suspected. Whitish yellow fluid aspirated from the cyst microscopically demonstrated CPPD crystals without bacteria. Finally, a diagnosis of CPPD-induced discitis was made. After the treatment with NSAIDs instead of antibiotics, all symptoms were completely resolved and her laboratory data showed improvement of the inflammation within 1 week. [Conclusion] This case demonstrated the importance of considering the possibility of CPPD-induced discitis as well as infec-

tious disease, when diagnosing acute low back pain with fever in old patients.

P3-249

Three cases of Henoch-Schoenlein purpura nephritis which experienced in our department

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Conflict of interest: None

[Objectives] Henoch-Schoenlein purpura nephritis is often reported spontaneous remission,we report three cases. [Results]1,63-year-old male patient. He was admitted to our hospital because liver abscess after cholecystectomy.We have consulted because palpable purpura,upper abdominal pain, abnormal urinalysis. In the renal biopsy,Proliferative changes was seen. We were relieved by the administration of steroids and tacrolimus. 2,75-year-old male patient. He was admitted to our hospital because purpura, melena, abnormal urinalysis.In colonoscopy revealed a multiple ulcers,and the renal biopsy showed proliferative change.We were relieved by a combination of steroids and cyclosporine. 3,37-year-old male patient. He had been admitted to another hospital because pyelonephritis stone. He was admitted to our hospital with abdominal pain, purpura.There was no proliferative changes in the renal biopsy, We administered dipyridamole.Aithough Ureteral stones recur and worse urinary findings, urinary findings showed improvement treatment for ureteral calculi. [Conclusion] Henoch-Schoenlein purpura nephritis was recover spontaneously. However there is proliferative change in the renal biopsy in our case,We need to consider immunosuppressive agent actively in addition to steroid therapy in such case.

P3-251

Comparison between clinical usefulness of anti-interleukin-6 receptor therapy and anti-tumor necrosis factor treatment in reactive AA amyloidosis complicating rheumatic diseases - follow-up report

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Conflict of interest: None

[Objectives] To compare the clinical usefullness of tocilizumab (TCZ) with that of anti-TNF agents (TNF) in AA amyloidosis complicating rheumatic diseases. **[Methods]** We compared 2 therapy groups (TCZ: 25 patients; TNF: 34 patients). We evaluated (1) treatment retention rates (Kaplan-Meier method), Multivariate Cox Hazard Analysis and safety profiles, (2) changes in SAA levels, (3) changes in eGFR, (4) changes in occurrence of proteinuria. **[Results]** 1. Treatment retention rates at 1 and 10 years were 92.0% (TCZ) and 72.7% (TNF) at 1 year and 20.0% (TNF) at 9 year, respectively (logrank test: p=0.0027). Significant clinical parameter of continuation of Biotherapy was TCZ(Hazard ratio: 0.127). Reasons for withdrawal were adverse events (2 in TCZ and 5 in TNF), primary lack of efficacy (2 in TNF), and secondary loss of efficacy (10 in TNF). 2. Median SAA levels fell from 207.8 to 4.8 µg/dL (TCZ) and from 122.3 to 31.8 µg/dL (TNF) (p=0.0143). 3. 18 cases(72.0%) in TCZ and 13 cases(38.2%) in TNF showed improvement in median eGFR, respectively (p=0.0127). 4. Proteinuria was resolved at last observation in 10 of 13 cases in TCZ and in 1 of 3 in TNF. **[Conclusion]** TCZ was confirmed to be superior to TNF in the treatment of AA amyloidosis complicating rheumatic diseases.

P3-252

Analysis of amyloid formation using human PBMC cultures

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Conflict of interest: None

[Objectives] To develop cell culture system that supports amyloid formation from human SAA, and to define conditions permissive to human SAA-derived amyloid formation in PBMC cultures. [Methods] PBMC were cultured in medium supplemented with recombinant SAA. Amyloid was identified by staining with Congo red. SAA/AA was characterized by N-terminal sequencing and western blotting. [Results] Use of serum-free medium proved to be the key to achieving amyloid formation. Cultures given SAA1.3 showed the most extensive amyloid deposition as assessed by the extent of Congo red staining and yield of insoluble, anti-SAA-immunoreactive material extracted from the cell fraction. This material, regardless of the precursor isoform, was composed of N-terminally intact SAA fragments of approximately 11, 9, 7, and 6 kDa, as well as full-length (12 kDa) SAA. The amount of 7 and 6 kDa fragments correlated most closely with the extent of amyloid detected by Congo red staining. [Conclusion] The system described here overcomes the relatively less amyloidogenic structure of human SAA and the seemingly inherent factors protective against amyloid formation and can be applied to testing inhibitor efficacy specifically against human amyloidogenesis.

P3-254

A case of rheumatoid arthritis that developed cholecystitis accompanied by amyloidosis

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Conflict of interest: None

A 55-year-old woman with a history of rheumatoid arthritis had been on hemodialysis for 3 years because of secondary renal amyloidosis. She presented with acute onset of right upper abdominal pain and vomiting while she was under cellulitis treatment in our hospital. Contrast CT scanning revealed gallbladder wall thickening and pericholecystic fluid. Since acute cholecystitis and biliary peritonitis were suspected, we performed an open cholecystectomy. Pathological examination showed no perforation, but edema and fibrosis were observed in the gallbladder wall. We therefore diagnosed her condition as acute cholecystitis and peritonitis. Amyloid depositions were identified in the lamina propria, vessels and adipose tissue. Immunological staining showed that the amyloid depositions contained amyloid A protein (AA) and ß$_2$ microglobulin. The patient was discharged 24 days after the surgery. The frequency of amyloid depositions in the gallbladder is reported to be 8.6%-75% of autopsy cases. Since the majority of the reported cases are amyloid light chain (AL) deposition associated with multiple myeloma, we report gallbladder amyloidosis accompanying rheumatoid arthritis.

P3-255

Two rash cases of secondary gastrointestinal amyloidosis in patients with rheumatoid arthritis

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Conflict of interest: None

[Case 1] A 78-year-old female with a history of rheumatoid arthritis for 5 years complained of sudden-onset diarrhea for 1 week. Colonoscopy revealed mucosal edema, redness and ulcers from the descending colon to the sigmoid colon. Histologically, amyloidosis was diagnosed by colonoscopic biopsy specimen. She had received total parenteral nutrition, predonisolone (PSL) and methotrexate (MTX). However, she died of infection on day 45 of hospitalization. [Case 2] A 71-year-old male with a history of rheumatoid arthritis for 25 years complained of sudden-onset watery diarrhea for 5 days. Colonoscopy and gastroduodenal endoscopy revealed mucosal congestion, redness, erosions and ulcers in whole colon except the rectum, the duodenum and the stomach. Histologically, amyloidosis was diagnosed by endoscopic biopsy specimens. He had received total parenteral nutrition, PSL and MTX, tocilizumab was started. [Discussion] Our two cases showed sudden-onset diarrhea and severe hypoalbuminemia. At first, inflammatory bowel diseases or infectious enteritis were suspected. Histological examination of biopsy specimens showed amyloid deposition. Diarrhea and hypoalbuminemia were very intractable and persisted. We report herein on these two cases with reference to the up-to-date literature.

P3-256

A case of Sjogren syndrome with pulmonary amyloidosis

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Conflict of interest: None

[Introduction] Lung diseases has been observed in about 10% of patients with Sjogren syndrome (SS), and pulmonary amyloidosis (PA) only in 0.5%. We report a case of multiple pulmonary nodular and cystic amyloidosis with SS. [Case] An 69-year-old female, who was incidentally found to have abnormal shadows on chest radiograph(CX-P), was referred to our hospital for further examination. A chest computed tomography (CT) scan showed multiple nodular shadows about 1cm in diameter. These lesions showed high uptake on a FGD-PET scan. Because lung cancer was suspected, video-assisted thoracoscopic lung biopsy was performed and confirmed PA after difficulty of pathological diagnosis by bronchoscopy and CT-guided percutaneous lung biopsy. SS was also suspected, and abnormal findings of tests fulfilled the criteria for primary SS diagnosis. Repeated CX-P indicated no changes in the size of nodules and cysts, and the patient had no pulmonary symptoms during the 1-year course of disease without treatment. [Discussion] Most reported cases of PA with SS had localized multiple nodules with cystic lesions, found incidentally, presented AL amyloid diagnosed by, surgical lung biopsy, and had good prognosis. PA should be considered in the differential diagnosis for multiple nodules in patients with SS.

P3-257

Clinical investigation of pneumocystis pneumonia in four patients

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Conflict of interest: None

【Objectives】Recently, rheumatism and collagen therapies were accomplished the dramatic paradigm shift in addition to conventional immunosuppressive therapies by the appearance of biological agents. However, in contrast, a lot of severe opportunistic infections including pneumocystis pneumonia had been reported. Once PCP is affected, disease is fatal. But this time we treated all cases by ST combination. In four cases of PCP, we compared with conventional reports by the analysis of patient backgrounds, episodic data and risk factors.【Results】The average age is 63.3, the ratio of male to female is 1:3. Underlying diseases are RA, overlap syndrome, wegener granulomatosis and dermatomyositis. In onset, diabetic patient was one case, complication of lung was one case, SpO2 was 90% in one case. The average of PSL was 29.4mg/day (7.5~50mg/day), two cases used MTX (8 and 10mg/week). The average of Alb was 3.3g/dl (2.4~4.1g/dl), the average of β-D-glucan was 65.8 pg/ml (24.5~137pg/ml). All cases were treated by ST combination.【Conclusion】This time, the much of cases of PCP which we experienced were elderly and used steroid. Early diagnosis and start of treatment of PCP by consideration of patient backgrounds and risk factors might be importance.

P3-258

An old case of acquired immunodeficiency syndrome who was diagnosed by combination with pneumocystis jiroveci pneumonia

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Conflict of interest: None

【Case】The patient was 73 years old male. Chest discomfort and dyspnea appeared. He was diagnosed respiratory pneumonia by chest X ray, and he admitted to our hospital on June 13th in 2012. Chest CT showed ground glass opacity on bilateral lung. Antibiotic was not useful, and βD - glucan level was high. So we considered pneumocystis jiroveci pneumonia, and started to give trimethoprim/sulfamethoxazole. Because HIV-1 WB antibody was positive, HIV-1 RNA level was 71000copy/ml, lymphocyte level was 400/μl, CD4 ratio was 13.1%, we diagnosed acquired immunodeficiency syndrome. Ttrimethoprim/sulfamethoxazole was changed to pentamidine isethionate due to systemic eruption. His symptom disappeared, ground glass opacity was improved on Chest CT. He was transferred to the other hospital on July 14th for anti HIV therapy.【Clinical significance】There might be several years no symptom period, but the attack at 73 years old is rare. It is guessed that he was not able to detect lymphopenia of no symptom period because he did not consult a hospital including a medical examination. In the case of atypical pneumonia, even pneumonia that it is thought that it developed to a physically unimpaired person has to think about possibility of the acquired immunodeficiency syndrome.

P3-259

Parvovirus infection case accompanied with arthritis symptoms was treated by salazosulfapyridines

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Conflict of interest: None

Parvovirus infection case accompanied with arthritis symptoms was treated by salazosulfapyridines Case:73 years old women Present Illness: She suffered poly arthlalgie Mar.2012 and labo data revealed anti CCP antibody more than 300, Rheumatoid factor 98IU/ml, CRP6.89mg/dl, power Doppler finding was synovitis. We diagnosed RA. She was prescribed salazosulfapyridines Aug 23 and after 4weeks the symptoms was decreased and CRP was decreasing to 1.03mg/dl. But 5 weeks she suffered whole body eruptions. SASP was stopped and followed up. But 7 weeks diarrhea, fever and peteciae were newly developed. Labo data wereCRP0.61mg/dl,INR4.40, sIL2 receptor1720U/ml,parvo virus V M 5.61 positive. PH: angina pectoris Warfarin K 2.5mg was prescribed Disccusion:She had high ACPA, This arthritis was reactive arthritis by parvo virus was unclear.

P3-260

An adult case of relapsing refractory coronary stenosis with parvovirus associated vasculitis

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Conflict of interest: None

[Background] The human parvovirus B19 infection presents slapped-cheek and various manifestations in children. The prominent symptoms in adults are fever and arthralgia, and it is important to distinguish from rheumatic diseases. Here, we reported the adult patient having relapsing refractory coronary stenosis with parvovirus associated vasculitis. [Case report] In March, 2005, a 41-year-old man was admitted in our hospital with high fever, polyarthralgia etc. He was diagnosed as HPV-B19 infection. He received NSAIDs and γ globulin therapy, yet, had hypercytokinemia. In April, his clinical symptoms were disappeared by receiving PSL30mg. However, in May, he presented chest strangulation and diagnosed as multiple stenosis of two coronary arteries and given an anticoagulation and Ca antagonist. Those stenosis lesions were progressive and administered percutaneous coronary angioplasty and γ globulin therapy. In October, this lesions still progressed and inserted a stent and treated by oral endoxan. Then it did not progress, and he had no symptoms. [Conclusion] This is the rare case report of adult onset Kawasaki disease-like coronary disease related to parvovirus infection. Although the stenosis lesions were progressive, the endoxan therapy was quite effective.

P3-261

Varicella Vaccination for Patients with Rheumatoid Arthritis

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Conflict of interest: None

(Case Report) We vaccinated seven patients with rheumatoid arthritis with varicella vaccine. They fulfilled the following criteria; methotrexate less than 0.4mg/kg/week, glucocorticoid equivalent of prednisolone less than 20mg, no biologic use, no other immunosuppressant use. Before vaccination, informed consent was taken on safety issues. From April 1 to October 31 of 2012, seven patients of 50 to 74 years old got vaccination. The treatment at the time of vaccination was, one on prednisolone, three on methotrexate, two on immunomodulatory agents, and one was before treatment. No patient reported significant adverse reactions. Until October 31, biologics have been introduced to three patients, and six patients are on methotrexate but no shingles have been reported. (Clinical implication) Immunosuppressants and biologics raise infection risks in patients with rheumatoid arthritis. American college of rheumatology recommends vaccination of varicella to patients with rheumatoid arthritis who use anti-rheumatic agents. In japan, varicella vaccination for shingles prevention is not approved though those used for chicken pox prevention is equivalent. Thus, varicella vaccine for the prevention of shingles for patients with rheumatoid arthritis should be warranted.

P3-262

Tuberculosis of the shoulder joint mimicking soft tissue tumor

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Conflict of interest: None

We reported a 77-year-old woman who complained swelling of the axillar region of the shoulder joint. Radiographs showed the erosion of the major trochanter of humeral head. Magnetic resonance imaging (MRI) showed a low signal intensity tumor on T1- and high signal intensity on T2-weighted images with marginal enhancement. The tumor detected in the axillar, clavicular, subdeltoid region. These tumor connected with glenohumeral joint. Open bipsy of the tumor was performed. Histopathologically, the tumor showed epithelioid granuloma with caseation and giant cell, therefore, tuberculosisof the shoulder joint was diagnosed. Tuberculosis of the shoulder joint is rare and the initial radiographs does not reveal the abnormal findings. It was reported that these cases were treated as a frozen shoulder. Li et al. reported it took 14.5 months on average to reach the final, correct diagnosis. In cases of the elderly,hemodialysis and RA patients who complained the shoulder joint pain for a long periods and showed the tumor, tuberculosisof the shoulder joint could be thought as a differential diagnosis.

P3-264

A case of polymyositis complicated by *Mycobacterium hecke-shornense*-induced deep abscess in the gluteus maximus muscle

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Conflict of interest: None

A 62 year-old man had been diagnosed 10 years earlier with polymyositis based on myalgia of proximal muscles, hyper-CK-emia, anti-Jo-1 antibody positivity, and muscular biopsy; and had been treated with prednisolone, cyclosporine, and methotrexate. The patient had felt malaise in the gluteal region from 4 months ago and noticed swelling of the gluteal region 2 months ago. On examination, mild swelling of the left gluteal region over the left lateral thigh was noted. On MRI, fluid retention was observed in the deep region of the left femoral muscle over the lateral region. In puncture fluid, the grade of collected tubercle bacillus was 1+, and nontuberculous mycobacterium grew on the 15th day and was identified as *Mycobacterium xenopi* using a DDH mycobacteria

kit. However, no case other than those with pulmonary involvement has been reported in Japan, and the isolate from our patient is sensitive to ethambutol. Finally, *Mycobacterium heckeshornense* was identified by DNA sequencing of the gene in the 16S rRNA. In our patient, levofloxacin + clarithromycin combination therapy improved inflammatory findings and 9 months have passed without recurrence of the gluteal abscess. In the future, it is important to accumulate the data of drug susceptibility of *M. heckeshornense*.

P3-265

An Autopsy Case of Leptospirosis with Resembled Symptoms of Systemic Lupus Erythematosus

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Conflict of interest: None

A 60-year-old man had admitted for thrombocytopenia. Besides that, lymphopenia, positive for antinuclear antibody and erythema circinatum, we diagnosed him as idiopathic thrombocytopenic purpura. H. pylori elimination and intravenous immunoglobulin therapies were carried out with moderate response on thrombocytopenia. Three months later, he admitted again for disordered consciousness and high grade fever. Glasgow Coma Scale was 13, and he showed jaundice, muscle pain including calf pain and erythema circinatum. He had thrombocytopenia, anti-DNA antibody positive, and elevation of inflammatory reaction. Because of the severe elevation of serum total bilirubin whereas minimal change of transaminase in addition to severe muscle pain, we suspected leptospirosis, but leptospiral antibodies were not detected. Then he was diagnosed as CNS lupus complicated with lupus hepatitis, and started with corticosteroid therapy. However, he failed to improve liver insufficiency and consequently died of pneumonia. Two days before death, Leptospira was detected in the blood culture sample which had been taken a few weeks before. We report this case with autopsy findings. We think this case seems suggestive to consider the differences of clinical findings between SLE and leptospirosis.

P3-266

4 cases developed bacteremia of Spirillum during immunosuppressive therapy to connective tissue disease

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Conflict of interest: None

We experienced 4 cases developed bacteremia of Spirillum during immunosuppressive therapy. To select proper treatment, we had to differentiate exacerbation of primary disease from infection of skin. Therefore we report these cases. Case 1) 55 years old, female, systemic lupus erythematosus (SLE). She were treated with prednisolone (PSL) and intravenous cyclophosphamide therapy (IVCY) and azathioprine. She developed acute cellulites. Bacteremia of *Helicobacter fennelliae* was confirmed and treated by Cefazolin. Case 2) 60 years old, female, SLE. She were treated with maintenance therapy of PSL. After artificial joint replacement for osteonecrosis of the femoral head, she suffered from fever associated with rush of her legs. Bacteremia of *Helicobacter fennelliae* was confirmed and treated by Imipenem/Cilastatin. Case 3) 70 years old, female, dermatomyositis. She were treated with PSL and IVCY. She suffered from fever and rush of her left leg. Bacteremia of *Campylobacter fetus* was confirmed and treated by Ceftriaxone (CTRX). Case 4) 51 years old, male, dermatomyositis. He were treated with PSL and tacrolimus. Rush appeared his arms and right leg. Bacteremia of *Helicobacter cinaedi* was confirmed and treated with CTRX.

P3-267

Pulmonary nocardiosis with cavity developed in a patient with granulomatous polyangiitis

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Conflict of interest: None

A 70 year-old male was diagnosed as granulomatous angiitis (GPA) 2 years ago based on cough, chest infiltrative shadows, proteinurina, hematuria, and high-tier PR-3 ANCA. He was treated with the combination of PSL and IVCY, but dose reduction was quite difficult. The chest CT on 24 Aug, 2012 showed cavity lesions on the middle and lower lobe of the right lung accompanied with infiltrative shadow on the left lower lung. Because pulmonary aspergillosis with bacterial pneumonia was suspected, we began treatment with TAZ/PIPC and VCZ. He was discharged with VCZ on 7 Sept because of the improvement of CT findings. However he was hospitalized again on 25 Sept as the cavity lesions got worse, and VCZ was changed to liposomal AMPH-B with no beneficial effects. Gram stain of induced sputum revealed GPR and Nocardia asteroids was cultured. S/T was contraindicated because of CKD, so we used linezolid (LZD) then changed to CTRX according to the sensitivity. The thickening of cavities and surrounding nodules improved. Pulmonary nocardiosis is relatively rare but sometimes reported in immune-compromised patients. Differential diagnosis is crucial among GPA, pulmonary asperegillosis, cryptococcosis, nocardiosis and TB, because all show similar cavity lesions.

P3-268

Long-term course observation of hepatitis B virus (HBV) reactivation by immunosuppressive therapy in rheumatiod arthrisits (RA) patient. : Hepatitis aggravation caused by tacrolimus (FK506) withdrawal under the treatment with antiviral agent

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Conflict of interest: None

【Introduction】 Here, we show the long-term course observation of patient who became HBV carrier after the HBV reactivation by immunosuppressive (IS) therapy in HBsAg negative. **【Clinical course】** At 58 years old, She developed RA. HBsAg was negative, then. At 65 years old, She was treated with Cychlophosphamide (CYC) because RA was refractory. And then liver function test (LFT) abnormality was developed. It was diagnosed as HBV infection and got better by withdrawal of CYC and administration of UDCA, but viremia was persistent. Because of persistent Arthritis, FK506 was started at 70 years old. 1 year later she showed recurrence of LFT abnormality. Entecavir was started because HBV DNA was continuously high level, and showed calming down of hepatitis and decrease of HBV DNA level. 1 year later, She quitted FK506 by herself and then LFT aberration was shown. But re-administration of FK506 resolved LFT abnormality. LFT and arthritis were stable, afterwards. **【Discussion】** In our case, HBV DNA level decreased by antiviral agent, but, not lower than detection limit, it was thouht to be one of the cause of hepatitis aggravation after IS agent withdrawal.We need to be careful about withdrawal of IS agent, even in a case thought to be HBV carrier and become acquired tolerance.

P3-269

The Case of an Elderly Rheumatoid Arthritis Patient Treated with Total Knee Arthroplasty Resulted in Delayed Postoperative Infection: An Examination of Tacrolimus Dosage and Postoperative Infection Risk

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Conflict of interest: None

[CASE] The patient was an 88-year-old female diagnosed with rheumatoid arthritis in 1990. Since 2010, Tacrolimus (TAC) was introduced at 1.5mg/day, effectively controlling the disease activity. Total knee arthroplasty (TKA) was also conducted on both knees. As a countermeasure to the increased disease activity afterwards, TAC dosage was increased to 3.0mg/day, successfully resulting in the disease re-controlling. A half year after the dosage escalation, she was diagnosed with post right-TKA infection. After the cleaning and debridement of inside the joint and administration of antimicrobial agent, the infection was subsided. [DISCUSSION] As increased blood concentration of TAC leads to the higher risk of renal dysfunction, caution has to be taken especially in treating elderly patients. Also, the risk of infection of the area surrounding the prosthetic joint should be predicted. According to the post-marketing surveillance, the infection incidence rate among the group with the blood concentration of 10ng/ml or more was three times more than that of group with the blood level of 10ng/ml or less. This fact also suggests that the monitoring of TAC blood level for post-TKA patients is effective in preventing the postoperative infection.

P3-270

Two cases of poststreptpcoccal reactive arthritis (PSRA)

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Conflict of interest: None

[Case 1] A 53-year old woman was admitted to our hospital because of high fever and left hip pain. Her blood tests showed elevated levels of CRP (13mg/dl). Magnetic resonance imaging (MRI) showed an abscess of the left iliopsoas muscle. Her laboratory tests showed a high titer of anti-streptolysin O (ASO) (1350IU/l) leading to a diagnosis of streptococcal infection. The patient responded to treatment with antibiotics, and her CRP level normalized. Eleven days after the treatment, she presented with symmetric persistent tenosynovitis of hands and feet and erythema nodosum; her CRP level was elevated (12 mg/dL). [Case 2] A 36-year-old woman complained of fever and sore throat. She was diagnosed with tonsillitis, and successfully treated with antibiotics. After 7 days, she presented with bilateral polyarthritis, Achilles' tendonitis and erythema nodosum. Her laboratory test showed elevated levels of CRP (10mg/dl) and a high titer of ASO (240IU/l). Two cases were diagnosed with PSRA. Recently, some cases of PSRA have been reported, however a diagnostic criteria has not been still confirmed. The clinical findings were different from those of acute rheumatic fever. Here, we report 2 cases of PSRA and review the relevant literature.

P3-271

A case of reactive arthritis, erythema nodosum, iritis, and tinnitus without respiratory symptoms of *Chlamydophila pneumoniae* and *Mycoplasma pneumoniae* infection

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Conflict of interest: None

A 22-year-old woman, who is a freshly recruited nurse, admitted to our hospital because of low grade fever, eruption, morning arthralgia, tinnitus, vertigo, bilateral conjunctival hyperemia, blurred vision, and photophobia. On physical examination, she had tender erythema on her both lower extremities, bilateral conjunctival hyperemia, tinnitus, and polyarthralgia involving her ankles, knees, and fingers. We diagnosed the eruption as an erythema nodosum, the eye lesions as an iritis, and the tinnitus with vertigo as a sudden deafness. Autoimmune diseases or some kinds of viral infections were suspected, however, we could not identify them by use of serologic tests. Then we took her history in detail again, and it is turned out that she cared patients suffering from *Chlamydophila pneumoniae* and *Mycoplasma pneumoniae* three months ago. Serologic tests were *C. pneumoniae* IgM 1.61(ID), IgG 2.73(ID) and *M. pneumoniae* antibody value 160(PA method). A symptomatic therapy was effective for a month. Although we could not identify the serological diagnosis of the infection, post infectious reactive disease is strongly suspected, considering her working environment and clinical course. Thorough history taking enabled us to correlate her symptoms and the post infectious reactive disease.

P3-272

Two cases considered to be a reactive arthritis-like clinical condition developed after vaccination and intravesical BCG administration

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Conflict of interest: None

[Case 1] A woman aged 19. Upon a checkup in our hospital due to a development of fever observed two weeks after receiving measles vaccine, her temperature was naturally reduced a month later even though the etiology was unclear. Even though the pathogenesis was not identified by another complete checkup conducted the next year due to an onset of fever and arthritis a week after receiving hepatitis B vaccine, the symptom was immediately improved by steroid administration. [Case 2] A man aged 65. Upon executing intravesical BCG therapy for bladder cancer, the patient had a high fever and arthritis developed after fourth administration. Although the symptom had not been improved after initiating administration of antitubercular agent in consideration of possible disseminated BCG infection, it was promptly improved by steroid administration. [Discussion] The symptoms of arthritis observed in these cases were so mild that these are not typical as reactive arthritis. It is desired to further accumulate cases regarding such clinical conditions as well as to make them widely known in the future.

P3-273

Two cases of autoimmune disease accompanying a myeloid neoplasm

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Conflict of interest: None

Case 1: A 54-year-old female who was diagnosed to have SLE in July 2009 was initially treated with 50mg/day of PSL. The PSL dose was gradually decreased and tacrolimus was added. However, her pancytopenia gradually progressed from April 2011. The PSL dosage was increased to 50mg/day, but her pancytopenia nevertheless continued to progress, and we also detected abnormal cells according to a peripheral blood analysis. We detected 70% blast cells that were positive for CD13,33,34,HLA-DR in her bone marrow examination, and diagnosed her to have acute myeloid leukemia. Case 2: A 70-year-old female was diagnosed with RA in 1978. She was treated with aurothiomalate, auranofin, azathioprine and penicillamine. She was treated with MTX beginning in 1984. Her WBC and PLT were occasionally decreased. We detected abnormal cells in her peripheral blood in August 2011, and noted 7% blast cells that had an abnormal karyotype in her bone marrow examination. We diagnosed her to have myelodysplastic syndrome. SLE or RA has been reported to be associated with lymphoma, but the simultaneous occurrence of autoimmune disease and a myeloid neoplasm is rare. However, the diacrisis of a hematopoietic tumor is considered to play an important role in the development of cytopenia in autoimmune disease.

P3-274

Successful management of methotrexate-associated lymphoproliferative disorder in the central nervous system of two patients with rheumatoid arthritis

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Conflict of interest: None

[Objectives] These are two case reports of RA patients who developed a mass lesion in central nervous system (CNS) during MTX therapy. [Methods] In one of two patients, the lesion was histopathologically diagnosed as methotrexate-associated lymphoproliferative disorder (MTX-LPD) after extraction of the lesion for diagnosis as well as for treatment against encephalopathy. Low does tacrolimus therapy was started to reduce exacerbation of RA disease activity after discontinuation of MTX. In another patient, it was thought to be as MTX-LPD because of a spontaneous regression of the lesion in the brainstem after discontinuation of MTX therapy even under an administration of etanercept, a TNF inhibitor. [Results] Successful management of MTX-LPD in CNS as well as of RA disease activity has been achieved for more than three years with tacrolimus therapy or for five months with etanercept therapy in each RA patient. [Conclusion] It is important for every physicians as well as rheumatologists to be aware of this possibility and initiate appropriate investigations, in order to detect these serious complications at earlier stage during MTX-LPD. Furthermore, it is also indispensable to manage the RA activity after MTX discontinuation.

P3-275

Efficacy of sitagliptin in patients with collagen disease complicated by steroid-induced diabetes

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Conflict of interest: None

[Objectives] We administered sitagliptin to patients with collagen disease complicated by steroid-induced diabetes at our hospital, and investigated its efficacy. [Subjects] Sitagliptin was given at a dose of either 50 or 100 mg/day to a total of 10 patients with collagen disease (2 men, 8 women), and an assessment was made after 12 weeks. [Results] The mean steroid dose at the start of sitagliptin administration was 12.0 mg/day of prednisolone equivalent. HBA1c (NGSP) decreased from 7.91% at baseline to 6.72%, and glycoalbumin also decreased from 19.2% at baseline to 15.7%. Fasting blood glucose did not change between baseline and after 12 weeks in one patient, but casual blood glucose improved from 186 g/dl at baseline to 116 g/dl after 12 weeks in nine patients. Serum C peptide level was 2.86 ng/ml at baseline and 3.13 ng/ml after 12 weeks, indicating no change. [Conclusion] Sitagliptin, a DPP-4 inhibitor that is thought to have a low risk of inducing hypoglycemia, was considered an effective and safe drug for steroid-induced diabetes.

P3-276

A case of vascular C5b-9 deposition was observed from stomach to large intestine in Degos disease

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Conflict of interest: None

[Case Report] A 68-year-old Japanese male presented with multiple pink papules without pain and atrophic erythematous with white lesions with peripheral dark reddish rims were found his back. A multiple ulcer was detected in endoscopy from stomach to large intestine. Although the patient was given high dosage of steroid, antibiotics, aspirin, dipyridamole, minocycline and intravenous immunoglobulin therapy, he died of gastrointestinal hemorrhage, perforation and septic shock. Pathologic examination of the resected intestinal specimen revealed pauci-inflammatory thrombotic microangiopathy with endothelial cell injury, fibro mucinous occlusive arteriopathy and vascular C5b-9 deposition was observed in the wall from the esophagus to the large intestine. Degos dieases falls under the alternative appellation of malignant atrophic papulosis based on the fatal outcome that frequently characterizes its clinical course. Based on the extent of vascular C5b-9 deposition, morphologic features of Degos disease include a pauci-inflammatory thrombotic microangiopathy syndrome with characteristic clinical features, including porcelain-like depressed infarcts of the skin concurrent with similar lesions involving the gastrointestinal tract.

P3-277

A case of lung lesions with pyoderma gangrenosum, successfully treated with cyclosporine

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Conflict of interest: None

A 65-year-old woman. In July 2012, she visited our department because repeated the recurrence of prednisolone (PSL) therapy. The ulcers were improved by cyclosporine (CsA). However, she was hospitalized for pancytopenia, acute kidney injury and infiltration of left lung. We started Antibiotic and stopped CsA because of

kidney disease. Laboratory findings and chest images were improved immediately. Nevertheless, fever, hypoxemia and consolidation of both lungs were newly appeared on the 7th hospital day. Hypoxemia and pancytopenia was worsened. No bacterial infections had been detected by transbronchial lung biopsy and bronchoalveolar lavage. Therefore we diagnosed the lung lesions and hemophagocytic syndrome accompanied with pyoderma gangrenosum. We started steroid pulse and restarted CsA therapy. Fever, hypoxemia, pancytopenia and chest images were significantly improved. She was discharged from the hospital on the 46th hospital day. Lung lesions with pyoderma gangrenosum are rarely reported. In our case, restart of CsA therapy played critical rolls.

P3-278

Effective Etanercept (ETN) Treatment of Rheumatoid Arthritis (RA) after suffering from Methotrexate (MTX) -Related Lymphoproliferative Disorder (LPD)

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Conflict of interest: None

【Objective】We experienced an effective ETN treatment of RA after suffering from MTX-related LPD.【Methods】A patient, 64-Year-old woman was diagnosed with RA in 2008. We began the administration of MTX. She got a fever in early April 2012 and hospitalized with liver dysfunction. She had lymph node swelling of mediastinum and axillary, splenomegaly, sIL-2R was increased to 6622. After MTX withdrawal, she was discharged the hospital for the symptoms turned mild. She visited our hospital in mid-April. lymph node swelling of mediastinum and axillary, splenomegaly had disappeared and sIL-2R was reduced to 2316. We diagnosed with MTX related LPD. And then, we were watching the progress of RA only PSL, but RA activity increased. Therefore, we started subcutaneous injection at ETN 25mg/week. And we were able to reduce administration of PSL because RA activity was reduced.【Conclusion】It is said that autoimmune diseases such as RA, incidence of LPD high compared to healthy volunteers, and immunosuppressive therapy added to further increase. MTX related LPD has the characteristics of spontaneous regression of the tumor for MTX withdrawal, usually different from the type of lymphoma. In this case, we experienced 1 case of an effective ENT's monotherapy after discontinuation of MTX.

P3-279

A case of post streptococcal reactive arthritis with acute progressive erosive arthritis

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Conflict of interest: None

A 65-year-old woman was admitted to our hospital because of arthralgia of left ankle, back and bilateral hip (which continued for more than one week). She was treated with non-steroidal anti-inflammatory drugs in other clinic, but her arthralgia was not improved. Laboratory tests showed leukocytosis (17400/μL), and elevation of C-reactive protein (13.4mg/dl) and anti-streptolysin-O antibody (480 IU/ml). Tests for rheumatoid factor, anticyclic citrullinated peptide and antinuclear antibodies were negative. Chest and abdominal computed tomography and a cardiac ultrasonographic examination showed no abnormalities. But her three blood-cultures yielded a growth of group G streptococcus. Treatment of antibiotics and rehabilitation were continued for more than 6 weeks. Though initial arthralgia of ankle, back and hip were improved immediately, only arthralgia of right wrist was not resolved. Furthermore joint X-ray detected joint space narrowing and erosions of right hand. This is a very rare case of post streptococcal reactive arthritis with acute progressive erosive arthritis.

P3-280

The continuous glucose monitoring (CGM) of steroidal hyperglycemia accompanied with polymyositis treated with Sitagliptin

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Conflict of interest: None

[Clinical significance] The hyperglycemia with the steroid dosage is complicated to be affected by meals. It is important to analyze movement of detailed blood glucose by continuous glucose monitoring (CGM) to control steroidal hyperglycemia precisely. DPP-4 inhibitor seems suitable for treatment of the steroidal hyperglycemia because of the feature that it is hard to cause hypoglycemia and weight gain, but more inspection is necessary. [Objectives] Monitoring of a detailed blood glucose change of the steroidal hyperglycemia and to analyse influence with the DDP-4 inhibitor dosage. [Methods] We analyzed CGM of a patient given 1 mg/kg of prednisolone, metformin 500 mg for polymyositis and we added sitagliptin 50mg and analyzed CGM again. [Results] The mean minimum blood glucose was 123 mg/dl, the mean maximun blood glucose was 400 mg/dl, the AUC upper limit excess was 123.7 mg/dl with 500 mg of metformin alone. After adding sitagliptin 50 mg, these parameters reduced to 84 mg/dl, 340 mg/dl, 106.3 mg/dl. [Conclusion] It seemed to lead to optimization of the steroidal hyperglycemia treatment to use CGM. Sitagliptin was effective for blood glucose control without producing hypoglycemia.

P3-281

2case of Adult Still Disease treated by Tosilizumab

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Conflict of interest: None

2 case of Adult Still Disease were treated by Tosilizumab. Tachyphylaxis was seen in one case.

P3-282

Slow clinical response with rituximab therapy in two cases of recalcitrant epidermolysis bullosa acquisita

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Conflict of interest: None

[Objectives] Epidermolysis bullosa acquisita (EBA) is an autoimmune bullous disease characterized by the presence of autoantibodies against type VII collagen. We report clinical response and autoantibody profiles in 2 patients with EBA treated with rituximab (RTX). [Methods] Case 1: A 60-year-old man diagnosed with EBA 4 years ago and Case 2: A 73-year-old man diagnosed with EBA 1 and half years ago. Both patients were non-responders to several long-term immunosuppressive treatment regimens and received 4 courses of intravenous RTX (375 mg/m^2), once in 2 weeks. [Re-

sults] Skin and oral lesions improved quite slowly after 37 weeks in case 2, and after 67 weeks in case 1. Anti-type VII collagen antibody ELISA index values declined continuously from 106.3 to 20.0 in case 1 and from 125.4 to 26.5 in case 2, respectively. Serum levels of BAFF were elevated significantly after RTX treatment and fluctuated inversely with the anti-type VII collagen autoantibody titers in both patients. [Conclusion] Slow response in both patients irrespective of continuous decline in anti-type VII collagen autoantibody titers might suggest strong affinity of low-titer autoantibodies for type VII collagen and/or functional damage and delay of recovery of type VII collagen after anti-type VII antibody binding.

P3-283

Elevation of KL-6 levels in two cases with rheumatoid arthritis and concomitant malignant tumors

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Conflict of interest: None

[Objectives] Case reports Case 1 A 55-year-old woman had rheumatoid arthritis (RA) in 1991. Infliximab (IFX) administration was initiated in 2007. Elevated levels of KL-6 (549 to 1000 or higher) were observed during the sixth course of IFX treatment, but there was no increase in the (SPD) level. Chest CT slice images prior to the ninth course of IFX treatment showed ascites in the superior border of the liver, and abdominal ultrasonography and MRI were conducted, which led to a diagnosis of ovarian cancer. During chemotherapy, the KL-6 level returned to normal (< 500). However, the patient died of the primary disease. Case 2 A 73-year-old woman had RA in September 2011. At the initial visit, her KL-6 level was as high as 586, but a chest X-ray examination revealed no abnormalities. Although the KL-6 level gradually rose, the SPD level was in the normal range. There were no abnormalities in the chest, but bile duct cancer and colon cancer were diagnosed by abdominal CT and MRI. Because surgery was not possible, chemotherapy was performed, but the patient died. [Discussion] If increased KL-6 levels with normal SPD levels and no IP findings by a chest examination were observed during the treatment course of RA, detection of malignancy is necessary.

P3-284

Sarcoidosis Presenting as Bilateral Swelling of Fingers and Toes: A Case Report

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Conflict of interest: None

We present a rare case of bone sarcoidosis. Case: A 57-year-old woman presented with swelling and pain in the fingers and toes. She was referred to our hospital because radiography indicated bone tumor. A chest radiograph revealed BHL.leading to a diagnosis of sarcoidosis. The primary initial symptoms were redness and swelling around the DIP joint of the right thumb and index finger, both big toes, and the left third toe. Blood tests showed the following results: CRP, 0.1 mg/dL; WBC, 3.46 × 10^3/μL; ACE, 21.2 U/L; and β2MG, 2.12 mg/dL. No abnormalities suggesting osteoporosis were observed. Translucent lesions were found at the distal phalanx of the right thumb and index finger, both big toes, and the middle phalanx of the left third toe, which also showed pseudarthrosis and epithelioid cell proliferation with lymphocyte infiltration in pathological examination. She was thus diagnosed with bone sarcoidosis. The swelling and pain in the limbs reduced with NSAIDs. Subsequently, a lucent lesion developed on the fifth left metatarsal, so we administered PSL at 5 mg/day. Bone lesions occur in 1–2% of sarcoidosis cases, and some lesions are self-limiting; however, bone sarcoidosis has a poor prognosis. In our case, the lesion worsened, necessitating continuous and careful observation.

P3-285

A case of pustulotic arthritis with onset of drug-induced hypersensitivity syndrome after oral administration of celecoxib

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Conflict of interest: None

A 64-year-old woman with pustulotic arthritis, onset of which was in August 2010, began taking celecoxib and salazosulfapyridine in April 2011. Beginning on May 23, 2011, edematous erythema was observed all over her body, with increased transaminase level and lymphadenopathy of the groin, and a diagnosis of drug-induced hypersensitivity syndrome (DIHS) was made. She was treated with PSL. DLST indicated positive for celecoxib and negative for salazosulfapyridine. In this case, reactivation of HHV-6 was observed, but no reactivation of EBV or CMV was observed. DIHS is a drug eruption caused by a limited number of medications, but there have been few reports of cases caused by celecoxib.

P3-286

Tight control of serum uric acid in gout patients is not necessary without ultrasonography double contour sign

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Conflict of interest: None

[Objectives] EULAR evidence based recommendatin for gout says maintaining the serum uric acid below the saturation point for monosodium urate (≤360 μmol/l) is necessary. The necessary of tight control for long term is doubleful, and patients is could not endure tight control for long term. We evaluated that the patients after tight control with ultrasonography double contour sign(DC sign) negative could stop thigh control or not. [Methods] We evaluated that 7 cases after tight control with negative DC sign were treated under 7.0mg/dL serum uric acid instead of 6.0mg/dL. [Results] All 7 cases had no flare of gout, and recurrence of DC sign(month 6<, <month 9) [Conclusion] When we treated gout patients without DC sign after tight contol, we could not have to treat it tight control. Ultrasonography is a good modality for gout.

P3-287

Clinical characteristics of rheumatoid arthritis (RA) patients with mono-arthritis of the knee at the onset

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Conflict of interest: None

[Objectives] Since the new criteria of ACR/EULAR 2010 gives weight to small rather than large joints, patients with mono-arthritis in a large joint do not meet the criteria even if rheumatoid arthritis is suspected clinically. In this study, we investigated patients with RA although mono-arthritis of the knee was the first symptom at the onset. [Methods] Five RA patients (all females) with mono-arthritis of the knee at the onset were subject to this study. The mean age at the onset was 63.4 year-old and the mean disease duration was 15.8 months. The laboratory data, disease activity and X-ray findings were investigated. [Results] Both CRP and MMP3 levels were elevated in all patients and anti-CCP antibodies with high-titer were detected in 3 patients. The radiographs of the knee showed joint space narrowing and periarticular osteopenia. All patients were treated with MTX and two were treated with MTX + biologics. After treatment, mean DAS28/ESR was improved from 4.85 to 2.75, and both levels of CRP and MMP3 were markedly reduced. [Conclusion] RA with mono-arthritis in a large joint at the onset is rare. Because destruction of large joints cause severe disability, physicians should diagnose in a comprehensive manner based on laboratory data, radiographic images and clinical symptoms.

P3-288

Ultrasonography is superior to aspiration menosodium urate in diagnosis for gout

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Conflict of interest: None

[Objectives] Gout is common disease. But the diagnosis sometimes is not easy. Difinite diagnosis is necessary for aspiration for menosodium urate (MSU). Nowadays ultrasonography is improved, and is helpful for diagnosis. [Methods] 42 cases finally gout is made ultrasonography double contour sign(DC sign) and MSU 2X2 table. [Results] MSU crystals identified No MSU crystals identified total DC sign positive 30 6 36 DC sign negative 1 5 6 total 31 11 42 [Conclusion] If the patients were doubtful for gout, at first we check DC sign before aspiration of refered joints.

P3-289

Patients who visit the emergency department

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Conflict of interest: None

[Objectives] To reveal the characteristics of patients with rheumatologic disease who visit the emergency department [Methods] Patients who visited the emergency department between January 2008 and December 2011 and who were subsequently hospitalized in our department were included in this retrospective study [Results] Of the total 220 patients, overall mortality was 5%. 28 patients were without known rheumatologic disease background. They were finally diagnosed as 4 with henoch schonlein purpura, 3 with polymyositis/ dermatomyositis, 2 with sle, 2 with RA, 1 with microscopic polyangiitis, 1 with polymyalgia rheumatica, 4 with adverse drug events, 5 with infectious events. Among the patients with known rheumatologic disease, RA was the most frequently seen (67%) and followed by SLE(12%), vasculitides(8%), polymyositis/dermatomyositis(5%). Among RA patients, 22% with infection(70% were pneumonia), 12% with trauma, 9% with disease flare. Among SLE patients, 39% with disease flare and 35% with infection(63% were UTI). [Conclusion] There ware tendency that with RA patients, the leading cause was infection especially pneumonia. With SLE patients, infection and disease flare were equally frequent, and with infection, UTI was most frequent.

P3-290

Effect of upper limb disabilities on general visual analog scale in patients with rheumatoid arthritis

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Conflict of interest: None

[Objectives] In recent years, the treatment goal of RA was changing from “relieve the pain” to “induction of remission” and we can lead a lot of RA patients to remission by methotrexate and/or biological agents. However, there are not a few RA patients who fall a remission due to high score of visual analogue scale (VAS). In this study, we speculate that upper limb functions could be a factor affecting VAS and assess upper limb functions in RA patients by Disabilities of the Arm, shoulder, and hand (DASH). [Methods] 52 RA patients whose upper limb functions were assessed using DASH were included. We retrospectively reviewed the clinical data. [Results] Simple regression analysis revealed the correlation between DAS28-ESR and DASH score. Among the patients with less than 2 in HAQ sore, nine patients with less than 2 (group A) in DASH and eleven patients with over 2 (group B) were studied separately. Patients who satisfied a criterion for Boolean remission were eight and three in group A and B, respectively. The mean VAS in A group was significantly higher ($p=0.03$) than that that in group B. [Conclusion] These result suggested that upper limb disabilities would be a factor of high VAS score and the improved functioning of upper limbs lead patients with high VAS score to remission.

P3-291

Trials to comprehend the specific foot complaints in patients with rheumatoid arthritis -health assessment questionnaire vs. open-ended questionnaire-

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Conflict of interest: None

[Objectives] Several literatures reported that health assessment questionnaire (HAQ) may not reflect functional disorder in rheumatoid arthritis (RA). We often meet out-patients suffering from foot deformities with low HAQ score. We aimed to comprehend the specific disorder in daily livings. [Methods] We enrolled 63 out-patients (15 males, 48 females) in this study. The mean age was 65.8 (26-91) and mean affected period was 11.5 years (0.2-36). We evaluated HAQ and foot deformity, and used an open-ended questionnaire. We studied foot complaint, foot deformity and functional disorder. [Results] The HAQ score correlated with age and affected period. In the open-ended questionnaire, 29 patients (46%) had disorder in their feet and complained pain and troubles in wearing or choosing shoes. Their HAQ scores showed no significant differences between the patients without disorder. [Conclusion] The HAQ is not supposed to explain complaints of foot.

Even in the patients with well controlled RA, patients with high HAQ score had foot deformities. Not only age, affected period but foot deformity would account for the disorder, HAQ would be inefficient for foot deformities. We concluded that foot care, rehabilitation, braces and scheduled observation are necessary for total care of foot lesion.

P3-292

A case of the difficulty in treating rheumatoid arthritis to develop shoulder joint infection by M. intracellelare

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Conflict of interest: None

[Objective] Non-tuberculous mycobacterial disease that developed large joints is rare. We report a case of M. intracellulare infection of right shoulder joint with rheumatoid arthritis. [Methods] The case is a 68-year-old man. He was introduced to our clinic because of the fistula formation at right shoulder. Large bone erosion of humeral head on plain X-ray and inflammation of right shoulder joint on MRI were observed. Since the antibiotic was administered, pus discharge wasn't improved. The curettage of focus was performed. Acid-fast bacilli were detected and on histological examination giant cell and epitheloid cell ware seen, so anti-TB drugs have been administered. The fistula was recurred after 6 months, so second operation was performed. The fistula was not healed, so radical surgery, that is resection of humeral head and acromion and transfer to the gap of pedicled latissimus dorsi myocutaneous flap were underwent. [Results] Now fistula was closed and during follow up. [Conclusion] For purulent arthritis and osteomyelitis transfer to defect of myocutaneous flap, abundant blood supply was reported good results, but there is little report of cases of mycobacterium infection treated by the same method, so it is necessary to observe carefully.

P3-293

Atypical femoral fractures in patients with rheumatic disease during use of alendronate: a report of two cases

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Conflict of interest: None

[Objectives] The present study reported on two patients with rheumatic disease, both of whom had long-term use of steroid and alendronate then sustained subtrochanteric femoral insufficiency fractures with no or minimal trauma. [Case Summary] One of the patients was 62-year-old woman who had been suffered from rheumatoid arthritis for 21 years. She had right thigh pain during going up the stairs. X-ray findings showed local cortical bone thickness and horizontal radiolucent zone in the sclerotic area of the subtrochanteric femur, and she was diagnosed as atypical femoral fracture. She was treated with 10mg of prednisolone for 14 years and alendronate for six years. The fracture was fixed prophylactically with intramedullary nail. The other patient was 48-year-old man who had been treated with 12.5mg to 20mg of prednisolone for Behcet's disease. He was also treated with alendronate for four years. He sustained subtrochanteric femoral fracture just after he stood firm to avoid falling down of his motorbike. X-ray findings showed transverse fracture with medial spike. The fracture was also fixed with intramedullary nail. [Conclusions] Prophylactic intramedullary fixation was recommended for alendronate-related subtrochanteric insufficiency fracture.

P3-294

Multiforcal osteonecrosis in patient with mixed conectivetissue disease, a case report

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Conflict of interest: None

[Introduction] Multifocal osteonecrosis (ON) is usually thought to be secondary to corticosteroid therapy or can be associated with systemic lupus erythematosus (SLE). We present a patient with mixed connective tissue disease (MCTD) who developed multifocal osteonecrosis. [Case report] A 40-year-old female, she was diagnosed with MCTD at 27 and treated with corticosteroid. When she was 32, curved varus osteotomy of the femur was performed, and when she was 38, total knee arthroplasty (TKA) was performed for ON. Afterward polyarthralgia in both foot, ankle, shoulder, elbow, wrist was continued. X-ray were normal, bone scintigraphy was not showed accumulation without right hip and left knee. But MRI revealed ON in tibia epiphysis, talus, calcaneus, tarsal bones, humerus diaphysis, elbow, and wrist. Her polyarthralgia have continued and she needs using opioid. [Discussions] Multifocal osteonecrosis can be associated with SLE, however there are few reports associated with MCTD. Previous reports mentioned osteonecrosis of the tibia epiphysis: 2%, humerus diaphysis: 3%, calcaneus: 6%. Low sensitivity of bone scintigraphy for diagnosing osteonecrosis was reported previously and MRI was useful for diagnosis in our case. We need careful observation for other joints in future.

P3-295

Curved periacetabular osteotomy for the acetabular dysplasia patient who had von Willebrand disease

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Conflict of interest: None

19 years-old woman had bilateral hip pain since 15 years-old. The right hip pain got worse, diagnosed as the acetabular dysplasia.According to preoperative examination, we recognized activated partial thromboplastin time (APTT) prolonged, von Willebrand factor antigen level felt, and von Willebrand factor decreased.So, we diagnosed as the von Willebrand disease. She preserved preoperative autologous blood donation 1000ml. Curved periacetabular osteotomy was underwent, and operation time was 1 hour and 40 minutes. Although amount of the intraoperative bleeding was unknown, the amount of intraoperative autologous blood donation was 343 ml. The amount of postoperative bleeding was 174 ml. Since we used autologous blood donation, there was no vital abnormalities, and postoperative haemoglobin level was 12.0g/dl. So, we didin't use VIII/von Willebrand factor and homologous blood transfusion. From the 3rd postoperative day, She started walking exercise. She was able to walk with no symptom and return to work six months later. von Willebrand disease caused bleeding disorder. So,this disease was One of the risk factor for periacetabular osteotomy which may occur intraoperative and postoperative over

bleeding. We should have considered about plan and management for the operation.

P3-296

Rheumatic arthritis of the knee that was diagnosed as a septic arthritis: case report

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Conflict of interest: None

45 year-old woman, who has rheumatoid arthritis since 19 years, has left knee swelling, redness, pain and recognized two subcutaneal masses at popliteal and lateral lesion of the knee 6 months ago. After then lateral mass was self-opened and the pus was discharged. A initially diagnosis of septic arthritis was established based on high CRP and accumulation of WBC at a home clinic. Antibiotics was used but inflammation persisted. She consulted us 2 months after onset. Her laboratory data showed that WBC was 12500 and CRP was 6.3 and X-P or MRI showed high destructive change of knee joint, joint swelling, synovitis and subcutaneal cysts. The culture of pus was negative. Arthroscope was done and this showed fully synovitis and no bacterial colony was seen in histology. Synovectomy in the joint and debridement of subcutaneal cysts were performed. After operation fistel was closed and pain, swelling and inflammation were decreased. A diagnosis of rheumatoid arthritis of the knee with fistel was established. Septic arthritis often resembles RA and exact and quick diagnosis is needed.

Luncheon Seminar

LS1-1

Practical use of musculoskeletal ultrasonography (MSUS) in rheumatology clinics. -Monitoring therapeutic response of adalimumab by MSUS-

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Conflict of interest: Yes

The situation that musculoskeletal ultrasonography (MSUS) shows its clinical potential is in the diagnosis of early rheumatoid arthritis (RA) and judgement of remission. MSUS can detect subclinical synovitis in a highly sensitive manner that is often missed by clinical examination. The detection of subclinical synovitis, as well as subradiographic bone erosion by MSUS helps rheumatologists in the early diagnosis of RA. In addition, in RA patients who are judged to be in remission by clinical examination, MSUS can detect subclinical synovitis which may progress into bone erosion or may result in clinical relapse and it helps rheumatologists to achieve true “treat to target”. By using MSUS in the early diagnosis and evaluation of remission in RA, we can expect the prognosis of RA patients to improve. On the other hand, the significance of MSUS in the evaluation disease activity and monitoring of clinical response to RA treatment is unknown. It is reported that some ultrasound joint scores correlate with disease activity scores such as DAS28, and ultrasonographic findings improve with effective treatment, but there is no evidence if the addition of MSUS to regular clinical examination improves the disease outcome. Disease activity and the requirement of therapy modification might be judged by regular clinical examination without MSUS. The role of MSUS in the monitoring of therapeutic response of RA patients in clinical practice will be discussed in this seminar.

LS1-2

The utility of musculoskeletal ultrasound in the diagnosis of rheumatoid arthritis

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Conflict of interest: Yes

Although the 2010 ACR/EULAR classification criteria for rheumatoid arthritis (RA) allow for earlier RA classification, several issues have been raised on their accuracy. Firstly, the new criteria require at least one clinically swollen joint and give the largest point to the joint involvement domain, in which joints with either clinical swelling or tenderness are counted. Early RA patients sometimes present without joint swelling and the joint examination has been repeatedly reported to be examiner-dependent and not reproducible. We investigated the impact of ultrasound on the 2010 ACR/EULAR RA classification criteria when the joint involvement was determined by using ultrasound. 109 patients with early arthritis underwent musculoskeletal ultrasound on 38 joints and the semi-quantitative scores for gray-scale synovitis and synovial power Doppler signals were recorded. When the presence of joint swelling and the number of involved joints were determined by ultrasound, the classification of RA was changed in approximately 20 % of the patients. Moreover, either sensitivity or specificity of the classification to identify the patients who required methotrexate treatment within a year was improved. Another issue with the 2010 ACR/EULAR RA classification criteria is that excluding differential diagnosis is required before applying the criteria. Ultrasound plays a significant role in the diagnosis of articular conditions other than RA such as osteoarthritis, psoriatic arthritis, and crystal ar-

thropathies. Degenerative/mechanical/age-related changes are especially important pathologies to be excluded in the diagnosis of RA and ultrasound is capable of differentiating between inflammatory and non-inflammatory diseases, providing information on the bone surface irregularity and the presence and distribution of synovial hypertrophy and accompanying abnormal Doppler signals.

LS2

Health Economic Evaluation of Biologic Agents

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Conflict of interest: Yes

Treatment of rheumatoid arthritis has improved significantly with the introduction of biologic agents. Biologics are highly effective, but the cost is higher than synthetic drugs, thus imposing a great burden on patients and payers. Attempts have been made in recent years to objectively evaluate the efficacy of high-cost medical care including biologic therapy from the health economics (HE) perspective. Cost-utility analysis is a method widely used for evaluating HE. Medical cost necessary to improve quality of life and the cost needed to treat adverse events are included in this analysis. Consequently, HE is greatly influenced by the balance between drug efficacy and safety. In sum, amongst drugs with similar pricing, HE of a drug with better efficacy and safety is considered superior. Likewise, amongst drugs with similar efficacy and safety profiles, HE of a drug with lower price is considered superior to the other. Like many countries where health economic evaluation has a great influence on drug price determination, the necessity for health economic evaluation was first discussed in 2010 in Japan for high-cost medical care, and the use of HE in the National Health Insurance drug price calculation is ongoing. We evaluated the HE of biologics based on IORRA database by the Markov Model simulation. The HE of tocilizumab (TCZ) was evaluated in comparison with methotrexate (MTX) and its validity was reported for the first time in the world (Jpn Pharmacol Ther. 2011;39:967-979). We also evaluated multiple biologic agents as a group in comparison with MTX (ACR 2012; #1831). In April 2012, drug price has been revised in Japan which resulted in an improvement of TCZ's HE. Our analysis revealed that, the HE of TCZ improves if TCZ's intervention takes place at an early stage before JHAQ scores worsen. In this Seminar, the results from these HE analyses will be reviewed and appropriate use of biologic agents will be discussed.

LS3-1

Pharmacotherapy for Rheumatoid Arthritis (RA) (Focusing on Non-biological DMARDs)

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Conflict of interest: Yes

RA therapy with a policy using biological drugs focusing on MTX in poor responders is being established, but the use of non-biological DMARDs is also important. MTX was approved at a dose of 16 mg/W, and the first prescription in poor responders became available. Also, the 2010 ACR/EULAR classification criteria expedite the start of MTX, and remission induction without biological drugs is expected. But, more than 485 deaths that causality with MTX cannot be ruled out have been reported, and prevention of side effects, early detection and measures are important. MTX administration to hepatitis B and C virus carriers is not desirable, and options for patients in whom MTX treatment is not feasible are BUC and SASP. Also, when MTX is used, HBs and HBc antibody should be measured, and HBV-DNA levels in positive patients should be monthly measured. Tuberculin test is also essential. Efficacy of MTX with BUC or SASP has been reported, and if a period before the start of MTX is needed, MTX addition after using BUC or SASP is desirable. Also, addition of these drugs should be considered for patients starting MTX, while it is important to avoid MTX in elderly patients and those with renal impairment or concomitant interstitial pneumonia. Though sufficient suppression of disease activity with MTX can generally prevent joint destruction, biological drugs should be started in patients with bone erosion, and concomitant MTX and adalimumab are useful in those with high disease activity. Combined MZR pulse therapy or TAC is also effective in patients whose MTX dose cannot be raised, and both drugs are options for those who cannot use MTX and are already using BUC and SASP. Efficacy of MZR at a once-a-day dose increasing blood drug levels has been reported, and blood TAC levels have been reported to be related to efficacy as well as side effects. Iguratimod efficacy has been confirmed in its monotherapy and simultaneous MTX, and accumulation of evidence is expected.

LS3-2

Combination of Disease-Modifying Anti-Rheumatic Drugs (DMARDs) Therapy for Rheumatoid Arthritis: Japanese Strategic Treatment of Aggressive RA (JaSTAR Study)

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Conflict of interest: None

Rheumatoid arthritis (RA) symptoms have become mild with early-phase accurate diagnosis and progress of treatment drugs. For RA treatment, if remission cannot be achieved mainly with methotrexate (MTX), a major trend of the treatment begins with consideration using of biologics. However, because biologics also have issues such as the presence of non-responders, long-term safety, and high drug costs, ACR recommends DMARDs combination therapy prior to the use of biologics. In Britain, combination therapy with MTX + DMARDs is instructed to perform before the start of TNF inhibitor or IL-6 inhibitor treatment. In the West, comparative studies between non-biologics and biologics have recently become active, and the TEAR study and Swefot trial conducted a multicenter clinical comparative study of MTX + salazosulfapyridine (SASP) + hydroxychloroquin (HCQ) triple therapy and MTX + biologics therapy. Two years later, the TEAR study showed that DAS28-ESR had no difference between the two treatment groups with equivalent response rates of ACR20 and 50, and the Swefot trial showed no difference in EULAR good/moderate response and ACR20, 50, and 70 response rates between the two groups. Based on these data, triple DMARDs therapy can be expected to produce efficacy comparable to biologics. However, HCQ has not been approved in Japan, and the same triple therapy as the West cannot be performed. Thus, a comparative study (JaSTAR Study) between triple DMARDs therapy with bucillamine (BUC) instead of HCQ and anti-TNFa + MTX therapy are being carried out in patients with a diagnosis of RA for less than three years and poor response to existing treatments. In this paper, on the basis of consideration of the interim study report, we make a proposal a new treatment strategy of using non-biological DMARDs for RA.

LS4

Recent Advances of Diagnosis and Teatment on ANCA-associated Vasculitis

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Conflict of interest: Yes

Anti-neutrophil cytoplasmic antibodies (ANCA) -associated vasculitis (AAV) includes granulomatosis with polyangiitis (GPA: Wegener's granulomatosis), microscopic polyangiitis (MPA) and Eosinophil granulomatosis with polyangiitis (EGPA:Churg-Strauss syndrome). These are intractable diseases that resulted in multiple organ failure, unless the appropriate immunosuppressive are introduced. One of the recent progresses on diagnosis is ANCA measurement system. Sensitivity and specificity improvements carried early detection of AAV. Currently treatments for AAV are Intravenous immunoglobulin therapy (IVIg) and rituximab treatment. IVIg is used for steroid-resistant neurological disorder of EGPA. Rituximab is a chimeric monoclonal antibody against the protein CD20, destroys B cells, and is used for treat non-Hodgkin lymphoma and several autoimmune diseases. Clinical study in Western countries showed that rituximab has the equal effects to cyclophosphamide (CYC) on induction-remission therapy for AAV. These treatments recorded in European clinical practice guidelines, advocated recently. In this seminar, I will talk focus on the recent advances of ANCA measurement and treatments, especially IVIg and rituximab therapy, for AAV.

LS5

Diagnostic and therapeutic approach for Sjögren's syndrome: Validation of American College of Rheumatology classification criteria and establishment of new therapeutic strategy, evidence from Japan

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Conflict of interest: Yes

Sjögren's syndrome (SS) is an autoimmune disease that affects salivary and lacrimal glands. The revised Japanese Ministry of Health criteria for SS (JPN) (1999), as well as the American-European Consensus Group criteria (AECG) (2002) is usually used in Japan. Although AECG is commonly used in western countries, the consensus for AECG has not been confirmed. In such a situation, ACR has published the classification criteria (2012). Corticosteroids and immunosuppressant are shown to be effective for serious organ involvements of SS. However efficacy of these drugs for dryness has not been clarified. Moreover, efficacy of TNF blockers has not been established, only anti-CD20 antibody (rituximab) has been shown to be effective. To resolve these unmet needs about SS, some new studies have started in Japan. 1) I would like to introduce the results of validation study performed by the research team of MHLW (Leader: Prof. Takayuki Sumida). Validation of JPN, AECG, and ACR criteria by using data of 694 patients indicated the superiority of JPN in Japanese SS. 2) I will also introduce the results of national 1st, 2nd surveys (2010) performed by the same team to clarify epidemiology, diagnosis, and treatments for SS in Japan. The 1st survey showed the estimated numbers of SS in Japan was about 68000. The data of 2195 SS from the 2nd survey showed mean age was 60.8 y old, M/F ratio was 1/17, primary SS 60%/secondary SS 40%. Corticosteroids, immunosuppressant, biologics, and salivary accelerators were administered in 34%, 16%, 3%, and 32% of SS, respectively. 3) To clarify the efficacy of abatacept for secondary SS associated with RA, we designed open-labeled, prospective, observational, and multicenter study (ROSE trial). 23 patients have been enrolled at Dec 2012. Midterm analysis at 6 months of 9 patients showed SDAI significantly decreased, and both salivary and tear volumes significantly increased ($P<0.05$). I would like to talk about these new findings and evidence from Japan.

LS6

Bearing materials of artificial joints for super-longevity

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Conflict of interest: Yes

Considering longevity of artificial joints, bearing materials are inevitably important. Sir John Charnley at Wrightington devised a combination of the stainless-steel femoral head and the acetabular socket of polytetrafluoroethylene (PTFE) to realize low friction arthroplasty for THA. However, PTEF did not show low friction and low wear performance in-vivo and Charnley was forced to do many retrieval surgeries of his implants because of periprosthetic osteolysis although in-vitro studies of this combination did show very good results. Charnley challenged a new combination of materials in 1962; the ultra-high molecular weight polyethylene (UHMWPE) and stainless steel, which showed good longevity. Since this achievement, the UHMWPE has been used a basic material for the artificial joints for more than 40 years while a number of changes for the better (for the worse in cases) have been adopted. Among a number of techniques to manufacture PE, it has been demonstrated that its quality is improved by the compression molding method. Highly cross-linking is thought to be one of the most successful modification methods of the UHMWPE. In general, gamma-irradiation is used to cross-link molecules of polyethylene avoiding increase in oxidation and decrease in mechanical properties. It has been shown that the highly cross-linking PE can decrease PE wear of the cup and risk of periprosthetic osteolysis in THA for more than 15 years. PE containing Vitamin E and PE coated with phospholipids are other promising modifications. On the other hand, such hard materials as Co-Cr have been adopted as a counterpart for PE to better its wear performance. Ceramics has also been used because of its hardness. Recently, an interesting material for the femoral head and the femoral component appears, which successfully manages toughness and hardness by oxidizing the surface of Zirconium and making it ceramics. Materials for the artificial joints are now progressing for super-longevity.

LS7

Tacrolimus in the therapeutic strategy for rheumatoid arthritis

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Conflict of interest: Yes

Major mechanism of action of tacrolimus is inhibition of calcineurin in T lymphocytes. We recently found that expressions of CCL3, CCL4, and CXCL8 were down-regulated by tacrolimus in rheumatoid synovial fibroblasts, suggesting a novel mechanism in patients with rheumatoid arthritis (RA). We investigated the safety and efficacy of tacrolimus 3 mg daily or placebo in addition to other DMARDs for 52 weeks in 123 early active RA patients. Tacrolimus group (n=61) showed significant improvements in ACR20 (70.5 *vs* 45.2%), EULAR response criteria of good and moderate (86.9 *vs* 56.5%), and DAS28 remission rate (45 *vs* 21%) than those in the placebo group (n=62). The mean changes in the Total Sharp score and erosion score were lower in the tacrolimus group, but the difference between groups was not significant. There was no significant difference between the two groups in the incidence of adverse events. In our University Hospital, 18.0% RA patients is receiving tacrolimus. In these patients, 85.9% were treated by combination with methotrexate or other DMARDs including biologics. Tacrolimus is a useful option for not only monotherapy but also combination therapies with other DMARDs.

LS8

Diagnostic imaging and treatment of osteoarthritis in rheumatoid arthritis patients

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Conflict of interest: None

Rheumatoid arthritis (RA) is a systemic inflammatory disorder which initially affects the synovium, and one common outcome is joint deformity and disability. It has been shown that bone erosions in RA can be repaired through reduction in disease activity with disease-modifying antirheumatic drugs. However, once severe cartilage degeneration occurs, cartilage can not be repaired as articular cartilage has limited potential to heal. As cartilage degeneration leads to osteoarthritis (OA), especially in weight bearing joints, it is difficult to prevent the progression of OA in patients with RA even in clinical remission. Thus the key to manage OA in RA patients is early diagnosis and treatment to prevent further joint destruction and maximize functional ability. Magnetic resonance (MR) imaging is a useful noninvasive evaluation method for osteoarthritis of the knee joint. Recently, several MR imaging techniques for monitoring the structure of articular cartilage have been developed as a useful and non-invasive tool for evaluating cartilage degeneration quantitatively. T2 mapping is an MR imaging technique that can evaluate the cartilage matrix status, such as collagen integrity and hydration within cartilage. In the meanwhile, T1ρ (spin lattice relaxation in the rotating frame) provides information on slow motions of nuclei. T1ρ mapping of cartilage has been shown to correlate with GAG concentration as well as water concentration. With above quantitative MR imaging techniques, we have been monitoring cartilage of the patients with OA as well as the patients with RA to predict long-term outcome and find out tailor made strategy for the prevention of cartilage degeneration. In this session, we will discuss the diagnosis and treatment of OA in RA patients using quantitative MR imaging techniques.

LS9

New strategy for the treatment of rheumatoid arthritis-related osteoporosis

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Conflict of interest: None

Joint destruction characterized with proliferated synovial fibroblasts and cytokine milieu is a major problem in rheumatoid arthritis (RA). Of note, synovial fibroblasts and joint-infiltrated T lymphocytes which express RANKL, an essential cytokine for osteoclast differentiation, play a fundamental role in the development of joint destruction. Moreover, numerous studies have documented that patients with RA have lower bone mass. For the treatment of RA, glucocorticoids (GCs) are sometimes used in combination with DMARDs. However, GCs are known to cause secondary osteoporosis. Thus, caution for bone and cartilage abnormalities should be exercised in the management of RA. Bone mass is maintained constant by the balance between osteoblastic bone formation and osteoclastic bone resorption. Recent advances for our understanding of the molecular basis of bone homeostasis led to a successful development of novel therapeutics for osteoporosis including bone anabolic agents. In this lecture, I will summarize the molecular pathogenesis of inflammation-induced bone loss and discuss the positioning of osteoporosis therapeutics in the management of RA.

LS10-1

Joint evaluation and T2T in the treatment of rheumatoid arthritis

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Conflict of interest: Yes

It is apparent from the past clinical studies that a concept of Treat-to-target (T2T) is important to lead treatment outcome to the higher level. Enough disease activity controls are necessary for the prevention of the joint damage, and it can be accomplished only by aiming at the true remission. As the first step, it becomes the main premise to evaluate disease activity precisely. However, it is more likely to be insufficient by the present evaluation method of disease activity. Our results of randomized controlled trial (PRECEPT study) that examined the effects of regular or half dose of etanercept on joint damage were the fine examples. The DAS (Disease activity score) 28 level decreased immediately in both groups without significant differences between groups. However, the rate of patients without joint destruction was significantly higher in regular dose group. In other words, enough "joint evaluation" will not be done by DAS evaluation to aim the suppression of joint damage. As a tool of sufficient joint evaluation, we give sonography to a candidate and obtain the preliminary results that can explain a difference of the joint destruction in PRECEPT study by using sonography. In this regard, let's think about what kind of treatment strategy we should take to inhibit thorough inflammation by precise evaluation. It is apparent to inflammatory suppression that use of biologics with MTX is advantageous. However, it may be in a useless treasure if the biologics will not be used appropriately. For example, in golimumab, two doses were approved only in Japan, and this might be very advantageous in practice of T2T. It was shown that a dose adjustment of golimumab depending on disease activity worked well in the clinical trial. Furthermore, golimumab might be suitable biologic for the tight control of the long term due to the lower anti-golimumab antibody production rate. I would like to try a commentary with our clinical data at these points.

LS10-2

Therapeutics and their impact on bone metabolism in rheumatoid arthritis

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Conflict of interest: Yes

Rheumatoid arthritis (RA) is a chronic inflammatory disorder characterized by massive bone and joint destruction, which leads to the deterioration of ADL and QOL of the patients. Recently, many molecular target drugs for RA which showed large impact on RA treatment have been developed. In particular anti-TNF-alpha drugs not only suppress joint inflammation but also strongly ameliorate bone and joint destruction in RA. TNF-alpha stimulates osteoclast differentiation by inducing production of receptor activator of nuclear factor kappa B ligand in synovial fibroblasts, and stimulates bone-resorbing activity and survival of osteoclasts. In addition, TNF-alpha suppresses osteoblastic bone formation by inducing Dickkopf 1, an endogenous inhibitor of Wnt signaling which suppresses bone formation. In this seminar, I would like to focus on the effect of golimumab, a fully humanized TNF-alpha monoclonal antibody that is specific for human TNF-alpha, on bone metabolism in RA patients.

LS11

Treatment with multi-drugs for pulmonary hypertension in patients with connective tissue disease

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Conflict of interest: Yes

Pulmonary hypertension (PH) is a critical complication with connective tissue disease. We will present how to manage the complication with PH. PH associated with connective tissue disease is classified to pulmonary arterial hypertension, PH with interstitial lung disease, and PH with leff heart disease. We must understand the different ways for the treatment of PH classified by various categories. In the present seminar, I would like to talk about the treatment of PH complicated with systemic lupus erythematosus, mixed connective tissue disease, and systemic sclerosis. I recommend the therapy with immunosuppressants in patients with systemic lupus erythematosus and mixed connective tissue disease. In contrast, the therapy is ineffective in patients with systemic sclerosis. Concerning the vasodilators for pulmonary artery, we can use three types of agents including endothelin receptor antagonist, phosphodiesterase 5 inhibitor, and prostacylin analogue. These drugs are effective for pulmonary arterial hypertension associated with connective tissue disease. However, it is unclear that the vasodilators might be effective for PH complicated with interstitial lung disease and/or left heart disease in patients with connective tissue disease.

LS12

It is time we overcame AA amyloidosis, a serious disease

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Conflict of interest: Yes

AA amyloidosis is categorized in the reactive amyloidosis which is caused by the deposition of AA fibril on the tissue in chronic inflammatory diseases, mainly rheumatoid arthritis. It has been recognized that once the AA deposition was presented, the deposition was increased and not decreased. Serum amyloid A (SAA), a precursor molecule of AA protein, is produced and augmented with cytokine stimulation mainly in hepatocyte. Recently it is proved that IL-6 activated STAT3, a transcriptional factor, essentially induces SAA mRNA, and NF-κB p65 complementally augments SAA mRNA induction by TNF-α or IL-1 combined with IL-6 stimulation. IL-6 blockade completely inhibits the production of SAA. Most of the specialist in RA treatment know that serum level of SAA and CRP are decreased and normalized after the IL-6 blocking therapy, on the contrary, these serum levels are decreased, but hardly reach into the normal range by the TNF-α blocking therapy When the deposited AA fibril is decreased, it is necessary to inhibit the elevation of SAA in serum. Therefore, an anti-IL-6R antibody, Tocilizumab or Actemura is an ideal therapeutic reagent for the treatment of AA amyloidosis by the inhibition of SAA production. We have organized the clinical study to compare the treatment with Actemura and Non-Actemura to the patients with AA amyloidosis in the population of RA. We observed the Tocilizumab therapy for two years. The deposition of AA fibril was decreased. Enteropathy and protein uria were improved. The renal abnormality was not increased. Therefore, we may overcome this AA amyloidosis near soon.

LS13

What we expect from certolizumab pegol, a new biologic DMARD

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Conflict of interest: Yes

This year, certolizumab pegol (CZP) was added to RA treatment, thus, seven biologics are now available in Japan. What is the necessity to add a new TNF inhibitor ? Biologics shifted the treatment to the next stage by its marked clinical effects. However, problems such as, reduction in efficacy due to anti-drug antibody formation, injection site reaction, slow response of efficacy, insufficient efficacy of monotherapy, are indicating needs for a new option. CZP is a (PEG) ylated, humanized, Fc-free, anti-TNF-α antibody. Because of lack of Fc region, CZP does not mediate CDC or ADCC and is hardly crosses placenta. In Japan, J-RAPID, a study with MTX, and HIKARI, a study without MTX, were conducted, and demonstrated significant clinical responses and inhibition of structural progression. The significant inhibition of bone destruction was recognized even without concomitant DMARD (PureMono) as early as week 24. The induction doses are only employed by CZP among all SC injected biologics, contributing to the rapid appearance of the clinical responses as early as week 1. Anti-CZP Ab was found in 1.2% of patients in the study with MTX. Although the percentage increased to 15.5% in the study without MTX, the ACR20 response of the antibody-positive patients was 50% at week 24. In an international study (REALISTIC) with diverse RA patients, representing clinical practice, CZP provided significant benefit regardless of prior anti-TNF drug use. The safety profile of CZP was similar to that of anti-TNF drugs in both international and Japan studies with 6.4% and 3.1% of injection site reaction. In summary, CZP is a new biologic DMARD with unique molecular structure that demonstrates rapid appearance of clinical responses and inhibition of structural damage regardless of MTX use and likely serves as an effective option for the patients nonresponsive to the existing biologics. Its position in the era with seven biologics will be discussed based on the evidences obtained for CZP.

LS14

Importance of the maintenance of remission in RA : Efficacy of ETN and its low immunogenicity

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Conflict of interest: Yes

The main goal of therapy of rheumatoid arthritis (RA) is a protection of joint destruction and early diagnosis / classification as well as early therapeutic intervention are considered to be indispensable. In this regard, a concept of treat to target (T2T) to achieve and maintain the remission is spreading. There has been emerging a definition of the RA patients with poor outcome named as rapid radiographic progression (RRP) or clinical relevance of RRP (CRRP). Interim results from our prospective cohort of RA patients treated with synthetic DMARDs in clinical practice show that early disease, high time-integrated DAS28 and high mTSS at baseline predict the development of CRRP at 1 year. Similar tendency was also found in the patients without use of MTX, suggesting again the importance of T2T at earlier stage toward the protection of joint destruction. An introduction of biologics is generally recommended in case synthetic DMARDs do not succeed in remission or low disease activity (LDA). In Japan, four kinds of TNF inhibitors (IFX, ETN, ADA, GLM), TCZ and ABT are now available toward patients with RA. Among these, TNF inhibitors are most popular at present and their significant efficacy toward radiographic progression is obvious through the results of randomized controlled trials (RCTs) or post-marketing surveillance (PMS). In contrast to anti-TNF-a Ab of IFX, ADA and GLM, ETN is a decoy receptor toward TNF receptor. Half-life of ETN is very short and its long-standing efficacy up to 10 years is already published.

These characteristics of ETN are quite useful to maintain the long-standing remission as well as protection of joint destruction in patients with RA that may associate with its low immunogenicity. In this LS, we are going to review the recent reports of ETN from RCTs / PMS and discuss the pharmaceutical characteristics of ETN.

LS15

The Role of Nonbiologic DMARDs in the Treatment of Rheumatoid Arthritis

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Conflict of interest: None

Previous therapy for rheumatoid arthritis (RA) aimed solely at relief of clinical symptoms, whereas it is practicable in the present era to actually attempt attainment of remission of the disease by utilizing rigorously controlled treat-to-target regimens consisting of methotrexate (MTX) and other nonbiologic disease-modifying antirheumatic drugs (DMARDs), as well as concomitant biologic drugs, thanks to the improvement of diagnostic techniques, enabling early diagnosis and early institution of treatment. While some RA patients can achieve the treatment goal through effective tactical use of MTX and other nonbiologic DMARDs even without the use of biologic drugs, it is also a fact that biologic drugs can hardly be used in certain other RA patients on account of cost problem, age, complications or adverse reactions such as infections although their diseases are primarily indicated for biologic drugs. It would thus be necessary to elaborate the usage of nonbiologic DMARDs in such patients. It is now feasible in Japan to prescribe MTX at sufficient doses from the early stage of RA, so that considerable therapeutic responses can be expected even with the use of this drug alone. On the other hand, some adverse reactions may be associated with MTX treatment; therefore, proper use of the drug keeping in mind the associated adverse reactions is essential. Concomitant use of other nonbiologic DMARDs may be a measure of choice in the case of poor response to MTX treatment alone. If MTX is contraindicated or cannot be used due to the associated adverse reactions in RA patients, they should be treated with a good command of tactical usage of nonbiologic DMARDs other than MTX.At this seminar, I would like to provide a brief guide to basic usage of MTX for achieving the treatment goal, contrivance of concomitant use of other nonbiologic DMARDs in the case of poor response to MTX treatment, and usage of nonbiologic DMARDs other than MTX in patients in whom MTX cannot be used.

LS16

New European type stem with bioactive treatement on its smooth surface - Designs which are considered the weak points of cementless stem-

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Conflict of interest: None

The cementless stem is used in more than 80% of the artificial hip joint in Japan. It is because there are many reports telling that the long-term prognosis of the cementless hip prosthesis is as equal as or even better than the cemented hip prosthesis. The pros are that a highly skilled and time-consuming procedure of the cementing technique is not required, trying again during operation is possible and the complication of the fat embolism is less likely. The cons would be the thigh pain and difficulty in removing the implant, both of which are ascribed to the stem side. Excellent long-term results of European cementless stem with a rectangular cross-section like Zweymuller have been reported recently. Less likely thigh pain and easiness of extraction are their good features, although there need to be some improvements against the fact that a radiolucent line or osteolysis around the proximal stem observed in 15-20% of cases. On the other hand, our 10 years study using the cementless hip joint with an alkali heat treatment at the porous portion gave excellent results in bone conductivity. However, the thigh pain was observed at 3% even after five years. Therefore, Zweymuller type stem was renovated with a few modifications: a little narrower stem with one-fifth reduced surface roughness so that easily extractable and the alkali heat treatment of the entire surface excluding the neck portion. By these modifications, it is expected that an earlier bone conduction over the entire stem would prevent the thigh pain and the radiolucent line or osteolysis at the proximal femoral stem. In last year from September to November, 70 cases of the total hip arthroplasty were proceeded using this new cementless stem in 10 facilities. The results show no complications related to the implant and a good initial fixation. By the time of this presentation we would be prepared to report the time course of 6 months after surgery.

LS17-1

BMP/TGF-beta signal as a potential treatment target for vascular remodeling in PAH - Novel antiproliferative mechanisms of Beraprost -

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Conflict of interest: None

Pulmonary arterial hypertension (PAH) is a progressive vascular disorder characterized by the occlusion of pulmonary arterioles as a result of the uncontrolled proliferation of endothelial and smooth muscle cells, leading to right heart failure and death. As the effect of vasodilatation therapy is limited, it is essential to gain insight into the pathogenesis of PAH and search the target to ameliorate the vascular remodeling. Heterozygous germ-line mutations of *BMPR2*, encoding a type II receptor of the TGF-β signaling, represent the genetic predisposition to the familial PAH. *BMPR2* mutation can reduce the ability of BMPs to regulate cell growth. Current evidence showed decreased BMP signaling and, by contrast, increased TGF-beta signaling promoted the process of vascular remodeling in IPAH. These data implied that the imbalance of BMP and TGF signaling has a critical role in the pathogenesis of PAH. Therefore, it would be logical to hypothesize that the intervention to disrupted BMP/TGF signal balance is a potential treatment strategy from the new insights from genetic studies. Our study showed that TGF-beta receptor (ALK5) inhibitor and P38MAPK inhibitor inhibited the altered proliferation of *BMPR2* mutant mouse PASMC. Prostacyclin analogues (Beraprost) inhibited the proliferation of human and mouse PASMC with *BMPR2* mutation by restoring the disrupted BMP/TGF-beta signaling at SMAD and the transcript of target gene, such as Id (Inhibitor of DNA binding protein) level. These results enhanced the potential role of BMP/TGF-beta pathway in the pathogenesis of vascular remodeling in PAH, and suggested that to repair imbalanced BMP/TGF-beta signaling is a strong candidate strategy in PAH treatment, which needs to be discussed.

LS17-2

Diagnosis and Treatment of Pulmonary Hypertension in Patients with Collagen Diseases

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Conflict of interest: None

Pulmonary hypertension (PH) is an extremely rare disease; however, PH has a high prevalence among patients with mixed connective tissue disease, systemic sclerosis or other autoimmune diseases. PH has thus great influence on the patient's ADL and vital prognosis. In recent years, effective therapeutic agents, such as prostacyclin derivatives, endothelin receptor antagonists and phosphodiesterase 5 inhibitors, have successively been introduced. PH proceeds asymptomatically during the early stage of pathophysiology, and in practically all cases, the disease is relatively advanced when subjective symptoms such as exertional dyspnea and palpitation are noted. These symptoms primarily indicate cardiac overload and are not necessarily characteristic of PH; partly causing delayed diagnosis. Improvement of vital prognosis may be expected by initiating treatment at an early stage, but it is essential to perform right heart catheterization (RHC) in order to make a definite diagnosis. Practically, however, it is difficult to conduct RHC in all collagen disease patients, and this diagnostic procedure is unsuitable for short-term follow-up. The relationship between anti-U1 RNP antibody and PH has generally been recognized, but it is impracticable to predict the concurrence of PH or the degree of PH progression solely based on the presence of this antibody. Chest X-ray, electrocardiography, cardiac ultrasonography, respiratory function tests and blood tests for uric acid, BNP, etc. are useful non-invasive simple screening procedures for PH. The present study investigated how to select suitable patients for RHC through assessments in order to determine in which types of patients these screening procedures should be performed and at what intervals, as well as whether any other useful screening methods are available. We also describe the characteristics of PH by underlying autoimmune disease, matters to be attended to regarding the selection of drugs, clinical prognosis, etc.

LS18

The present conditions of the conservative treatment for the inflammatory joint diseases and the future prospects

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Conflict of interest: Yes

The representative of the inflammatory joint disease is rheumatoid arthritis. The major future of osteoarthritis is cartilage degeneration but osteoarthritis is not rarely complicated with inflammation. I describe the present conditions of the conservative treatment to be common to these joint diseases and the future prospects. The representative of a drug used for both diseases is a non-steroidal anti-inflammatory drug (NSAIDs). NSAIDs show anti-inflammatory and analgesic effects by inhibiting cyclooxygenase (COX). Whereas COX-1 expressing physiologically is associated with gastrointestinal protection, renal blood flow maintenance, platelet function maintenance, and NSAIDs develops adverse events such as upper gastrointestinal injury, renal dysfunction, platelet dysfunction by inhibiting these functions. The upper gastrointestinal injury is the most frequent adverse events and has been thought to induce by the chronic administration conventionally. But it is shown that the endoscopic ulcer exceeds 20% with two weeks administrated of conventional NSAIDs for healthy adults. Choice of the COX-2 inhibitor and combination of PPI or misoprostol are recommended for preventing the upper gastrointestinal injury. Local treatment for the joints includes hyaluronic acid and steroid intraarticular injection therapy. The steroid may induce cartilage degeneration by inhibiting Wnt/β -catenin signaling. The administration of hyaluronic acid can expect not only the lubrication improvement but also analgesic and antiinflammatory effects. DKK-1 inhibiting Wnt/β-catenin signaling is induced by inflammatory cytokines including TNF α. Dkk-1 inhibited bone formation, and induced chondrocyte apoptosis. Therefore, it may be suggested that an antibody for DKK-1 may inhibit cartilage degradation. Also, efficacy for the cartilage degeneration of lubricin which is the mucinous glycoprotein is confirmed in animal models of the osteoarthritis.

LS19-1

Emerging Treatment Using Golimumab in Rheumatoid Arthritis: Best Use of Golimumab for Inducing and Maintaining Disease Remission

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Conflict of interest: Yes

RA is a systemic autoimmune disease characterized by synovitis and articular destruction persisting from the early stage of the disease. It has been, therefore, strongly recommended to set the goal of RA treatment at inhibiting the disease activity by tight control and achieving clinical remission soon after disease onset. By the treatment to target, it will be possible to minimize the progression of structural destruction and to improve the physical function and QOL of patients. For the strategic treatment, it is necessary to use MTX at sufficient dose levels as an anchor drug firstly and then to make a decision to use TNF inhibitors, if disease control with MTX alone is not sufficient. Based on results of studies using anti-TNF humanized antibody golimumab (GLM) in combination with MTX (GO-FORTH Study) and GLM mono-therapy (GO-MONO Study), both carried out in Japan, GLM 100mg as well as GLM 50 mg were approved in Japan in 2011 for the first time in the world. Favorable outcome of RA treatment is expected, if one of the two regimens, i.e. the standard dose (50 mg) GLM + MTX therapy and the high dose (100 mg) GLM + MTX therapy, is selected appropriately depending on the disease activity in individual cases (selecting the high dose GLM + MTX therapy for cases with higher disease activity and more rapid radiographic progression). Once treatment succeeds in achievement of clinical remission, sustained clinical and structural remission will be the next goal of the treatment for the long period. GLM is a biologic created by using transgenic mouse and can be characterized by very high retention rate during long-term treatment with it. This seminar will outline the importance of efficient induction of clinical remission of RA through tight control beginning soon after disease onset, and also the importance of long term maintained remission from the viewpoint of chronic outcome through long-term use of GLM with getting leverage out of its characteristics and product profile.

LS19-2

History of the development of TNF inhibitors: do we need additional therapies?

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Since 1998, TNF inhibitors have been available in the United States, with the approval of etanercept, a human recombinant receptor Fc fusion protein, for the treatment of rheumatoid arthritis, followed shortly by the approval of infliximab, a chimeric monoclonal antibody to TNF in 1999 and adalimumab, a fully human monoclonal antibody to TNF in 2002. In the later part of the last decade, certolizumab, a PEGylated humanized Fab fragment, and golimumab, a fully human monoclonal antibody to TNF, were approved. TNF inhibitors have been shown to be effective clinically, improve function and inhibit radiographic progression in patients with early RA, MTX naïve RA, patients with an incomplete re-

sponse to MTX (in combination with MTX or as monotherapy) and in patients who failed TNF inhibitors previously. These medications have made a dramatic difference in our ability to control RA clinically and radiographically and have been very helpful in reversing the deterioration of function of RA patients which was the norm prior to their introduction. Before these medications were developed, we had to understand the key role of TNF as a mediator of inflammation and joint destruction in RA. The initial work on understanding the role of TNF occurred in the 1960's but didn't come to fruition until seminal work was done in the 1970's and early 1980's. With this as a background, Professor's Marc Feldman and Ravindar Maini were able to use a chimeric monoclonal antibody to TNF, originally named CA2 (and subsequently given the name infliximab), for the successful treatment of RA and also realized that most, if not all TNF-I, are more effective in combination with MTX. This presentation will review the central role of TNF in inflammation and it's inhibition as a treatment of RA, with a chronology of the development of TNF inhibitors, as well as a discussion of the seminal works with each of the approved TNF-I and a brief discussion of what else we need to do to treat RA more effectively.

LS20

Suppression of bone and joint destruction by cytokine regulation-clinical and basic consideration

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Conflict of interest: Yes

Current biologic cytokine regulation for the management of rheumatoid arthritis (RA) target TNFα or IL-6, both play a central role in the pathogenesis of the disease, such as synovial inflammation or activation of osteoclastic bone resorption. They may provide a complete suppression of clinical symptom, however imcomplete or not effective in some population of patients. Anti-TNFα antibody exerts cytotoxic effects through transmembrane TNFα, but its effect is limited without combination with MTX. Tocilizmab is the only biologic agent to demonstrate superiority to MTX for patients with limited/no exposure to MTX when used as monotherapy. Recent reports suggested the crucial role of MTX in suppression of IL-6 production in RA. TNFα, interleukin (IL)-1, IL-6, and IL-17 are the most important pro-inflammatory cytokines triggering inflammatory bone loss by regulation of RANKL expression. IL-6/sIL-6R complex directly induced RANKL expression in RA-SF, and it is essential for RANKL induction by TNFa and IL-17. Furthermore, IL-6 in combination with TGF-β is responsible for the differentiation of naive T cells into TH17 cells. The only TNF antagonist that is known to bind and neutralize a ligand other than TNFα is Etanercept, which binds members of the lymphotoxin (LT) family, LTα and LTα2β1. Elevated LTα, LTβ, and LTβR transcripts have been observed in synovial tissues of RA patients, pointing to a role for the LT pathway in the pathogenesis of this disease. Increased soluble LTαβ levels were associated with increased levels of pro-inflammatory cytokines LTα3, TNFα, IL-8, IL- 12, IL-1β, IFN-γ, and IL-6 in inflammatory joints. LTα3 isoform also capable to induce similar proinflammatory gene expression to LTαb. Why the regulation of TNF and IL-6 is essential in the disease control of RA? Is cytokine hierarchy different among patients? Translational research from "bedside to bench" would be needed to select s better treatment option.

LS21

Results of the Use-Results Survey of Abatacept Conducted as All-Case Surveillance

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Conflict of interest: Yes

Abatacept is a biological product targeting T cells, which are thought to play a major role in the development of rheumatoid arthritis. Blocking the costimulation between T cells and antigen presenting cells, abatacept improves rheumatoid arthritis through suppression of the hyperactivation of T cells. Since appearing on the market in September 2010, a use-results survey in all patients who have used abatacept (All-Case Surveillance) has been conducted, similarly to previous surveys on other biological products. At the end of June 2011, the number of cases reached the target of 4000. Case registration has been continued, and as of October 2012, more than 10,000 patients were receiving abatacept in Japan. In this seminar, use experience of abatacept in many patients will be explained with a focus on the results of the use-result survey (hereinafter the "All-Case Surveillance"), comprising approximately 4000 and 3000 cases, respectively, for the safety and efficacy analyses. The data from the All-Case Surveillance will provide highly important information including the frequency of adverse drug reactions, risk factors for safety, and time courses of disease activity for up to 24 weeks. Although the size of the All-Case Surveillance is so large that almost no comparable observational studies exist, the observation period spans only 24 weeks. Because rheumatoid arthritis is a chronic disease treated over a long period, following treatment courses for 24 weeks or longer is still significant. Therefore, the long-term utility of abatacept will be presented based on the efficacy and safety results in 156 cases observed for 52 weeks or longer in the multicenter study (Tsurumai Biologics Communication Registry [TBCR] Study) conducted at institutes affiliated with the Department of Orthopedic Surgery of Nagoya University School of Medicine.

LS22

Usefulness of PPIs in patients receiving NSAIDs

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Conflict of interest: Yes

Although DMARDs are the mainstay of RA management, NSAIDs are still important drugs for controlling symptoms of RA patients. Recently mucosal injury to small intestine is said to be associated to NSAIDs use, but gastro-duodenal ulcer due to NSAIDs(NSAID-related ulcer) is the most frequent and important adverse effect. To prevent NSAID-related ulcers, it is efficacious to use misoprostol, COX-2 selective inhibitors and anti-acid drugs such as H2 receptor antagonists (H_2RA) or proton pump inhibitors (PPIs). However, misoprostol is frequently associated with gastrointestinal side effects such as diarrhea and has low compliance related to q.i.d. dosage. H2 RA is significantly less effective than PPIs. Recetly combination of low-dose aspirin and clopidogrel is recommended for the prevention of cardiovascular events and is also used among RA patients. NSAIDs-related ulcers are not uncommon when COX-2 inhibitors are used with low-dose aspirin and /or clopidogrel. In addition long-term use of COX-2 inhibitors may be associated with thrombotic complications. As PPIs seem to be the best drugs for the prevention of NSAID-related ulcers, lansoprazole and esomeprazole are offically approved for the prevention of relapse of gastro-duodenal ulcers associated with low-dose aspirin use. In addition esomeprazole seems to be useful when clopidogrel is prescribed because there will be little competitive inhibition of CYP2C9, which will activate anti-thrombotic effect of clopidogrel. However, long-term use of PPIs may be associated with various adverse events; infections such as pneumonia and

Clostridium difficle enteritis, musculoskeltal problems such as osteoporosis and femoral neck fractures. Therefore, to prevent NSAID-related ulcers, we should think to stop NSAIDs first. If patients need NSAIDs, we should use COX-2 inhibitors combined with PPIs.

LS23-1

Diagnosis and pathology of pulmonary arterial hypertension associated with connective tissue diseases

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Conflict of interest: None

Echocardiography is an essential screening test for pulmonary arterial hypertension associated with connective tissue diseases (CTD-PAH), and it is important to assess the tricuspid pressure gradient (TRPG) during this procedure. In the diagnosis of CTD-PAH on echocardiography, reducing false negatives is more important than reducing false positives, though both false positives and false negatives occur. CTD-PAH was confirmed in all three patients with systemic sclerosis (SSc) in whom an increase in TRPG of ≧35 mmHg was observed on exercise echocardiography and who consented to undergo right heart catheterization. Therefore, exercise echocardiography may reduce false negatives. The pathology of CTD-PAH may vary depending on the concomitant primary disease, specifically systemic lupus erythematosus (SLE), mixed connective tissue disease (MCTD), and SSc. In SLE and MCTD, CTD-PAH is often diagnosed at onset or during the active stage, and patients may respond to immunosuppressive therapy. In contrast, in SSc, CTD-PAH is often diagnosed in patients with a long disease duration, and immunosuppressive therapy is ineffective. These tendencies suggest that inflammation and spasms in the pulmonary vessels are involved in the pathophysiological mechanism of CTD-PAH in SLE and MCTD, while thickening and stenosis of pulmonary vessels are involved in SSc. However, on exercise echocardiography, TRPG was significantly higher in patients with MCTD and SSc than in healthy individuals, while no difference was observed for SLE. This finding suggests that the thickening and stenosis of pulmonary vessels observed in SSc may also occur in MCTD, and that MCTD may have the characteristics of both SLE and SSc.

LS23-2

Treatment strategy for pulmonary arterial hypertension associated with connective tissue disease based on long-term treatment results

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Conflict of interest: Yes

Connective tissue disease (CTD) is a chronic and systemic disease associated with high incidence of different complications in multiple organs, therefore, it requires long-term follow-up and well-balanced flexible strategy consists of systematic treatments. We will present the current situation and future potential of treatment of pulmonary arterial hypertension (PAH) associated with CTD (CTD-PAH) based on our treatment results of CTD-PAH patients who have met the diagnostic criteria for pulmonary hypertension. Seventy fifth percentile survival times after PAH treatment was drastically improved from 1.9 years to 10.3 years when sequential goal directed therapy was applied. However, a stratified analysis of these patients showed the prognosis of the patients with PAH associated with systemic sclerosis (SSc) (SSc-PAH) is tended to be worse than that of patients with CTD-PAH and PAH associated with systemic lupus erythematosus. Analysis of SSc-PAH patients showed they have relatively high pulmonary capillary wedge pressure and are frequently associated with interstitial lung diseases. From this result, it is assumed that clinical condition of pulmonary hypertension caused by left heart disorder (group 2) and lung diseases (group 3) may coexist and PAH treatment strategy targeting at idiopathic PAH may have therapeutic limitations for CTD-PAH treatment. In order to elucidate these issues, several large registry studies are ongoing. To overcome therapeutic limitations, early intervention is encouraged. Prevention of PAH is also expected. It is important to consider the incident rate of PAH and establish a severity measurement for mildly symptomatic PAH patients to optimize therapeutic strategy. CTD-PAH treatment should be initiated after careful differential diagnosis. It is important to confirm whether SSc is the underlying disease upon determining applicability of PAH treatments or immunosuppressive therapy to these patients.

LS24-1

Treatment of rheumatoid arthritis with biological agents in the last and next decades

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Conflict of interest: Yes

In 2003, infliximab has become available in Japan, which brought us a paradigm shift in the clinical practice of rheumatoid arthritis (RA). Ambiguous clinical evaluations, such as a degree of global clinical improvement, were replaced with ACR/EULAR response using composite measures, and even the rate of clinical remission. Similarly, Steinbrocker's radiographic stage and functional class were substituted by modified Sharp score and HAQ-DI in the evaluation of joint destruction and subsequent functional disability. The establishment and spread of above measures promoted the development of new agents and clinical trials examining those agents. It should be noted that the proper use of methotrexate (MTX) is critical for the outcome of RA patients treated with most biological agents. Further, the dosing regimen of biological agents should be determined in individual patient by the cytokine levels to be neutralized and the consequent disease activity, instead of body weight of the patient. Adequate use of MTX and biological agents resulted in rare occurrence of severe disability requiring total joint replacement, secondary amyloidosis and rheumatoid vasculitis. Unmet needs in the next decade include the management of patients with severe comorbidities, the programming of the optimization of therapeutic strategy considering costs and safety issues for each patient, and agents targeted to new molecules. In addition, cooperated treatment actions to flare of synovitis, including the self-management by patients, because synovitis might be a dynamic inflammatory state varying with environmental factors such as joint overload.

LS24-2

Does orthopaedic surgery provide better joint function for rheumatoid arthritis in the biologic era?

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Conflict of interest: Yes

During these 10 years after clinical application of biologic DAMRDs in Japan, they showed attractive clinical effects on disease activity of rheumatoid arthritis, and rheumatologists and orthopaedic surgeons made big efforts for their proper and safety use. Functional impairment of patients with high disease activity has been controlled to the minimum, which was difficult to avoid by conventional DAMRDs. Among some population of patients, biologic DMARDs prevented joint destruction, or achieved structural repair of the joint. Comprehensive disease control (CDC) includes 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 inadequate response to the medical treatment, or with long-standing disease who missed the "window of opportunity". 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. In addition, 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 better disease control by biologic DMARDs. Substantially they would be surgical reconstruction of biologically stable joint with reasonable range of motion and better patients oriented functional assessment in a short term, and preservation of better long-term clinical results. Treat to target strategy by combination therapy of orthopaedic surgery and medial treatment would be necessary for preservation of relevant joint function, as well as adjacent joint.

LS25

Treatment of osteoporosis: an update

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Conflict of interest: Yes

Japan is one of the most rapidly aging countries in the world, and more than 10 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 the most popular cause of loss of mobility and economic burden. Remarkable progress has been made during the last decade in the treatment of osteoporosis by anti-resorptive agents such as bisphosphonates and a selective estrogen receptor modulator (SERM). However, the fracture prevention using these agents is not sufficient and several adverse events have been recognized. In this seminar, I would like to focus on the state of the art of the treatment of osteoporosis and introduce novel anti-osteoporotic drugs. In addition, I will also introduce some drugs which are under development.

LS26

Pain Management for Rheumatoid Arthritis Patients

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Conflict of interest: None

Rheumatoid arthritis (RA) is an inflammatory autoimmune disease, and controlling the autoimmune response and suppressing the excessive inflammation is the optimal way to control the pain. However, symptomatically controlling the pain alone without suppressing the inflammation is undesirable, especially from the standpoint of the long-term prognosis. In recent years, methotrexate and biologic agents have brought about a paradigm shift in the treatment outcome of rheumatoid arthritis, and we entered an era in which it became feasible to make preventing joint destruction, maintaining physical function, etc. As a result, there may even be the view no therapeutic interventions are necessary besides those that achieve pain management secondarily as an effect of controlling the autoimmune response. However, it is never acceptable to neglect attempting to improve patients' short-term QOL. Discrepancies between global ratings by physicians and patients' global ratings have fairly often been pointed out, but they have also been said to be attributable to physicians' attaching importance to the number of swollen joints when making global evaluations, as opposed to patients' putting greater emphasis on their pain level. Aside from the argument as to whether or not pain is the essence of disease activity evaluations, it should be kept in mind that pain accounts for a high proportion of patients' global evaluations and that physicians may underestimate patients' pain. Until recently, the situation in Japan was such that there were few alternatives to NSAIDs as a treatment for any non-cancer pain, but in the past few years there have been new developments in analgesic drugs. One has been the advent of COX-2 inhibitors as an expanded form of NSAIDs and addition of indications and expansion of the dose range of acetaminophen, and, further still, the advent of weak opioids for the treatment of non-cancer chronic pain.

LS27

How to use convetional DMARDs in biologics era?

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Conflict of interest: Yes

RA is defined as the inflammatory joint disease with extra joint manifestation and consequently brings the patients the joint damage and disability. The important goal of RA therapy is to maximally reduce disease activity and minimize the irreversible joint damage. Treatment for RA patients should begin as early as possible and be performed aggressively, with frequent assessments of disease activity and adverse events. The achieving remission or low disease activity condition should be maintained as long as possible after the initiation of RA therapy. The treatment with DMARDs should be started once diagnosis of RA decided. The conventional DMARDs will probably remain the preferred initial treatments for RA. Off course, MTX is key drug of RA therapy. In Japan the guideline recommends the early use of MTX (6-16 mg/week). Delaying the administration of DMARD therapy reduces the possibility for patients to achieve disease remission, and is associated with more rapid radiological progression. If the low disease activity is not achieved within 3-6 months, another conventional DMARD or a biologic DMARDs should be added to the treatment regimen or DMARDs should be switched to another DMARD with or without a glucocorticoid. Once low disease activity is achieved, the treatment goal for the early RA may be remission. The biologic DMARDs provide a remarkable change in rheumatologist's drug choice. However, the use of both conventional and biologic DMARDs needs to be continued indefinitely to sustain clinical benefit. The many clinical experts have suggested the combination use of different DMARDs. However, there is no consensus regarding the combination of DMARDs for the treatment of RA because of lucking clinical RCT data. Some of reports concluded that a limited number of DMARD combinations were more effective than monotherapy for treating established RA. I will talk recent data of combination therapy with conventional DMRADs.

LS28

Therapeutic strategy of CTD-PAH-For the better QOL of all patients

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Conflict of interest: Yes

Pulmonary hypertension is one of the most life-threatening manifestations in connective tissue diseases. Estimated incidences of pulmonary hypertensions are 7-16%, 5-11%, 2-9%, 0-1.5% in mixed connective tissue disease, systemic sclerosis, systemic lupus erythematosus, and dermatomyositis/polymyositis, respectively, in Japan. Pulmonary hypertension in patients with connective tissue diseases can be multi-factorial. In systemic lupus erythematosus, Libman-Sachs endocarditis can cause left heart failure associated pulmonary hypertension. Interstitial lung disease is reported in 6 % of patients with systemic lupus erythematosus and that can directly lead to pulmonary hypertension and indirectly due to hypoxemia. Thrombotic complications in artery and vein are often associated with anti-phospholipid antibody, and chronic pulmonary thromboembolism is one of the established etiologies of pulmonary hypertension. In addition, vasculitis is also a potential cause of pulmonary hypertension. Early diagnosis of pulmonary hypertension is imperative to prevent irreversible tissue damage. Symptom-oriented screening of pulmonary hypertension is not efficient because early manifestation can be subtle and non-specific. For patients with mixed connective tissue disease, regular echocardiogram can be recommended. However, unfortunately, even echocardiogram does not have sufficient sensitivity in the early stage, and addition of pulmonary function test with DLCO has been advocated. Exclusion of chronic pulmonary thromboembolism with V/Q scintigraphy or PE scan should be preceded before the confirmatory but invasive right heart catheterization is performed. To improve survival rate and QOL of connective tissue disease patients with pulmonary arterial hypertension, institution of systematic screening and diagnostic protocol is crucial.

LS29

Gout as monosodium urate crystal deposition arthropathy: clinical application of musculoskeletal ultrasonography and dual-energy computed tomography

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Conflict of interest: None

Gout is an inflammatory arthritis caused by monosodium urate (MSU) crystal deposition due to persistent hyperuricemia. Excess total body urate pool accompanies with the deposition of MSU crystal in joints and soft tissues, and various factors cause shedding of the crystal which induce intra/peri-articular inflammation. Treatment of gout consists of dissolution of excess total body urate pool by life-style modification and urate-lowering therapy, and suppression of inflammation by pharmacologic therapies such as non-steroidal anti-inflammatory drugs. Principle of pharmacologic therapy in daily clinical practice is urate-lowering therapy with the target of serum urate level <6 mg/dl, which is not sufficient to prevent gout attack in short term. It should be recognized that treating to target serum urate level is just a therapeutic procedure to achieve the true target of MSU crystal disappearance in joints and soft tissues. American College of Rheumatology has currently published management guidelines for gout in 2012, still there not be evidence fully available for daily clinical questions such as risk of developing gout in patients with asymptomatic hyperuricemia, duration of anti-inflammatory prophylaxis/treatment for gout attack/gouty arthritis, or appropriate dose escalation of urate-lowering therapy to prevent attack. Imaging modalities such as musculoskeletal ultrasonography and dual-energy computed tomography directly detect focal MSU crystal deposition and inflammation, which would enable management of gout reflecting local condition. Current data and images are reviewed to determine utility and limitation of imaging evaluation in patients with gout in terms of MSU crystal deposition arthropathy.

LS30

The basics apt to be forgotten in treatment of osteoporosis - What we need to remind ourselves -

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Conflict of interest: Yes

The advent of alendronate and risedronate, having anti-hip fracture efficacy, in 1990s was accompanied by a decline in incidence of hip fracture in 2000s in many countries. But study in Japanese population showed the increases in hip fracture. So we, in Japan, have to cope with this situation efficiently seeking the possible reason for it. Three fundamental refreshments of our stance against the public health problem due to osteoporosis seem to be necessary. The first is to keenly recognize the importance of the evidence-based-medicine for successful result in preventing a fracture. We must not overlook the fact that we have only two drugs approved in Japan, alendronate and risedronate, having the anti-hip fracture efficacy. We must know that we can prescribe the teriparatide preventing a vertebral fracture in the patients with high risk for it. The second is to recognize the importance of the nutrients for the bone health and the prerequisite of the good efficacy of medication. Especially, vitamin D and K status is essential. Fortunately, we can easily detect the shortage in vitamin D and K using widely used biochemical tests and replenish them with the medication approved in Japan. And it is important to remind ourselves to avoid the hypercalciuria due to overdose of active vitamin D. The third is to give the positive benefit-risk balanced prophylactic medicine to all of patients. For example, alendronate and risedronate have the benefit for anti-hip fracture efficacy, while their long-term use is associated with bisphosphonate-related osteonecrosis of the jaw (BRONJ) and atypical subtrochanteric and diaphyseal femoral fractures. Accumulating recent reports on alendronate and risedronate confirmed their positive benefit-risk balance. It is important to stand to avoid the drugs that have an unknown or unfavorable benefit-risk balance. These three items seem to be necessary for improving preventive medicine against osteoporosis related fracture.

LS31-1

The suppression of joint destruction in RA by IL-6 inhibition- The new paradigm shift aimed for desirable future in RA patients –

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Conflict of interest: Yes

Rheumatoid arthritis (RA) is characterized by chronic synovitis leading to progressive joint damage from the early phase, and finally causes the cartilage destruction and bone resorption in the joints. As a result, many RA patients suffer from permanent disability. Although the exact cause of RA is still unknown, insights into its pathogenesis have confirmed the activation of self-reactive lymphocytes and the macrophages in the synovial tissue, the secretion of pro-inflammatory cytokines, the proliferation of synovial fibroblasts, pannus formation, the production of tissue-destructive enzymes and the activation of osteoclasts. RANKL(receptor activator of NF-κB ligand) and MMPs (matrix metalloproteinase) also play an important role in the mechanism of joint destruction. Tocilizumab (TCZ) – an IL-6 receptor inhibitor can be an effective treatment option in order to inhibit the pathology of RA. IL-6 plays an essential role in RA since IL-6 induces the expression of RANKL and MMPs through STAT3 and ERK pathway. Thus, we

consider that IL-6 plays a critical role in bone and cartilage destruction in RA inflammation. On the other hand, we consider combination therapy of CDK4/6 inhibitor and cytokine inhibitors would be an effective treatment in RA. CDK4/6 inhibitor blocks the cell cycle of synovial fibroblasts. Combination of CDK4/6 and TCZ was superior to monotherapy in inhibiting the progression of joint destruction without causing excessive immunosuppression in mice RA models. Coordinating inhibition of the immune system and inflammation is desirable. We hope this can lead to a new paradigm shift in RA treatment, which could eventually provide remission to all RA patients. In this seminar, we will discuss the rationale of IL-6 blockade, the efficacy of TCZ from the insight of basic research, and CDK4/6 inhibitor that we expect as a new therapeutic agent.

LS31-2

Significance of IL-6 inhibition in the treatment of rheumatoid arthritis

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Conflict of interest: Yes

In this decade, various therapeutic strategies for rheumatoid arhtritis (RA) targeted to inflammatory cytokines have been developed. Amonf these, humanized anti-IL6 receptor antibody, tocilizumab (TCZ) is the only agent to inhibit IL-6 signaling. With TCZ high clinical remission rate was achievable in not only MTX or DMARD-inadequate responders (MTX-IR or DMARD-IR) but patients who had been resistant to TNF antagonists (RADIATE study). In REACTION study, which is a retrospective study done in 4 major rheumatology institutes including our hospital, clinical remission rate defined by DAS28-ESR was 44% after one year treatment with TCZ even though these patients had long disese duration (more than 12 years) and 63% of them were resistant or intolerant to anti-TNF therapy. In SAMURAI study, TCZ could inhibit radiological progression in DMARD-IR RA patients without concomitant DMARDs and TCZ monotherapy was significantly more effective than MTX in MTX-IR patients in SATORI study. Similarly, ACT-RAY study revealed TCZ monotherapy (switch to TCZ) was as effective as combination therapy of TCZ and MTX (add TCZ to MTX) in MTX-IR patients at week 24. These data suggest TCZ might be effective without MTX. In addition, in ADACTA trial, remission rate of TCZ monotherapy was significanly higher than that of adalimumab monotherapy (39,9% vs 10.5% at 24 week). These data suggest that inhibition of IL-6 may be more efficacious than that of TNF without MTX. Lastly, the subanalysis of RISING study revealed that remission rate was lower in patients whose serum infliximab concentration was high enough (more than 1.0 mg/ml) but had high plasma IL-6 level (≧ 10 pg/ml) at week 54. On the other hand, remission rate was higher if plasma IL-6 level was suppressed (<10 pg/ml) at week 54. These data will support the importance of IL-6 inhibition in the management of RA treated with TNF antagonists. IL-6 seems to be the best target cytokine for the treatment of RA.

LS32

Update on the management of osteoarthritis - pathophysiology and guideline -

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Conflict of interest: Yes

The current goal of the treatment of osteoarthritis (OA) is "improvement of joint symptom" such as pain. Recent treatment guidelines indicate the importance of non-pharmacological and pharmacological treatments including patient education, aerobic exercise, and weight loss for obesity. Intra-articular steroid injection is recommended for local osteoarthritic inflammation. Intra-articular hyaluronan injection is also recommended especially in Japan. Surgical treatments are recommended in patient refractory to the above conservative treatment. On the other hand, none was able to show a clear clinical efficacy of structure modifying OA therapy. Thus, OA treatment is far behind the recent progress of the treatments for other skeletal diseases, such as rheumatoid arthritis and osteoporosis. With the advances in the understanding of the pathogenesis and molecular mechanisms of OA, new strategies that control the disease progression should emerge.

LS33

The Safety and Efficacy of Abatacept

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Abatacept is a selective co-stimulation modulator that inhibits T-cell activation by binding to CD80/86, and modulating its interaction with CD28. Significant advances in our understanding of rheumatoid arthritis and its management have been made in the last decade, resulting in earlier intervention with biologic disease-modifying anti-rheumatic drugs, particularly in patients with evidence of aggressive, erosive disease. The T-cell co-stimulation modulator abatacept, will be discussed, exploring clinical evidence on its clinical outcomes over short and long-term treatment in different patient populations, and the effects of abatacept on structural damage. Abatacept efficacy has been shown in Methotrexate naïve patients. In Methotrexate and other disease modifying anti-rheumatic medications incomplete responders. Efficacy as anti-TNF incomplete responders has been established. All of these patient populations will be discussed. The safety profile of Abatacept has been studied for up to seven years and in over 12,000 patient years. This safety profile and how it compares to other biologic therapies will be reviewed. This safety profile has lead to the earlier use of Abatacept in rheumatoid arthritis.

LS34-1

Mizoribine, tacrolimus, and corticosteroid combination therapy for lupus nephritis

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Conflict of interest: None

Lupus nephritis (LN) is a major manifestation of SLE and has the worst prognosis. The ideal therapy for LN should induce an early response and remission, prevent flare-ups, have minimal adverse effects, and result in reductions in mortality and end-stage renal disease. The suitability of cyclophosphamide-based treatment regimens, which are the standard therapy for LN, remains a matter of debate, and alternative treatments are therefore required. At Himeji Red Cross Hospital, multitarget therapy with a combination of corticosteroid and 2 immunosuppressors (mizoribine and tacrolimus) with different mechanisms of action was attempted to induce remission of LN. We retrospectively studied 14 consecutive patients with LN. The study involved 14 patients (mean age, 46.0 years; 14 women; 12 new cases; urinary protein, 4.3 ± 2.6 g/day; 1 case of ISN/RPS class II, 5 of III or IV, 5 of V, and 3 of III+V). Complete nephritis remission in 64.3% and 100%, systemic lupus erythematosus disease activity index (SLEDAI) remission in 28.6% and 75.0% were observed with prednisolone doses of 12.5 and 8.7 mg/day at 6 and 12 months, respectively. At 6 months,

complete nephritis remission (60.0%, 80.0%, and 33.3%) and SLEDAI remission (40.0%, 20.0%, and 33.3%) was observed with prednisolone doses of 11.6, 13.8, and 11.7 mg/day for class III or IV, V, and III+V, respectively. The therapy was highly effective and tolerable. Favorable outcomes of multitarget therapy at our hospital in each histological type suggest its diverse applicability.

LS34-2

Recommendations for lupus nephritis and Immunosuppressive therapy

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Conflict of interest: Yes

A number of immunosuppressants have been used for the treatment of systemic lupus erythematosus in daily practice, and they contribute to improve the prognosis of the affected patients. Among them, azatioprim and cyclophosphamide are conventional drugs with some evidence. Recently two recommendations for the management of lupus nephritis were published; one from ACR and the other from EULAR/ERA-EDTA. Both are evidence-based and practical for the daily practice. In those guideline, Mycophenolate mofetil (MMF) plays an important role for the treatment. Apart from those recommendations, tacrolimus has been proven usuful as well in Japanese patients. Recently, we analysed a longitudinal renal survival in our lupus nephritis (LN) patients. This retrospective analysis was consisted of 187 Japanese patients given a diagnosis of LN by renal specimen (1984–2009) and followed for 11.9±7.2 years. End point was defined as death or end stage renal failure. Fourteen patients died and 8 patients had end stage renal failure at the last visit. Kaplan-Meier analysis revealed the 10-year renal survival of 94.3%. Male gender and proteinuria (≥ 3.5g/gCr) at baseline were identified as independent poor prognostic factors in Cox regression analysis. Although high renal survival rate was observed, male gender and proteinuria (≥ 3.5g/gCr) at baseline may be critical factors in predicting renal outcome. Through this study, we compared the outcome and event s with immunosuppressants. There were no clear correlations between the drugs and outcome, therefore, cyclophosphamide would not contribute for improvement of lupus renal survival. In this seminar, those guidelines will be interpreted. In addition, current and potential strategies for the better management of patients with lupus nephritis will be explored.

LS35

Gastrointestinal damage caused by administration of non-steroidal anti-inflammatory drugs - Selection of anti-ulcer drugs -

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Conflict of interest: None

NSAIDs have been shown to exert anti-inflammatory effects by decreasing the production of prostaglandin (PG) by inhibiting cyclooxygenase. NSAIDs inhibit the production of PG, which promotes bicarbonate and mucous secretion in gastrointestinal mucosa. Therefore, NSAID-induced inhibition of gastrointestinal mucosal PG production is considered to augment the incidence of gastrointestinal ulcers. Indeed, the prevalence of gastroduodenal ulcers has been reported to be as high as 15% in patients treated with NSAID administrations. NSAID-related ulcers have characteristics that distinguish them from non-NSAID-related ulcers. First, patients with NSAID-related ulcers have fewer symptoms as compared to those with Hp-related ulcers. However, they frequently develop bleeding complications. In addition, it is increasingly apparent that NSAIDs frequently cause mucosal lesions in the intestine. To determine gastrointestinal complications, history taking focused on stool discoloration, along with repeated testing to detect stood occult blood are considered to be necessary. When clinically relevant gastrointestinal lesions are found, interruption of NSAID administration is the most effective way to heal gastrointestinal lesions. When a lesion is found in gastroduodenal mucosa, administration of proton pump inhibitors (PPIs) is one of the best options. For prevention, 2 types of drugs are generally used. Patients with a history of gastroduodenal ulcers are reported to have the highest risk to develop NSAID-related ulcers during administration. Therefore, prophylactic administration of PPIs has been approved for patients with a history of gastroduodenal ulcers. To provide gastrointestinal protection in cases without such history, administration of PG analogues has been used. PG analogues are used for mucosal protection in the lower gastrointestinal tract.

Evening Seminar

ES1-1

Early therapeutic intervention targeting long-term outcome in patients with rheumatoid arthritis

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Conflict of interest: Yes

Recent advances in the treatment of rheumatoid arthritis (RA) have made it possible not only to achieve clinical remission, but also to maintain long-term sustained remission. The combination of biologics targeting TNF and MTX has revolutionized the treatment of RA, producing significant improvements in clinical, structural and functional outcomes. Critical factors for clinical remission include structural remission, the beneficial effect of which is most evident in early RA patients receiving early therapeutic intervention. HOPEFUL1 Study involving MTX-naïve early RA patients demonstrated that 40% achieved clinical remission and 70% did structural remission within 1 year by the treatment with adalimumab and MTX but that a 6-month delay in starting adalimumab treatment resulted in irreversible radiographic progression, reaffirming the importance of early therapeutic intervention for RA. Similar results have been reported from OPTIMA and PREMIER Study. The OPTIMA Study also demonstrated that early intervention with adalimumab resulted in high ration of Bio-free remission after achieved remission. HONOR study using adalimumab in patients with long-standing RA encountered during routine clinical practice have also shown that, after a reduction in disease activity to clinical remission or low disease activity by adalimumab in combination with MTX, patients can successfully remain in clinical remission without adalimumab with no radiological and functional damage progression of articular destruction. Taken together, early and appropriate intervention in RA is critical to aim for this ultimate therapeutic goal and is an essential therapeutic strategy not only to prevent the radiographic progression of joint destruction but also to achieve biologic-free remission and to improve long-term outcomes in patients with RA.

ES1-2

Molecular mechanism of bone and joint destruction in rheumatoid arthritis

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Conflict of interest: Yes

Rheumatoid arthritis (RA) is a progressive inflammatory disease characterized by synovitis of many joints. Proliferating synovitis and cartilage and bone destruction are observed in the inflammatory joints. Proinflammatory cytokines such as TNF-α, which are produced by inflammatory synovium, have been known to induce bone and joint destruction in RA. Cartilage destruction in RA is induced by the proteases produced by the proliferating synovium, and bone destruction is mediated by osteoclasts, primary cells for bone resorption. Recent studies have revealed an essential role of receptor activator of NF-kappaB ligand in the differentiation of osteoclasts in RA. Previous studies have revealed that anti-TNF-α drugs effectively suppress bone and joint destruction in RA.

ES2-1

Pathological characteristics of pulmonary arterial hypertension associated with connective tissue diseases

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Conflict of interest: None

Pulmonary arterial hypertension (PAH), pulmonary veno-occlusive disease (PVOD) and pulmonary capillary hemangiomatosis (PCH) are included in the same group (Group 1) of clinical classification of pulmonary hypertension (PH). Histologic changes in the small pulmonary arteries (i.e., intimal thickening and medial hypertrophy) are similar in these three diseases. PVOD is histologically characterized by intimal fibrosis that narrows and occludes pulmonary veins. PCH is histologically characterized by localized capillary proliferation within the lung in which capillaries invade the pulmonary interstitium, vessels and, less commonly, airways. PAH associated with connective tissue diseases (CTD) is frequently resistant to PAH therapy. Recent studies indicate that the difficulties in the management of PAH is associated with fibrous remodeling of pulmonary veins and venules.

ES2-2

Treatment of pulmonary hypertension associated with lung connective tissue disease: use of immunosuppressive and pulmonary arterial hypertension drugs

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Conflict of interest: Yes

Pulmonary arterial hypertension (PAH) is a subset of pulmonary hypertension (PH), and now recognized that PAH can be treatable with potent effective drugs against PAH. The clinical outcome of idiopathic PAH has been substantially improved by the use of PAH drugs in large doses or in combination. Furthermore, the normalization of pulmonary hemodynamics is likely to be achievable in the near future. With the recent progress in the treatment of PAH, we again recognize the importance of the clinical classification of PH and high prevalence of PH in patients with connective tissue disease (CTD), including mixed connective tissue disease, systemic lupus erythematous and systemic sclerosis. There are huge variety of organ involvements in patients with CTD. A typical example is pulmonary lesions such as interstitial lung disease and vasculopathy (e.g. PAH, vasculitis and chronic thrombotic pulmonary embolism). These are the most common causes of PH. PH can also be observed in cardiomyopathy and portal hypertension. Thus, this complexity of the cause is a major feature of PH in patients with CTD, and it hampers the treatment. In fact, the clinical outcome of PAH associated with CTD (especially systemic sclerosis) is worse than that of idiopathic PAH under treatment with PAH drugs. In this seminar, we present data to support the validity of our therapeutic strategy for PAH associated with CTD. First, we discuss the alternative use of immunosuppressive drugs according to disease type. We also discuss how to choose and use the different classes of PAH drugs such as phosphodiesterase 5 inhibitors. Finally, we provide tips on the use of diuretics, oxygen and anti-coagulants as supportive therapy based on the concept of out-of-proportion PH. We hope that this seminar will make a meaningful contribution to the treatment of PAH associated with CTD, leading to improvement of the clinical outcome and QOL of patients with this disease.

ES3-1

Positioning of Golimumab Primarily Used for Intractable Cases of Rheumatoid Arthritis Resistant to Treatment with Biological Preparations

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Conflict of interest: None

Gomulimab (GML, Simponi®) is a completely humanized anti-TNFα monoclonal antibody preparation marketed in Japan in September of last year as the 6th biological preparation. GLM can be characterized by high affinity for TNFα and unlikelihood for formation of antibody to this drug. These characteristics are derived from its origin (an antibody created from transgenic mice). GLM has been additionally shown to alleviate or improve the clinical symptoms and physical function and to suppress articular destruction by means of only one subcutaneous injection in 4 weeks. During clinical practice, GLM (the 6th biological preparation) is often used for therapy-resistant intractable cases of rheumatoid arthritis (RA) having responded poorly to multiple biological preparations. Regarding the efficacy of biological preparations, it has been reported that the responses of patients having received treatment with multiple biological preparations before (switched cases) usually show poorer responses than patients without prior treatment with biological preparations (naïve cases). With these borne in mind, I compare the responses to GLM between naïve cases and switched cases managed at our facility and discuss the efficacy of GLM in intractable cases of RA resistant to other biological preparations. The study involved 3 naïve cases and 22 switched cases treated with GLM for 24 weeks or more at our facility. GLM dose level was 50 mg in 23 cases and 100 mg in 2 cases. The treatment continuation rate at 24 weeks was high and there was no evident adverse event. In evaluation of clinical efficacy following 24 weeks of GLM treatment, all of DAS28ESR score, CRP level and MMP-3 level decreased significantly over time in both the GLM naïve group and the switched group, indicating significant improvement of the condition, although most of the patients from the switched group had failed to respond to other biological preparations before GLM treatment. Furthermore, disease remission was seen in both the naïve group and the switched group after 24 weeks of GLM treatment. Thus, both the response rate to GLM and the GLM treatment continuation rate were high even in switched cases having received treatment with multiple other biological preparations before and probably falling under the category "intractable cases," and the responses in the switched group were comparable to those in the naïve group. In addition, MMP-3 level decreased significantly following GLM treatment, allowing us to expect GLM's effect in suppressing articular destruction. Evaluation of this therapy by diagnostic imaging is desirable from now on.

ES3-2

Discussion over Bio Switch during Clinical Practice

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Shono Rheumatology Clinic

Conflict of interest: Yes

In Japan, 6 biologics (Bio) are available for use in the treatment of rheumatoid arthritis (RA) as of the end of 2012. We may say that no physician specializing in RA now questions the possibility of controlling the disease activity of RA patients by the use of Bio. When Bio is used during clinical practice, an optimal type of Bio is selected based on general assessment of the features of individual types of Bio, the presence/absence of concomitant MTX use and the lifestyle of the patient concerned. When Bio therapy is introduced to Bio-naïve patients, any type of Bio can exert at least some efficacy, but the response to Bio can differ to some extent or other in cases where a type of Bio is switched to another type of Bio. Now, a new treatment concept "Treat to Target (T2T)" is being accepted widely in clinical practice. Under such a trend, introduction of new Bio therapy is increasing for patients previously treated with other types of Bio (Bio-switched cases), more markedly than for Bio-naïve patients. Among the new types of Bio, golimumab (GLM), marketed in 2011, is a fully human anti-TNFα antibody created from transgenic mouse. In addition to the high convenience (one subcutaneous injection in 4 weeks) unsurpassable by other products, GLM has shown a high clinical remission achievement rate also at our facility. Today, I will discuss how to use GLM during clinical practice, bearing in mind the treatment strategy T2T. My discussion will cover not only Bio-naïve patients but also Bio-switched patients, taking into account changes in clinical symptoms after switching of the preceding Bio to a new Bio, as well as the type of the preceding Bio, the extent of experience with the preceding Bio, background variables of each patient, and so on.

ES3-3

Regulation of Inflammatory Cytokine TNFα with an Appropriate GLM Dose Level – Does 50 mg suffice? Should 50 mg be increased to 100 mg? Should 100 mg be adopted at the beginning?

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Conflict of interest: Yes

The newest anti-TNAα monoclonal antibody preparation "golimumab (Simponi®, abbreviated as GLM)" has two striking advantages: (1) a preparation for subcutaneous injection once in 4 weeks and (2) a completely humanized anti-TNFα monoclonal antibody preparation prepared from transgenic mice and unlikely to induce neutralizing antibody formation. Another important feature of this new preparation is that this preparation has been approved in Japan (for the first time in the world) for use at a dose level 100 mg/4 weeks (double the global standard dose level 50 mg/4 weeks), thus allowing selection of treatment at a dose level 100 mg for cases difficult to control at the dose level 50 mg. This is a great advantage of this product over the two existing preparations for subcutaneous injection which cannot be used at dose levels higher than the global standard. The evidence supporting GLM dose increase was obtained in the domestic clinical trial GO-FORTH Study in which our facility also participated. In that study, cases having failed to show 20% or more alleviation in tenderness and number of swollen joints at 14 weeks after the start of treatment relative to the pretreatment baseline were rated as "early escape." There were 9 patients for whom the dose level was increased to 100 mg from Week 16 on because of poor responses to the 50 mg treatment. Treatment at the increased dose level was continued for 36 weeks (from Week 16 to Week 52) in 6 (67%) of these 9 patients. For these 6 patients, ACR20/50/70 in Week 52 were 83%, 33% and 17%, respectively, thus demonstrating the efficacy of dose increase. How about the post-marketing clinical results on GLM? During this seminar, we will present the latest TBCR data and discuss how to adjust the GLM dose level to enable inflammatory cytokine TNFα regulation, focusing on the data from cases kept at the dose level 50 mg, cases with dose increase from 50 mg to 100 mg and cases initially treated at 100 mg.

ES3-4

Sweet Spots for Simponi

Satoshi Ito
Niigata Rheumatic Center

Conflict of interest: Yes

Golimumab (GLM) was approved as the 6th Bio in Japan. In clinical trials, treatment with GLM yielded favorable outcome, with or without MTX. However, considering the recent spread of treatment with Bio, we cannot deny that the disease activity of the patients enrolled was lower than that of the patients enrolled to clinical trials on other Bio. At our facility, we attempted to make full use of GLM's characteristics. The drug was administered to 25 patients (4 males and 21 females). In one of these patients, GLM was used at the time of loss of the efficacy of ETN. In this case, GLM was later switched to TCZ because of lack of responses. In the remaining 24 patients, GLM was effective and has been used to date. The mean age of 25 patients were 64.7. There were 8 Bio-naïve cases and 17 Bio-switched cases. GLM is characterized by: (1) convenience in the frequency of administration (once in 4 weeks), (2) effective even without MTX, unlikely to induce anti-GLM antibody and (3) 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 (2) patients unable to receive MTX at sufficiently high dose levels (a: switching from losing efficacy of ETN or ADA without MTX; b: switching from MTX in patients receiving IFX+ MTX when the MTX dose level needs to be reduced), and (3) patients failing to show sufficient responses to dose increase or shortened dosing interval of IFX and (4) patients having relapse of the disease despite IFX treatment aimed at "Bio-free condition". If the effectiveness of GLM in the patient group (4) is established, it seems possible to discontinue IFX therapy after reaching stable remission of the disease by switching IFX to GLM. We plan to apply switching to GLM also to patients maintaining remission with IFX and unwilling to discontinue it. If this therapy is established, the burdens on both the patient and the medical facility must be reduced.

ES4

Scientific overview on pain of rheumatoid arthritis

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Conflict of interest: Yes

Rheumatoid arthritis (RA) is chronic inflammatory musculoskeletal disease characterized by pain, stiffness, swelling and tenderness of the synovial joints. Normal synovial joints must meet requirement of mobility and bearing property without pain. Pain-free is most important factor of joints function. At present there are many assessments of disease activity of RA, including Disease Activity Score 28 (DAS28), Simplified Disease Activity Index (SDAI), Clinical Disease Activity Index (CDAI), Boolean Score and so on. In these assessments, the patients' opinions do not always match those of their physicians. Because these assessments have a higher proportion of pain and there are differences of opinions for the pain between them. In this issue, it is often discussed whether assessment for pain is objective or not. The International Association for the Study of Pain's widely used definition states: "Pain is an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage". As pain has two-side of sensory and emotion, pain assessment inevitably becomes objective and subjective. Recent advancement of neuroscience shows that emotion plays an ever-greater role in pain. In the treatment of RA, pain should be evaluated in pathway from peripheral to central nerve, and considered all the various factors together.

ES5-1

An Effective Treatment Strategy of Inhibiting Interleukin-6 (IL-6) in RA - Exploring the Relationship between RA Pathogenesis and Cytokine Inhibition Therapy -

Tsutomu Takeuchi
Division of Rheumatology, Department of Internal Medicine, School of Medicine, Keio University

Conflict of interest: Yes

The treatment of Rheumatoid Arthritis (RA) has improved significantly over the past decade. The introduction of new biologic agents, the importance of early treatment intervention, and the new remission criteria have induced a lot of research which enhanced the treatment of RA in Japan. It is known that 30-45% of patients prescribing Infliximab (IFX) attain clinical remission at week 52, and serum trough level (STL) of 1.0μg/ml of IFX is the threshold for measuring clinical response. However, not all patients obtain clinical remission (CR) or low disease activity (LDA) even with a trough level above the threshold. This led us to evaluate the existence of other factors involved in the pathogenesis of RA except TNF. The SAKURA cohort observed 62 treatment-naïve early RA patients. Both TNF and IL-6 levels were measured to identify the relationship between cytokine levels and radiographic changes after initiating MTX. Logistic regression analysis showed that patients with lower IL-6 levels had a higher rate of not progressing joint damage. Thus monitoring IL-6 levels could be valuable to recognize efficacy when treating RA. The RISING study measured serum IL-6 levels in patients using IFX with STL over 1.0 μg/ml at week 52. CR and LDA were achieved in patients with lower IL-6 levels (<10pg/mL) than in higher IL-6 levels (>10pg/mL). Hence inhibiting IL-6 is essential for management of disease activity and inhibiting joint damage for RA. For its part, we measured the efficacy of Tocilizumab (TCZ) which inhibits the binding of IL-6 and IL-6 receptor. The remission rate of DAS28-ESR, SDAI, CDAI, and Boolean criteria in 101 patients at week 52 were 77.8%, 45.5%, 42.6% and 34.7%, respectively. The retention rate was over 80% irrespective of previous biological treatment. This result also supports the significance of inhibiting IL-6 in RA. In this symposium, we will outline the importance and relevance of IL-6 inhibition in the RA pathogenesis and treatment strategy.

ES5-2

Treatment of Early Rheumatoid Arthritis (RA) on the New IL-6 Consensus Statement

Ferdinand Breedveld
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Strategies of RA treatment have also changed drastically in the past decades. Up until the 1980s, treatment followed by the 'pyramid approach' in which the drugs considered least toxic such as analgesics and non-steroidal anti-inflammatory drugs (NSAIDs) were prescribed first. 'Second-line' DMARDs were regarded more toxic and were only initiated after failure of the first-line drugs or in case of progressive erosive disease. However, once the toxicity profile of NSAIDs and DMARDs has been shown to be similar, and the debilitating outcome of RA patients was recognized, the more intensive 'saw-tooth' principle was introduced which advocated earlier, continuous and serial use of DMARDs. In the past decade, four important further changes have led to considerably improved treatment outcomes. First, early diagnosis and prompt initiation of DMARD therapy led to earlier suppression of disease activity with long-term impact. Second, DMARD combination therapies, especially those including corticosteroids, have proven superior without more toxicity than DMARD monotherapies. Third, the advent of the targeted therapies or biologic agents, which have shown to be highly effective both in DMARD-naïve patients and in patients who failed previous DMARD therapy. Fi-

nally, so called 'tight-control' (frequent evaluations and adjustments of therapy with validated tools aiming at a pre-set goal of minimal disease activity), has been proven to result in better outcomes than in 'routine care'. As a result of these changes, sustained disease remission has become an achievable goal of RA treatment. The BeSt (acronym for 'Behandel Strategieën') study has combined these therapeutic innovations, starting with early, tightly controlled treatment (via aiming at a low disease activity score) in four different treatment arms, including initial monotherapy (arms 1 and 2) and initial combination therapy with either prednisolone (arm 3) or with a biologic agent (arm 4), in patients with recent-onset RA[2]. This approach has resulted in a remarkable clinical improvement and reduction of radiological damage progression in the majority of patients. The observation that clinical remission could be achieved and, in part of the patients, could be maintained and illustrates the window of opportunity for changing the disease outcome, even in patients who had already progressed to full-blown RA. A recent consensus statement on the usage of Tocilizumab in RA treatment recommends that these treatment principles should be followed. Current available information on blocking IL-6 reveal the importance of this treatment option to improve the outcome of patients with RA.

ES6-1

Treatment strategy by cytokine control based on prediction of clinical outcome

Daniel Aletaha
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Treatment strategies for rheumatoid arthritis (RA) have clearly advanced over the last decade: a very straightforward approach of treating disease activity to a predefined target has been established ("Treat-to-Target" Initiative) and has already been promoted by various Rheumatology Organisations. The main characteristic is an approach that calls for (1) setting a clear target, (2) doing a proper and formal assessment, and (3) adjust therapy if the pre-defined target has not been met. For this strategy, obviously not all patients with RA will be able to reach the state of remission, which is the ultimate target. In several situations, low disease activity may also be acceptable:(1) in patients with chronic, long-standing disease; (2) if biological drugs are in use, as they have shown to limit structural progression of RA also in low disease activity; and (3) in the presence of isolated (i.e. not disease activity related) pain. In all cases, treatment decisions need to be made after three to six months. Only therapy of patients, who do not show any significant improvement at three months, needs to be adjusted. In all other patients, particularly in those have already improved their disease activity at three months but without yet reaching the target, therapy should be continued and the treatment changed only if at 6 months after initiation the target has not been reached. Following these novel treatment strategies, and considering the mentioned aspects, there will be the opportunity for optimized treatment for RA patients, but without unnecessary overtreatment.

ES6-2

The regulation of cytokine production by methotrexate and biological agents

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Conflict of interest: Yes

The critical roles of tumor necrosis factor (TNF) and interleukin (IL)-6 in the pathophysiology of rheumatoid arthritis (RA) have been evident from outstanding efficacies of biological agents specifically targeted to those cytokines. Recent advances in technology enabled us to measure various cytokines even at the concentration of 1 pg/ml. Therefore, we examined the effect of methotrexate (MTX) and biological agents on cytokine production. Plasma samples obtained from early RA patients receiving MTX at the mean dose of 9 mg/week without concomitant biologics for at least 6 months demonstrated that IL-6, but not TNF, production was down-regulated in most patients. And the low plasma IL-6 level was significantly associated with radiographic non-progression. Thus, the fact that MTX efficacy depends on the down-regulation of IL-6 production may well explain the results from a recent clinical trial suggesting modest increase in the efficacy of tocilizumab, an anti-IL-6 receptor monoclonal antibody, with concomitant MTX. When we see the sub-analysis results from the RISING study, examining the dose-dependent efficacy of infliximab in RA patients who had shown an inadequate response to MTX, elevated plasma IL-6 level before infliximab treatment was remarkably decreased soon after the treatment. The association of infliximab trough level and IL-6 down-regulation at 54 weeks suggested the importance of sufficient dosing of infliximab for each RA patient. Abatacept, a biological agent not directly targeted to cytokines, showed only modest, if any, effects on cytokine (including TNF and IL-6) production, implicating the different mode of action from other biologics. Based on above data, future treatment strategies for RA will be discussed from the view of regulating the production and the action of cytokines.

ES7-1

Safety of biologics: approach to unsolved issues

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Conflict of interest: Yes

Six biologics have been launched in Japan and widely used in clinical practice for patients with rheumatoid arthritis (RA). Certolizumab pegol (CZP, Cimzia®) consists of a humanized immunoglobulin fragment (Fab) conjugated to polyethylene glycol (PEG). Pegylation of this molecule yields a longer half-life and reduces need for frequent injection. Major safety profiles of CZP from a pooled analysis across all doses in RA are as follows. Ten randomized controlled trials and their open-label extensions included 4,049 patients by November 2011, with a total of 9,277 patient-years (PY). The incidence rate (IR) of serious infections was 4.33/100PY, and was consistent with the IR reported from British Society of Rheumatology Biologic Registry (4.2/100PY). There were 43 cases of tuberculosis (TB) infection (0.47/100PY), of which 39 (90.7%) occurred in Central and Eastern European regions with relatively high prevalence of TB. There were no new or unexpected safety signals. Various meta-analyses have been published to compare the safety of biologics. Results of meta-analysis is significantly influenced by clinical trials analyzed, length of treatment with placebo, and length of total exposure period of a drug, and results of meta-analysis should be interpreted with critical appraisal. There are several issues under investigation about safety of biologics such as risk for malignancy, reactivation of hepatitis virus, and treatment of patients planning pregnancy. In this symposium, I would like to discuss these unsolved issues pursuing better treatment for our RA patients.

ES7-2

Intensive treatment and treatment holiday in patients with rheumatoid arthritis

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Conflict of interest: Yes

It has passed 10 years after Infliximab, the first anti-TNF Antibody, was approved for RA in Japan for the first time. Since then, many biologic DMARDs were introduced, and effective use of them, especially TNF inhibitors, has been discussed and estimated. The combination of TNF inhibitors and MTX has revolutionized the treatment of RA, and clinical remission became a realistic treatment goal. One of next goals is to enable long term cost saving and safety, and it has been questioned whether the discontinuation of TNF inhibitors is a possible option for RA patients. European studies of BeSt and OPTIMA demonstrated that introduction of TNF inhibitors with MTX to early RA patients allowed some patients to maintain clinical remission after withdrawal of TNF inhibitors once they had achieved clinical remission or low disease activity. We have also reported that 'treatment holiday' of TNF inhibitors without functional impairment and radiographic damage is feasible even in established RA patients through intensive treatment in the RRR study using infliximab and the HONOR study using adalimumab. It was shown that successful biologic-free remission was associated with deep remission at discontinuation. In this seminar, the knowledge from the 10-year experience with TNF inhibitors, especially the recent evidence of the successful biologic-free remission, will be presented to discuss the optimum strategy for the best use of TNF inhibitors.

ES7-3

Prediction in RA

Désirée M van der Heijde
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Prediction in RA can be defined in various ways: to know predictors for bad outcome to be able to select patients who are most in need to start effective treatment; to predict before treatment start which patient will respond to which treatment to select the treatment that has the best risk-benefit for the particular patient; to predict which patient will respond ASAP after the treatment has started to be able to decide in which patient to continue treatment. There are several factors associated with bad outcome: RF and/or anti-CCP; high disease activity; and early occurrence of erosions. However, these all function well at a group level, but not at an individual patient level. Therefore prediction models have been built to combine several factors. An example is to predict fast radiographic progression in the BeSt trial (Visser et al. Ann Rheum Dis 2010;69:1333). Reliable factors to predict which patient is responding best to which treatment before the start of the therapy are lacking. Also predicting a good response to treatment after treatment start has proven not to be very successful. Therefore there is recently more emphasis on prediction of non-response: not reaching the desired state. An example of such a state is low disease activity, remission or no radiographic progression. This has been applied to the RAPID 1 trial (van der Heijde et al. J Rheum 2012;39:1326) and to the REALISTIC study (Weinblatt et al. EULAR 2012. SAT0145). In both studies it was clear that patients who do not respond fast (<6-12 weeks) with a certain change in the level of DAS28 are very unlikely (<5% probability) to achieve a state of low disease activity after one year. So you know early after start of treatment in which patient treatment can be stopped if low disease activity is the aim of your treatment. This is very advantageous in patient management to be able to switch fast if necessary.

ES8

Rheumatoid Hand Surgery 2013

Keiichiro Nishida

The needs for hand surgery among patients with rheumatoid arthritis have been increasing even in the biologic era. The theme of the current symposium is "Surgical techniques and trouble shooting for standard rheumatoid hand surgeries". In this symposium, Dr. Ishikawa will talk about "Artificial finger joint arthroplasty of metacarpophalangeal joint", including surgical indication, long-term outcome, techniques for revision surgery. "Wrist arthroplasty" will be presented by Dr. Nakagawa, in focus with indication and surgical technique of partial wrist arthrodesis. Finally, Dr. Iwamoto will talk about "Finger joint arthroplasty", especially for Swan-neck deformity. The lecture includes the simultaneous management of MP and DIP joint deformity. Not only expert for hand surgery, young orthopaedic surgeons, rheumatologists, physical and occupational therapists are all encouraged to join us for deep and fruitful discussion.

ES9-1

Treat to Target in Daily Clinical Practice. The DREAM experience

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Objective. There is strong evidence from clinical trials that a 'treat to target' strategy is effective in reaching remission in rheumatoid arthritis (RA). However, the question is whether these results can be translated into daily clinical practice and clinical remission is a reachable target indeed. The study aims to investigate whether in early RA a treatment strategy aiming at Disease Activity Score (DAS) 28 <2.6 is more effective than 'usual care' treatment for reaching clinical remission after 1 year. Methods. Two early RA inception cohorts from two different regions including patients who fulfilled the American College of Rheumatology criteria for RA were compared. Patients in the tight-control cohort (n=126) were treated according to a DAS28-driven step-up treatment strategy starting with methotrexate, addition of sulphasalazine (SSZ) and exchange of SSZ by anti-tumour necrosis factor in case of failure. Patients in the usual care cohort (n=126) were treated with methotrexate or SSZ, without DAS28-guided treatment decisions. The primary outcome was the percentage remission (DAS28<2.6) at 1 year. Time to first remission and change in DAS28 were secondary outcomes. Results. After 1 year, 55% of tight-control patients had a DAS28<2.6 versus 30% of usual care patients (OR 3.1, 95% CI 1.8 to 5.2). The median time to first remission was 25 weeks for tight control and more than 52 weeks for usual care ($p<0.0001$). The DAS28 decreased with −2.5 in tight control and −1.5 in usual care ($p<0.0001$). Conclusion. In early RA, a tight control treatment strategy aiming for remission leads to more rapid DAS28 remission and higher percentages of remission after 1 year than does a usual care treatment.

ES9-2

T2T-based treatment strategy in order to achieve ultimate goal in rheumatoid arthritis

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Conflict of interest: Yes

Treat to Target (T2T) aims to integrate clear outcome target

and tight disease control for rheumatoid arthritis (RA) in standard practice. Now it is widely accepted and expanded to more than 65 countries across the globe. However, the WEB survey for implementation of T2T in daily clinical practice in Japan has revealed a challenge of T2T-based routine practices, bacause of lack of time, resources and understanding not only by physicians, but also by RA patients. This implys that we need to overcome the issues in order to get T2T real in the practice. The T2T strategy defines that treatment should be adjusted every 3 months until the desired treatment target is reached. It is important to evaluate outcome by appropriate composite measure at appropriate time, by which ultimate therapeutic goal can be achieved. In modern treatment strategy for RA, methotrexate (MTX) is essential and first line drug, particularly in RA patients with poor prognostic factors. HOPEFUL 1 study for MTX-naïve early RA patients demonstrated that progression of joint destruction after 6-month treatment with MTX+placebo could not be reversed by delay addition of adalimumab, underscoring the initial treatment strategy in early RA. Actually, sub-analysis of PREMIER study reported that the DAS28 score in MTX group at 3 months successfully predicted the progression of joint destruction at 6 months. This is also confirmed in HOPEFUL 1 study, adding further evidences to support T2T strategy. Up to the initial evaluation in 3 months after starting MTX, rapid dose escalation strategy is recommended by EULAR. This first 3 months is a very important period for RA treatment to prevent subsequent radiographic progression of joint destruction. Given these recent studies in RA treatment, we will discuss how we should evaluate outcome and achieve ultimate goal in real world.

Annual Course Lecture

ACL1

Medical management of rheumatoid arthritis with biological agents

Tsutomu Takeuchi
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Conflict of interest: Yes

The biological agents that we can use for the patients with rheumatoid arthritis (RA) in Japan are 7 agents, including 5 TNF-targeted (infliximab, etanercept, adalimumab, golimumab and certolizumab-pegol), one IL-6 receptor targeted (tocilizumab) and one T cell targeted agent (abatacept). While the targets and even products are same, the route of administration such as intravenous or subcutaneous can be selected or dose and intervals can be changed. In this seminar, I will review the basis how to maximize the efficacy of biologics and comprehensively discuss which targets should be selected in individual patient based on the recent head to head trials and circulating cytokine level data. In addition, I will discuss the rationale to determine the dose and interval of the biologics, showing the data from RISING, JESMR, GO-FORTH and GOMO-study. For safety, on target risks, particularly severe infection/opportunistic infection, and unique adverse events to biologics such as infusion reaction and immunogenecities would be discussed. The experiences of biologics in daily clinical practice are also shown, reviewing the observational cohort data in Japan. Given such fundamental knowledge, timing of introduction of biologics in early RA shown in HOPEFUL-1 study, treatment target, evaluation timing and items will be discussed, introducing the importance of Treat to Target strategy. Finally, biologics-free remission can be touched by a series of Japanese evidences including RRR, HONOR, BRIGHT, ENCOURAGE, DREAM and ORION study. At the end, I will review the recent development of biological agents and discuss the perspectives of the biologics in near future.

ACL2

Juvenile idiopathic arthritis Up-to-Date

Yasuhiko Itoh
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Conflict of interest: None

The therapeutic strategies against childhood rheumatism have been dramatically progressed these years. Especially biological agents contribute to this progress.

ACL3

Differential diagnosis of rheumatic diseases

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Conflict of interest: None

According to the classification of American College of Rheumatology, more than 100 disorders that involve joint, muscle and bone are classified into “rheumatic diseases”. In particular, systemic rheumatic diseases such as connective tissue diseases or collagen vascular diseases are the most important for rheumatologists, since these diseases impair not only joint but also systemic organs. These are also classified into autoimmune diseases, since most disorders are based on immunological abnormality and characterized by autoantibody production. Each disease or even the same disease with different subset reveal different clinical manifestation, course

and prognosis, therefore precise diagnosis and evaluation of pathophysiology are very important to decide the treatment. The 2010 ACR/EULAR classification criteria for rheumatoid arthritis (RA) targets the patients "with more than one definite clinical synovitis (swelling) not better explained by another disease". Therefore, the first step for diagnosis of RA is to rule out various other rheumatic diseases. It is the most important for differential diagnosis of rheumatic diseases to distinguish mono (oligo) arthritis and polyarthritis, and acute and chronic arthritis, when we see patients who complain joint pain. Presence or absence of swelling (arthralgia or arthritis), distribution (small or large joints), symmetricity and deformity are also important clinical information for differential diagnosis. Systemic symptoms, skin manifestation and organ involvements are also indispensable for diagnosis. After detailed patient history and physical examination, serologic and radiologic examination should be done. Antinuclear antibody, rheumatoid factor, anti-citrullinated protein antibody and other disease-specific marker autoantibodies are very useful to diagnosis and differential diagnosis of systemic rheumatic diseases. However, we should realize their specificities and sensitivities of these serologic markers.

ACL4

Social Health Insurance Systems Related to Rheumatic Diseases

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Conflict of interest: Yes

Social insurance systems is now an important issue how to correct the huge healthcare expenditure arising from rapid aging of the population and the increase in the number of patients receiving expensive advanced treatments. As far as treatment of rheumatic diseases is concerned, the increase in the use of biologics has been causing a sharp increase in healthcare expenditure. However, if tight control of rheumatic diseases, beginning at early stages, enables the patients to continue job, housework, etc., the loss of work force due to the disease may be reduced. Treatment with biologics involves high expenses as a problem. However, if selection of patients and the timing of use are appropriate, biologics can provide a very excellent means of treatment also in terms of cost effectiveness. At the same time, attempts should be made to supply less expensive treatment through combined use of DMARDs such as MTX or generic drugs. Rheumatic diseases often develop when patients are busy working, making housework, caring for infants/small children and so on. Patients with this kind of disease tend to have difficulty continuing their job or housework, necessitating assistance of various kinds. Utilization of social insurance systems to reduce the economic burdens and anxiety of patients is very important so that patients can continue receiving the treatment needed. The current systems involve some unfair aspects (e.g., large differences in the amount of out-of-pocket expenses among different local communities), and it is inevitable that the services enjoyable by patients differ depending on the attending physicians. Physicians providing treatment of rheumatic diseases are therefore required to have sufficient knowledge about social insurance systems. It is also important for physicians to attempt providing treatment at lower expenses.

ACL5

Lung complications of rheumatoid arthritis patients - in the era of biologics treatment

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Conflict of interest: None

Methotrexate and biologics are used in rapidly growing number of patients with rheumatoid arthritis (RA),with good control of symptoms and disease progression. Yet adverse events, especially respiratory diseases have emerged as major obstacles against the safe execution of this therapy. They comprise infection and interstitial lung disease (ILD), the former of which we will discuss in detail, because they are treatable. Pulmonary infections in RA patients are related to the underlying disease. Among those, airway diseases and chronic ILD are important. Bronchiectasis (BE) has been attracted attention more and more recently. Many researchers have reported high incidence(30~40%) of bronchiectasis in RA patients, utilizing HRCT. It is postulated that persistent and excess inflammation in the bronchial wall is the pathogenic factor of BE. It is now being recognized as one of extra articular manifestations of RA. Bacterial pneumonia, when occur on the basis of BE, is difficult to treat because causative organisms are often different to the ordinary community acquired pneumonia. Excess occurrence of tuberculosis (TB) and non-tuberculous mycobacteriosis (NTM) have been noted as another serious adverse events of not only in TNFα blocking therapy but also IL-6 inhibitor use. TB is now well controlled through screening for latent infection prior to the beginning of therapy and prophylaxis. As for NTM, the situation is complicated. Because of difficulty of treatment, biologics are generally prohibited for RA patients with this disease. Recent researches revealed fairly good prognosis of patients with slowly growing mycobacteria, such as M.avium. *Pneumocystis* pneumonia (PCP) is now the most serious complication of novel immunosuppressants, including MTX and biologics. Its diagnosis and treatment is often difficult in RA patients. but on the conquest of such hurdle, good prognosis can be accomplished.

ACL6

Treatment Starategy of Rheumatolid Arthirtis for Japanese Patients

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Conflict of interest: Yes

Personalized medicine is imperative to accomplish satisactory disease control and quality of life without substantial risk of adverse event in rheumatoid arthritis. Initial treatment plan is made based on duration of the synovitis before treatment, prognostic factors of joints such as pre-existing bone erosion and anti-CCP antibody positivity, disease activity, comorbid condition such as interstitial lung disease, patient age and social situation which affect urgency of establishing remission, etc. Disease modifying antirheumatic drugs (DMARD) are sorted into conventional oral DMARD and biologic DMARD. Oral DMARD monotherapy, combination of oral DMARDs, and biological DMARD with or without oral DMARD can be options. After remission of rheumatoid arthritis is achieved, de-escalation of DMARD can be an issue to discuss with patients. Careful de-escalation and prepared plan of re-escalation in case of flare are recommended.

ACL7

Required Advance in Surgical Treatment for Patients with Rheumatoid Arthritis

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Conflict of interest: Yes

The advent of biologics has revolutionized the management of rheumatoid arthritis (RA). It has also brought at least three changes in the surgical strategy for RA. The reduced disease activity could

decrease the fragility in bone and soft tissue resulted in easy procedure and handling in delicate surgery, and improve the preoperative anemia. The remission of RA also could provide the patients with the motivation for further functional or cosmetic recovery and for the better quality of life. One of changes is that we need the out-of-box strategy for the further improvement of function. However, notwithstanding these advances, disease control is still inadequate in many patients with RA. It means the increase in variation of surgical techniques and indication. The need both for the surgical skill and diagnostic skill of progressed disability of patients is subsequently enhanced. This is another change after the advent of biologics. On the other hand, biologics have the potential for the serious adverse effects including infection. So, patients treated surgically under biologics should be carefully followed both in perioperative and long-term postoperative period. The skill for protection against and early detection of surgical site infection is required more than ever before. That is the third one. Most of joint surgeries used for patients with RA developed many decades or one hundred years ago and the indication for them are established during the era without biologics. Required advance in surgical treatment in RA is the surgical techniques and indication adequate for the recent advance of total management of RA, and the understanding abovementioned three changes after biologics. Specifically, we need the skill for shoulder and ankle arthroplasty, hand surgery for functional and cosmetic recovery and metatarsal head preserving forefoot surgery etc. in treatment of RA, besides the pharmacotherapeutic skill succeeding in sustained control of RA activity.

ACL-LS

Methotrexate (MTX) therapy for rheumatoid arthritis (RA)- The dawn of the high-dose era-

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Conflict of interest: Yes

A recent paradigm shift of the treatment of RA is to aim for remission by the T2T strategy, using DMARDs as early as possible in the disease process. Among the DMARDs, MTX is considered to be the anchor drug and should be used first in patients with active RA. In Japan, an increase in dose of MTX up to 16mg/week was approved in February 23, 2011, as well as the use for initial choice of RA therapy and the MTX therapy for RA finally entered in the high-dose era. Now, more than 85% of RA patients at Tokai University Hospital receive MTX by monotherapy or combination with other DMARDs or biologics and more than half of the patients receive MTX with doses beyond 8mg/week. If MTX is used in adequate doses up to 16mg/week, higher efficacy and remission rate will be obtained. However, we have to be apprehensive for an increase in dose-dependent increase in serious adverse events. Since MTX was approved in Japan, 465 patients who died during MTX therapy by adverse events have been accumulated until December 2011. Cytopenia, pneumonitis, infections, and lymphoproliferative disorders are major fatal side effects. In addition, a certain number of case of fulminant hepatitis by the reactivation of HBV and tuberculosis during MTX therapy was reported. Therefore, it is important to decide a starting and maximum dose and the speed of dose escalation while considering the risk benefit ratio. The revised edition of the JCR recommendations for the use of MTX in RA was published in March 2011. THe recommendations consist of 9 parts, including indication, how to use, screening and monitoring, safety considerations and so on. Now, the Post Marketing Surveillance is ongoing to elucidate the efficacy and safety of high-dose MTX therapy for RA and the results of the surveillance will provide new evidence. In this lecture, I disucuss the practical points for the use of high-dose MTX on the basis of the JCR recommendation and review the latest information regarding efficacy and safety.

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