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ABSTRACT SUPPLEMENT

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JAPAN COLLEGE OF RHEUMATOLOGY ABSTRACT SUPPLEMENT

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ABSTRACTS

President's Address

Past, Present, and Future of Rheumatology

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Conflict of interest: None

Rheumatoid arthritis (RA) is derived from the term 'rheum' in Greek at the first century AD. Most of the rheumatic diseases reported in those days were gout. The first description of RA was observed in 17th century. The term 'collagen disease' and 'rheumatology' were introduced in 1940s. The progress of immunology identified pathogenic cells, i.e. lymphocytes, in RA, and the introduction of molecular biology clarified a significant role of inflammatory cytokines in the pathogenesis of RA. Recent advances encompasses to the identification of disease susceptibility genes and environmental factors including smoking. Initial treatment strategy was 'pyramid' treatment starting with NSAIDs. Its goals were improvement of pain and activity of daily living. However, introductions of methotrexate (MTX) in 1980s and biologics in late 1990s have caused a paradigm shift. Treatment goal is now remission, and not only clinical, but also structural and functional remission can be achieved with early diagnosis and treatment. New classification and remission criterion were developed in 2010 and 2011, respectively, and 'tight control' and 'treat-to-target' are the new concept of the RA treatment. However, there are many 'unmet needs' in the treatment of rheumatic diseases. Adverse effects of biologics such as infection, and high costs are still problematic, and low molecular compounds with low costs and high efficacy with safety are being expected. Corticosteroids with or without immunosuppressive agents are still basic strategies and no good molecular targets have yet been found in other rheumatic diseases such as lupus. A drug lag, i.e. a delay in the approval of new drugs and regional gap of health care of RA are the issues to be solved in Japan, but high qualities of clinical trials, postmarketing surveillance are the advantages of Japanese rheumatologists. The past, present and future of rheumatology in Japan will be discussed in this presentation.

Symposium

S1-2

Evidence obtained from the global studies with biological agents

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Conflict of interest: Yes

In 1993, open label study using a chimeric anti-TNFα monoclonal antibody, infliximab, has attracted the Rheumatologist for its dramatic effect in the patents with Rheumatoid Arthritis (RA). Placebo controlled double blind study with infliximab further confirmed and established the excellent clinical efficacy in RA treatment, providing the historical milestone for biological era in RA. Not so long after these studies, TNFR2-IgGFc fusion protein, etanercept has been approved in RA in 1998, followed by infliximab in 1999, and adalimumab, golimumab and certolizumab-pegol. Studies focusing on the established RA with inadequate response to MTX such as ATTRACT study demonstrated the excellent efficacy and manageable tolerability, followed by those on the early RA with ASPIRE, ERA, PREMIER studies. TEMPO and PREIMIER studies also demonstrated the superior clinical and structural efficacy when used combination with MTX. Strategic comparison study (BeST study) has been established the significance of changing the treatment very 3 months according to the disease status and at same time biologics can be stopped in about half of the patients when clinical treatment target has been achieved in the consecutive two visits in early RA. Among the global implementation process of the "Treat to Target", OPTIMA trial is now going on for obtaining supportive evidence for it. PRESERVE and CERTAIN trails has also been going for the RA with moderate or even low/moderate disease activity. In contrast, IL-1ra had not been successful as like those with anti-TNF, whereas humanized monoclonal antibody against IL-6 receptor initially developed in Japan has been appreciated and accepted its surprising efficacy, comparable to those with anti-TNF. Now several studies using agents targeting against IL-6/IL-6R are running. Apart from the anti-cytokine biologics, enough evidence for rituximab, a chimeric anti-CD20 on B cells and abatacept, CTLA-4-IgFc fusion protein has been accumulated. I would like to introduce these collective information from studies abroad and discuss the future perspective of the biologics.

S1-3

Paradigm shift of the treatment of rheumatoid arthritis by biologics in Japan

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Conflict of interest: Yes

Rheumatoid arthritis (RA) is a representative autoimmune disease characterized by chronic and destructive inflammatory synovitis that causes severe disability and mortality. A new concept of treat-to-target is emerging in treatments of RA, whereby patients are treated according to prespecified goals, such as clinical remission. Conventional DMARDs, most commonly MTX, remain the cornerstone of RA treatment. Patients for whom MTX produces an inadequate response are treated with biological agents targeting TNF and IL-6. Accordingly, four TNF-inhibitors, infliximab, etanercept, adalimumab and golimumab, an IL-6 receptor inhibitor tocilizumab and a T-cell costimulatory signal inhibitor abatacept are domestically commercialized. In addition to clinical examinations, post-marketing nation-wide surveillance, multi-central retrospective studies and post-marketing clinical studies have been inten-

sively performed in each biologics and a large amount of clinical evidence has been accumulated. For instance, the combined use of a TNF inhibitor or IL-6 inhibitor and MTX has produced previously unseen significant improvements in clinical, structural and functional outcomes and has revolutionized the treatment goal of RA to clinical remission. Accordingly, maintenance of clinical remission makes long-term structural and functional remission possible. Furthermore, after the maintenance of remission biological-free remission can be achieved in some patients. However, we have to pay special attentions that rheumatologists also have to treat, manage and prevent patients from disadvantage timely and appropriately when and/or before adverse events due to the use of biologics are occurred. Thus, we have to realize that whole body management of patients is prerequisite when we use biologics for the treatment of RA.

S1-4

Merits and demerits of biologic treatment for RA

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Conflict of interest: Yes

It has passed nearly 10 years since the first biologics was introduced for RA in 2003, and the 10 years from 2003 was the decade of biologics. Discussion on the wide variety of changes in this decade is crucial. Merit 1: RA treatment has been improved. Introduction of biologics enabled to treat patients who were resistant to conventional therapy. Remission has become a realistic goal, and patient's outcome has improved. Patients has become feeling better to their future. Merit 2: Detailed examination of patients has become required. Daily practice of RA patients has improved and rheumatologists are paying more attention to drug safety. Merit 3: Rheumatology has become popular. Number of attendee to JCR has greatly increased, many study groups have been established, and academic activity in rheumatology has become active. Merit 4: Clinical and epidemiological research in rheumatology has become active. After starting all case PMS of biologics, rheumatologists recognized the importance of clinical research. Many articles have been accepted in the top-ranked English written journals. Demerit 1: Incidence of infection has increased. All biologics have immunosuppressive agents, and as the consequences, patients are susceptible for infections. Demerit 2: Large financial burden was generated. RA patients as well as government have to pay to the expensive drugs, and it is a big burden to the national health care system. Demerit 3: Specialization of RA treatment has been accelerated. Since physicians are requested to have detailed knowledge in using biologics, some general practitioners are not favor to treat RA patients. Demerit 4: Excessive hope is generated. Biologics is a hopeful therapy but excessive hope may cause misleading. The term 'drug free remission' is used too easily. It is quite valuable to inspect what has happened in the last 10 years after the introduction of biologics to consider what we should be in the next ten years in the management of RA.

S2-1

Pathology of interstitial lung disease with juvenile dermatomyositis

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Conflict of interest: None

Juvenile dermatomyositis (JDM) display differing prevalence of features in comparison with adult-onset dermatomyositis. The average age of onset is 7-years-old in JDM and 40 to 60-years-old in adult DM. In general, JDM have greater likelihood of calcinosis and less association with interstitial lung disease and malignancy. Muscle and skin biopsy in JDM shows the plasmacytoid DCs (pDC) are predominant components. pDC are located in perivascular legion of inflamed mescle and skin. Type I interferon, which are produced by pDCs, are important in the pathogenesis of JDM. A recent report demonstrated a correlation between serum IFNa activity and muscle enzyme activity in JDM patients. Because of the few numbers of reports about interstitial lung disease (ILD) in JDM, little is known about the pathogenesis of ILD/JDM. We retrospectively reviewed the clinical information and laboratory data of severely ill cases who were diagnosed as defined and probable JDM. There were 12 ILD cases. Six cases of them died and the major cause of death of JDM in Japan were ILD. The lung pathology of the example of death is all the examples diffuse alveolar damage, suggested existence of prominent blood vessel inflammation. The death cases had mild grade of skin and muscle disorder and higher levels of serum AST, ALT and KL-6. Serum CK levels were lower than those of the recovery groups. The dead cases tend to have the high levels of serum BAFF and IL-18, however, a correlation between serum IFNa levels and severity of ILD. Moreover, in almost cases of JDM/ILD, anti-MDA5 antibody is positive aand death cases had a tendency with higher levels of that antibody. To reduce the mortality of JDM in Japan, conquest of ILD is improvement. Together with these findings, the pathology of ILD in JDM will be discussed in this symposium.

S2-2

Progress in diagnosis: junenile ideopathic arthritis (JIA)

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Conflict of interest: None

The diagnosis of juvenile idiopathic arthritis (JIA) has traditionally been based on the Durban Criteria since its introduction in 1997, it is now being modified by and benefiting from the recent developments of rheumatology and innate immunology. A new classification criteria for rheumatic arthritis is proposed by ACR/EULAR in 2010, in which the usefulness of the traditional serum factors, anti-CCP antibodies is emphasized. Anti-CCP antibody, which is less frequently seen in patients with articular type JIA than in those with adult-type rheumatic arthritis, is occasionally observed in patients with RF-negative polyarticular or extended oligoarticular JIA, and thus now is considered to be an important prognostic predictive factor of JIA. Several other factors may be promising prognostic predictive factors: CCL5 concentration in the articular fluid is defferent between extended and persistant oligo JIAs, high-frequency HLA allele which are different between oligo- and poly-articular JIAs. Also, recent developments in joint ultrasonography confer a great favor. It has become a simple and precise bedside test for the diagnosis and evaluations of infants with JIA who can not describe their symptoms. Clarifications of the movements of cytokines in systemic JIA are advancing owing to the development of biological medicines. As the cytokines such as IL-6, IL-18, and Heme oxgenase-1 (HO-1) shows higher levels in systemic JIA than in other types, they may be useful in the diagnosis. Gene analyses have become important in differentiating systemic JIA with atypical clinical symptoms from autoinflammatory syndrome. FDG-PET/CT is now used for the diagnosis of fever of unknown origin. Depending on the disease types, JIA not only shows various clinical signs and symptoms but also has a variety of cytokines and gene expressions. Thus, understanding and clarifications of these features will help us for the diagnosis, evaluation of the prognosis and treatment of JIA.

S2-3

Diagnosis of Sjögren's syndrome in children

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Conflict of interest: None

Sjögren's syndrome (SS) is a systemic autoimmune disease involving the exocrine glands, especially the salivary and lachrymal glands. Many patients with SS also suffer from extra-glandular involvement; therefore, early diagnosis and close observation are required. Historically, as the diagnostic criteria for SS emphasized subjective sicca symptoms, many pediatric patients were not diagnosed with SS because there was no indication that they had such symptoms. As sicca symptoms are caused by damage to the exocrine glands, when diagnosing SS it is essential to determine whether the exocrine glands are involved, regardless of whether patients complain of subjective sicca symptoms or not. With the support of the Pediatric Rheumatology Association of Japan and the Japanese Society for Sjögren's syndrome, we have established a working group with the aim of developing diagnostic criteria for SS in children. To date, we have collected data from more than 90 patients. In this presentation, we discuss problems faced in the diagnostic process using three sets of major criteria, the revised Japanese criteria, the European-American Consensus Group criteria and Sjögren's International Clinical Collaborative Alliance (SICCA) criteria, and discuss some proposed criteria for children.

S2-4

Progress in the Treatment of Juvenile Idiopathic Arthritis (JIA)

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Conflict of interest: None

Juvenile idiopathic arthritis (JIA) is a heterogenous disease with chronic arthritis consists of some subtypes such as systemic arthritis, oligo-arthritis and poly-arthritis. Considering the clinical diversity of this disease and importance of early therapeutic intervention, "a proposal for JIA guidance on diagnosis and treatment" was published from the Subcommittee of Pediatric Rheumatology of Japanese College of Rheumatology in 2007. The guidance made a remarkable progress in the treatment of JIA patients in Japan. As to the treatment strategy, the guidance clearly differentiated patients according to subtypes of JIA. The guidance also indicated to use methotrexate (MTX) by 10 mg/m^2/week, the global standard dose in the world, which afterwards lead official approval to use increased dose of MTX up to 16mg/week in RA. The guidance also recommended to use biologic agents by pediatric rheumatologists in patients who were refractory to the initial therapy by 3 months. As a result, numerous novel information as to efficacy and safety of biologics are now accumulating among pediatric rheumatologists in Japan. For example, more than 20% of systemic JIA patients who had been refractory to conventional steroid therapy attained drug-free remission by tocilizumab in our treatment strategy designed by IL-6 kinetics in this subtype. In addition, radiographic analysis on carpal length revealed that the biologic agents can prevent the progression of joint destruction in JIA patients. On the other hand, unexpected psychological health problems are now emerging in adolescent patients who had achieved clinical remission by biologic agents. By presenting the data above in the treatment of JIA, progressions and emerging problems would be discussed.

S2-5

Cryopyrin-associated periodic syndrome (CAPS)

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CAPS including familial cold auto-inflammatory syndrome (FCAS), Muckle-Wells syndrome (MWS), neonatal-onset multisystem inflammatory disease (NOMID), is a rare systemic autoinflammatory syndrome associated with mutations in *NLRP3* gene causing excessive production of interleukin-1beta. Recently, advances in understanding the mechanism of inflammatory response of pediatric rheumatic diseases have made the novel therapeutic drugs. Molecular intervention therapy includes various "molecules" which relate to pathogenesis of the diseases and designs to inhibit specific components of inflammation and immune responses, such as cytokines, chemokines and signal transduction. IL-1 beta blockers, such as anakinra and canakinumab, rilonacept, have been applied to CAPS. In Japan, canakinumab has been approved in 2011. It is significant to consider the understanding of the inflammation condition to be treatment to consider the inflammatory condition of CAPS.

S3-1

The clinical meanings and pathogenetic roles of Myositis-specific autoantibodies and their corresponding autoantigens

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Conflict of interest: None

Recently, many myositis-specific autoantibodies (MSAs) have been reported. They are closely associated with characteristic clinical features of idiopathic inflammatory myopathy (IIM). These target autoantigens play roles in transcription, translation and protein synthesis. To date, the direct association between autoantibody/ autoantigen and pathogenesis of IIM has not been clarified, but several reports suggest their roles in disease initiation and perpetuation. In this symposium, I will focus on two MSAs, anti-aminoacyl-tRNA synthetase (ARS) antibody and anti- Melanoma differentiation-associated gene 5 (MDA5) antibody, and discuss the roles of their corresponding autoantigens in pathogenesis of IIM. Anti-ARS(+) patients show a common clinical manifestation named anti-synthetase syndrome (ASS). Some ARSs not only catalize aminoacylation of tRNAs but also work as chemokines which may cause inflammation. There is a report on a model of IIM following immunization of histidyl-tRNA synthetase, which is recognized by anti-Jo-1 antibody, suggesting the role of ARS in pathogenesis of IIM. Anti-MDA5(+) patients frequently develop acute progressive IP with poor prognosis. Such patients also show cytopenia, hyperferritinemia and elevated serum IL-6 level, suggesting that macrophage activation may plays a role in their pathophysiology. MDA5 is a cytoplasmic molecule which recognizes viral RNA and induces innate immune responses. The finding that MDA5 is one of myositis specific autoantigens is strikingly interesting because many reports have suggested the possible association between myositis and viral infection, in particular Coxsackie B virus. Recently, increasing reports have suggested that SNPs in

MDA5 gene were associated with susceptibility to autoimmune diseases and that the disregulation of MDA5 expression or function may cause the autoimmune pathway. Further investigation on the role of anti-MDA5 or MDA5 in myositis and concomitant interstitial pneumonia is needed.

S3-2

Molecular pathogenesis of interstitial lung disease with idiopathic inflammatory myopathies.

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Conflict of interest: None

Interstitial lung disease (ILD) is frequently refractory and complicated by idiopathic inflammatory myopathies including polymyositis (PM) and dermatomyositis (DM). PM/DM associated with ILD (PM/DM-ILD) was one of the major predictors for prognosis in PM/DM. It is important for clinicians to manage PM/DM-ILD appropriately and to comprehend its pathogenesis sufficiently. The clinical form of PM/DM-ILD was divided to two subsets, rapidly progressive ILD (RP-ILD) occasionally complicated with clinically amyopathic dermatomyositis (CADM) and chronic progressive ILD (chronic-ILD) such as aminoacyl-tRNA synthetase (ARS) syndrome. The pathohistology of ILD included UIP, NSIP, organizing pneumonia and diffuse alveolar damage. Anti-myositis specific autoantibody can predict the clinical manifestations, the response to treatment and the prognosis of PM/DM. The presence of anti-CADM-140 (MDA5) antibody indicates that RP-ILD is complicated with CADM and that the response to treatment is refractory. The presence of anti-ARS antibodies indicates that the response to treatment is relatively good over the short term, although recurrence and chronic progression are revealed in this form. Taken together, the pathogenesis of ILD with PM/DM is heterogeneous and complicated. Unlike myositis in PM/DM, the pathogenesis of PM/DM-ILD has remained unknown. Environmental factors, immunogenetics, the activation of CD8 T-cells in the lung and autoantibodies are associated with the pathogenesis of PM/DM-ILD. We found biomarkers such as ferritin and IL-18 in PM/DM-ILD as well as an association between single nucleotide polymorphisms such as STAT4 and IFIH1 and susceptibility to PM/DM-ILD. In addition, activated alveolar macrophages are implicated in RP-ILD with CADM, which we have confirmed by autopsy. Similarly, alveolar macrophages have a vital role in lung fibrosis with idiopathic pulmonary fibrosis. We will now describe the molecular pathogenesis of PM/DM-ILD by reviewing previous studies.

S3-3

Molecular mechanisms in Polymyositis / Dermatomyositis

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Conflict of interest: None

The inflammatory myopathies (IM) are a heterogeneous group of muscle disorders characterized by proximal and symmetric muscle weakness, variable degree of creatine kinase (CK) elevation, and inflammatory exudates of variable distribution within the muscle fascicle. Based on distinct clinical, histological and immunopathological characteristics, the IM can be separated into four distinct subsets: polymyositis (PM), dermatomyositis (DM), necrotizing autoimmune myositis (NAM) and sporadic inclusion body myositis (sIBM). Among them, sIBM, the most common IM in the elderly, is clinically, histopathologically and pathogenetically distinct from other subsets. From the clinical standpoints, the IM, except for sIBM, may be associated with skin changes, cancer, or collagen disease and may present with circulating myositis-specific/associated antibodies. These clinical or serological characteristics are also useful in the classification of IIM and often correlate with defined IM clinical phenotypes. Muscle pathology provides useful information about path mechanisms of IM. To obtain maximum diagnostic information, proper choice of biopsied muscle, proper processing of muscle including immunohistochemistry, and proper interpretation of pathological findings are essential. Dermatomyositis is a complement-mediated microangiopathy leading to destruction of capillaries, hypoperfusion and inflammatory cell stress on the perifascicular regions. In PM and sIBM, cyto-toxic CD8-positive T cells clonally expand in situ and invade major histocompatibility-I-expressing muscle fibers. The cause of NAM is multifactorial, and the pathological finding of multiple necrotic fibers with scarce inflammation is characteristic. In this review, I aim to provide the fundamental aspects on muscle pathology and the unique patho mechanisms of each subset. I also try to outline recent findings concerning pathogenesis of IM from the aspects of muscle pathology.

S3-4

Pathogenesis of polymyositis/dermatomyositis: dermatological aspects

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Conflict of interest: None

Polymyositis (PM) and dermatomyositis (DM) are autoimmune inflammatory diseases that affect muscle and skin. DM presents characteristic skin rashes, including heliotrope rash and Gottron's papules, that are induced by chronic physical irritations. This phenomenon is called "Kebner's phenomenon". By contrast to clinical cutaneous symptoms, pathological findings in DM are not specific; they resemble to those observed in lupus erythematosus (LE). The pathological findings in DM include liquefaction, mononuclear cell infiltration, and mucin deposition. The majority of cell infiltrates is CD4+ T cells with acitvated phentype. Additionally, macrophages and plasmacytoid dendritic cells are also observed in the skin lesions. Plasmacytoid dendritic cells secrete interferon-alpha and most of T cells express CXCR3. Furthermore, DM typically shows more severe vasculopathy compared with LE. The cutaneous manifestations of DM and their pathogenesis will be reviewed and discussed.

S3-5

Molecular pathology of polymyositis and dermatomyositis

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Conflict of interest: None

We have established C protein-induced myositis (CIM) as a murine model of polymyositis (PM). It is induced readily by a single immunization of a recombinant fragment of myosin-binding protein, C-protein, emulsified with complete Freund's adjuvant (CFA) in C57BL/6 mice. Immunohistochemical analysis and peripheral T cell clonality in PM indicated involvement of CD8 T cells in pathogenesis of autoimmune myositis. Studies on CIM revealed that C-protein-reactive CD8 T cells were definitively en-

gaged in the muscle injury. However, activation of autoreactive CD8 T cells was not enough for development of the myositis, which required activation of innate immunity in the local muscle tissues. Actually, lymph node cells from CIM mice after incubation with C-protein pulsed bone marrow DCs transfered myositis only when CFA or other TLR ligands were injected into footpad of recipient mice. We hypothesized that muscle injury and repair could activate innate immunity of the muscle tissues in PM as a substitute of CFA. To verify this hypothesis, we examined whether bupivacaine injection, which induces muscle necrosis, could trigger autoimmune myositis. We speculated that regenerating muscle fibers could contribute to myositis because myogenic stem cells proliferate and differentiate into muscle fibers and secrete several chemokines in muscle repair. To clarify the role of regenerating muscle fibers in autoimmune myositis, we evaluated their expression of chemokines. We found that muscle injury could trigger infiltration of the autoaggressive T cells. Myotubes differentiated from murine myoblasts and regenerating muscle fibers seen after bupivacaine injection expressed CCL8 and CXCL10. The receptors of these chemokines were expressed by infiltrating cells of CIM. We conclude that regenerating muscle fibers could trigger autoimmune myositis by secreting chemokines that could attract activated autoreactive T cells.

S3-6

Role of mast cells in the pathogenesis of polymyositis

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Conflict of interest: None

Mast cells have long been recognized as the major effector cells in allergic diseases such as asthma, allergic rhinitis, and atopic dermatitis. In addition, recent studies have revealed a new role of mast cells in the pathogenesis of autoimmune disease models including autoantibody-induced arthritis, experimental autoimmune encephalomyelitis, and insulin-dependent diabetes mellitus. While mast cells are located in skeletal muscle, their roles in the pathogenesis of autoimmune skeletal muscle diseases have not been clarified. Recently, a murine model of polymyositis, namely C protein-induced myositis (CIM), has been established by Sugihara et al. CIM has been shown to exhibit similar pathological features to those found in human polymyositis including a massive infiltration of CD8+ T cells and macrophages in the endomysium of skeletal muscles. However, the role of mast cells in the development of CIM remains unknown. To address this issue, we first examined the incidence and severity of CIM in mast cell-deficient WBB6F1-KitW/KitWv mice (W/Wv mice). We found that the incidence and histological scores of CIM were significantly reduced in W/Wv mice as compared with those in wild-type (WT) mice. In addition, reconstitution of mast cells in W/Wv mice with bone marrow-derived mast cells (BMMCs) restored the incidence and histological scores of CIM. These results indicate that mast cells play critical roles in the development of CIM and suggest that mast cells could be possible therapeutic targets in patients with polymyositis.

S4-1

Refractory lupus nephritis

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Conflict of interest: None

Lupus nephritis is one of the important organ involvement of systemic lupus erythematosus (SLE), is complicated with 50~80% of the SLE and controls the convalescence. With class III or IV to accept a proliferative change to a glomerulus, even a large quantity of steroid dosage repeated a recurrence until approximately 30 years ago, and there were many cases it fell into end-stage renal disease (ESRD) in the long term, and to be forced to hemodialysis induction by, and it existed among lupus nephritis particularly to be intractable. Nowadays, treatment of the lupus nephritis divide into two stages called a remission induction therapy and the maintenance therapy, and a group of National Institute of Health (NIH) is assembled in the 1970~80 by combination of steroid and intravenous cyclophospamide pulse therapy (IVCY) having shown that long-term convalescence is good prognosis. Steroid an axis by the induction of remission therapy, and IVCY plays a key role, and it is that use immunosuppressive therapy such as tacrolimus together by the maintenance therapy. However, it is approximately 50% that reach the complete remission in the present when immunosuppressive therapy came to be provided widely, and, as for the case to recur for two years after the induction of remission, there is the report with 30%. In addition, according to the survey by Japanese dialysis medical society, the case to lead to ESRD by lupus nephritis in this country does not necessarily decrease with around 300 in these ten years. In recent years biological agents attracts attention as new treatment of SLE including lupus nephritis from such a thing for unmet medical needs of the lupus nephritis. In this symposium, I discussed possibility for unmet medical needs of the lupus nephritis from an existing immunosuppressant and a clinical trial of some biological agents.

S4-2

Refractory neuropsychiatric syndromes of systemic lupus erythematosus (NPSLE)

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Conflict of interest: None

Symptoms in NPSLE are extremely diverse, ranging from depression, psychosis, and seizures to stroke. Without specific diagnostic tools, the diagnosis of NPSLE is very difficult. Despite reports of associations between NPSLE and specific autoantibodies (anti-ribosomal P and NMDAR2, etc), the mechanism in which these autoantibodies occur NPSLE has not been identified. The association between the intrathecal IFN-α production and NPSLE has been reported. Immune complexes (IC) formed by autoantibodies in the CSF of NPSLE produced significantly higher IFN-α in a bioassay containing plasmacytoid dendritic cells. IC levels in the CSF of NPSLE were significantly higher than in non-NPSLE. But significant association between IC levels in the CSF and IFN-α levels in the CSF was not shown. It has been unclear whether the intrathecal IFN-α influence the appearance of NPSLE. Cytokine/chemokine levels have been measured in the CSF of NPSLE as the diagnostic tools, the activity markers and the pathogenetic factors. Recently we measured 28 kinds of cytokines/chemokines in the CSF and serum samples which were obtained at the same time. In NPSLE patients, the levels of IL-6, IL-8, IP-10, MCP-1 and G-CSF were higher in the CSF than in the sera. Furthermore, these levels in the CSF of NPSLE were significantly higher than in non-NPSLE, respectively. Importantly, the largest differences occurred in CSF IL-6 levels. In NPSLE, the intrathecal levels are not influenced by the serum levels, indicating that the production of IL-6, IL-8, IP-10, MCP-1 and G-CSF might take place in CNS. These measurements, especially IL-6 might be useful for the diagnosis of NPSLE. The therapy including high dose steroids, intravenous pulse steroid and/or cyclophosphamide has been employed in NPSLE. But the prognosis of NPSLE has not been improved. The effectiveness of biological agents such as rituximab in NPSLE pa-

tients has been reported. The use of biological agents might fulfill the unmet medical needs.

S4-3

Unmet needs in polymyositis/dermatomyositis

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Conflict of interest: None

Although patient registry in Ministry of Health, Labour and Welfare was hard to analyze, recent digitalization of the patient data allowed us to investigate profiles of Japanese polymyositis (PM) / dermatomyositis (DM) patients. We now estimate that patient population of PM/DM is approximately 17,000. The ratio of males to females is 1:3. Peaks of the onset age are 5-9 and 50-60. Half of the treated patients seem to have muscle weakness. Forty % accompanies interstitial pneumonitis (IP). While corticosteroid is the primary medicine, 40% are treated with immunosuppressants. The Japanese version of the diagnostic criteria has not been renewed for twenty years, and can not include amyopathic DM. International efforts have been made to establish a new criteria. Immunosupressants approved here are azathioprine and cyclophosphamide although calcineurin inhibitors and methotrexate have been used widely as off labels. Biological agents have been tried recently but have not proven effective. They include rituximab and tunmor necrosis factor inhibitors. Tocilizumab and abatacept will be in the next line for clinical trials. Muscle weakness after the treatment could be due to steroid myopathy. We have tried to inhibit steroid myopathy in an animal model of PM. It has been accepted that concurrent initiation of steroid and immunosuppressants: calcineurin inhibitors alone or with cyclophosphamide are necessary to treat acute progressive IP. Although serum ferritin level and CADM-140 autoantibody and anti-amionoacyl tRNA synthase antibodies are useful to predict the course of IP, test for Jo-1 antibody is the only approved test. Lastly, we did not have good models for PM/DM until we developed a C-protein induced myositis as a model of PM. It served to explore therapeutic agents. We still need a model for DM.

S4-4

Pulmonary arterial hypertension

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Conflict of interest: Yes

Pulmonary arterial hypertension (PAH) had been thought to be an intractable disease for a long time. Recently, several new drugs were developed and the efficacy of them has been established. They are an endothelin receptor antagonist, a phosphodiesterase 5 inhibitor, and prostanoids. PAH had been rare complication with connective tissue disease, however, by recent reports it is believed not to be rare. Especially, mixed connective tissue disease (MCTD), systemic sclerosis (SSc), and systemic lupus erythematosus (SLE) are the connective tissue diseases frequently associated with PAH. In the present symposium, I would like to discuss the strategies of the treatment for PAH involved in those three diseases. I believe the best treatment might be different among three diseases.

S4-5

Thrombotic microangiopathy associated with connective tissue diseaes

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Conflict of interest: Yes

Thrombotic microangiopathy (TMA) is a clinical syndrome, comprised microangiopathic hemolytic anemia, destructive thrombocytopenia and multi-organ failure due to microthrombi. Connective tissue diseases are the most common underling diseases for TMA, and there would be two types of TMA associated connective tissues diseases. One is called Thrombotic Thrombocytopenic Purpura (TTP) and the other non-TTP. In conditions of high shear blood flow, ULVWF multimers secreted from stimulated endothelial cells. They are then cleaved by ADAMTS13 between Tyr1605-Met1606 residues located within the A2 domain. As a consequence of ADAMTS13 inhibotors (anti-ADAMTS13 autoantibodies), ULVWF multimers are not cleaved after their secretion from endothelial cells, but remain anchored to the cells. Passing platelets adhere to the ULVWF strings anchored to P-selectin to form large, potentially occlusive, platelet thrombi. The use of plasma exchange for TTP is reasonable, as this procedure removes ULVWF and replaces the lack of the protease in the congenital forms, leading to the significant improvement of the prognosis. On the other hand, non-TTP TMA is still one of the most difficult diseases to be treated among all complications associated with connective tissue diseases. Systemic lupus erythematosus (SLE) is the most common underling disease of TMA. We organized an epidemiological study for TMA associated with SLE. From 19 lupus referral centres, 27 cases with TMA were identified for three years among 6,392 patients with SLE. The prevalence of TMA-SLE was 0.14% per year, with the average age of onset 42±14 years old. The time between SLE onset and TMA was 10±7.5 years, and 15 cases (56%) had active lupus. Seven out or 27 cases (26%) died of TMA, and the survivers were younger and more platelet count compared with the dead patients. We will discuss what is the better management of TMA complicated with connective tissue diseases.

S4-6

Vasculitis-ANCA associated vasculitis-

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Conflict of interest: None

Anti-neutrophil cytoplasmic antibody (ANCA) associated Vasculitis (AAV) includes microscopic polyangiitis (MPA), granulomatosis with polyangiitis (GPA, Wegener's granulomatosis) and Churg-Strauss syndrome. Early diagnosis and development of the treatments had led to improvements of the prognosis. Nevertheless, there are still unmet needs in the AAV. Many problems still remain unsolved to improve the prognosis of AAV. 1) The role of ANCA, MPO, anti-heat shock protein antibody, neutrophil extracellular traps (NETs) and anti-lamp2 antibody in the field of aetiopathogenesis, 2) Sensitive biomarkers that reflect disease activity, also during smouldering disease, are needed. Whether or not serial rise in MPO-ANCA titer at remission stage can predict future relapse of MPO-ANCA-AAV? 3) ANCA measurement system including capture ELISA. 4) Several prospective, randomized controlled studies to determine the efficacy and safety of the new immunosuppressive treatments for AAV are ended and reported, in Europe and North

America. However, the clinical characteristics and the effect of immunosuppressive treatments of AAV have regional and ethnic differences. The most common AAV in Japan is MPO-ANCA positive MPA and half of the patients with GPA have MPO-ANCA. One of the most common causes of death is infection during immunosuppressive treatment. Recently, in Japan, intravenous immunoglobulin therapy for steroid-resistant nervous disorder of CSS was covered by national insurance. Cyclophosphamide and azathioprim for vasculitic syndromes were also covered it. We will discuss recent advances in the pathogenesis, the way of early diagnosis and new treatments for AAV.

S5-1

Pathological diagnosis of pulmonary manifestations of connective tissue diseases

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Conflict of interest: None

Pathological features of connective tissue diseases (CTD) are variegated, showing interstitial lung diseases (ILD), airway disease, pleural and vascular changes. In this symposium, pathological characteristics of RA, SJS, PM/DM, and SSc are presented. 【CTD-ILD】 Pathological diagnosis of CTD-ILD has been applied by international consensus statement of idiopathic interstitial pneumonias (UIP, NSIP, OP, DAD, etc). However, it is often difficult to apply only one histological pattern in the case of CTD-ILD. Thus, the description of the primary and secondary lesion in each case is practical for therapeutic indication. Surgical lung biopsies of RA reveal predominant UIP and NSIP with secondary lesion of OP and DIP. SJS reveals NSIP, OP and lymphoproliferative disorders. PM/DM often shows NSIP, OP, and acute lung injury. SSc reveals also NSIP, UIP and OP. CTD-UIP cases reveal remarkable interstitial inflammatory cell infiltration, increase in lymphoid follicles, and low frequency of fibroblastic foci, compared with those of IPF/UIP. Autopsy lungs demonstrate small honeycomb changes with remarkable traction bronchiectasis in the lower lobe of CTD-UIP cases. CTD-ILD cases are often complicated with acute exacerbation and opportunistic infection, which are the direct cause of death.【Small airway disease】 RA and SJS often reveal follicular bronchiolitis, nonspecific cellular bronchiolitis, obliterative bronchiolitis and bronchiectasis.【Vascular changes】 Perivascular collagen deposition, pulmonary hypertension, and alveolar hemorrhage are observed. 【Pleural lesion】 Fibrous thickening of visceral pleura and active pleuritis occur. 【Present problem of CTD-ILD】 Most of NSIP cases are classified as undifferentiated CTD (Kinder, 2007), and lung dominant CTD (Fischer, 2010), and autoimmune-featured ILD (Vij, 2011) have been proposed. Thus, clinico-radiologic-pathologic reevaluation is necessary for the cases with only pulmonary manifestation and ILD preceding definite CTD.

S5-2

Imaging evaluation of lung lesion of rheumatic diseases

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Conflict of interest: None

Lung complication is one of the most important complications in patients with rheumatoid arthritis (RA), because lung complication may determine the prognosis of RA patients. The prognosis of interstitial pneumonia seems to be better than that of idiopathic interstitial pneumonia of same pattern, but prognosis of nonspecific interstitial pneumonia (NSIP) pattern and usual interstitial pneumonia (UIP) pattern is not so different in interstitial pneumonia in RA (RA-IP). Some differences of patterns are observed in types of collagen vascular diseases. RA shows varying types of lung lesions; chronic interstitial pneumonia (CIP) with NSIP, UIP and less commonly desquamative interstitial pneumonia (DIP) pattern, organizing pneumonia (OP), diffuse lymphoid hyperplasia (DLH), bronchiolitis, necrobiotic nodules and so on, although interstitial pneumonia in collagen vascular disease patients is most frequently NSIP pattern in general. Concerning acute onset lung injury, OP and acute exacerbation of CIP is relatively common, but *de novo* rapidly progressive interstitial pneumonia is rare. Differential diagnoses of acute-onset lung complication in patients with treating RA patients include infection and drug induced lung injury (DLI). Recent wide use of TNF inhibitors may change the situation; proportion of infectious diseases has been increased. Among infectious diseases most frequent form is bacterial pneumonia. In patients treated with TNF inhibitors and mesothrexate (MTX), pneumocystis pneumonia (PCP) and tuberculosis is important. PCP shows bilateral diffuse or widespread patchy ground glass opacities on CT, it seems to be impossible to differentiate PCP from DLI solely based on imaging findings. It is mandatory to integrate clinical, imaging, laboratory and pathological findings in order to make a precise differential diagnosis between acute-onset lung complication of RA itself, infectious diseases including PCP, and DLI.

S5-3

Interstitial pneumonitis in polymyositis/dermatomyositis patients: diagnosis and treatment

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Conflict of interest: Yes

Interstitial pneumonitis (IP) is a common complication of polymyositis (PM) and dermatomyositis (DM). IP develops simultaneously with myositis in the majority of patients, but precedes or follows the onset of myositis in the minority. Clinical course and prognosis varies by patients, ranging from those in whom IP remains asymptomatic and hardly progresses to those in whom IP progresses rapidly over weeks and has very high short-term mortality. The latter patients are commonly unresponsive to corticosteroids, an only approved drug for this disease, but evidence suggesting that the early use of immunosuppressive drugs could improve its prognosis has accumulated over years. Though the clinical course is difficult to be predicted early after the onset, several factors associated with poor prognosis have been identified, such as DM or amyopathic DM, serum CPK within normal range at the onset of IP, presence of anti-CADM-140 antibody in serum, serum KL-6 above 1,000 U/mL, elevated serum ferritin levels, presence of consolidation or ground-grass opacities in CT, and lung biopsy showing diffuse alveolar damage. Patients with acute or rapidly progressive IP or whose prognosis is predicted poor based on the presence of these factors should thus receive initial treatment regimen that includes high-dose corticosteroids and immunosuppressive drugs. Cyclosporine, tacrolimus, and cyclophosphamide are used commonly in these settings based primarily on small retrospective reports, and thus prospective clinical studies are needed to evaluate the efficacy and safety of the aggressive initial treatment with corticosteroids and immunosuppressive drugs and to evaluate comparative efficacy and safety of immunosuppressive drugs against each other. Further advance in our understanding of the mechanism underlying the inflammation and excessive fibrosis in this disease is expected to identify cellular or molecular targets for more effective treatment and, ultimately, for better prognosis.

S5-4

Pulmonary manifestations in ANCA-Associated Vasculitis

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Conflict of interest: None

Microscopic polyangiitis (MPA), granulomatosis with polyangiitis (WG) and eosinophilic granulomatosis with polyangiitis (Churg-Strauss syndrome) are included in ANCA-Associated Vasculitis (AAV). Lung lesion is a very common and important clinical features in AAV. In MPA, diffuse alveolar hemorrhage and pulmonary fibrosis (PF) are the most frequent manifestations. Our recent studies on the HRCT findings in 32 PF patients associated with MPA demonstrated high frequency of UIP, fibrotic-NSIP and combined pulmonary fibrosis and emphysema (CPFE) pattern with honeycoming, traction bronchiectasis, ground-glass opacity and emphysema. In most of these cases, the histologic pattern of PF was classified as UIP and/or fibrotic-NSIP pattern. In addition, the high incidence of histological findings such as extensive interstitial fibrosis, lymphoid hyperplasia, and bronchiolitis, are characteristics observed in PF associated with collagen vascular diseases, which are not observed in idiopathic PF. The median survival time (MST) after diagnosis of PF was 62.2 months. In some cases with PF preceded the development of MPA. Therefore, clinicians should be aware of MPA as an underlying disease of PF, in order to avoid overlooking and misdiagnosing this condition as idiopathic PF. The MST in UIP pattern/MPA was comparable to those with idiopathic PF (41.4 vs 25.7 months) in our institution. In WG, solitary or multiple nodules, frequently cavitated, and masses are the most common findings on chest images. Asthma is a cardinal symptom of CSS. To induce remission, patients received a severity-based regimen according to the appropriate protocol by JMAAV (Japanese patients with MPO-ANCA-associated vasculitis) study group: low-dose corticosteroid and, if necessary, cyclophosphamide or azathioprine in patients with mild form; high-dose corticosteroid and cyclophosphamide in those with severe form; and the severe-form regimen plus plasmapheresis in those with the most severe form.

S5-5

Opportunistic infection in patients with rheumatic diseases

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Conflict of interest: None

There have been many progresses in the treatment of rheumatic diseases, such as biologics for rheumatoid arthritis (RA), while various opportunistic infection matters as a complication. As pneumonia is the most common cause of hospital admission of patients with RA, respiratory infection is known as a frequent complication in patients with rheumatic diseases. Since the respiratory infection can be life-threatening, early diagnosis and appropriate therapy are necessary. Diagnosis of respiratory infection is sometimes difficult in patients with rheumatic diseases because they often have lung abnormalities, such as interstitial pneumonitis and alveolar hemorrhage that can emerge regardless of the activity of other symptoms. Drug-induced lung diseases due to methotrexate or the biologics and other non-infectious lung disorders also contribute to the difficulty in the differential diagnosis. RA and systemic lupus erythematosus (SLE) are known as risk factors of infection and the therapeutics and complications of the disease are also risk factors. In patients with RA, prednisolone is the biggest risk factor of pneumonia even if the daily dose is 5 mg or less. The biologics for the treatment of RA include tocilizumab that acts against the IL-6 receptor, abatacept that inhibits the costimulation of T cells, and TNF-α inhibitors. Basically, all of these biologics suppress host defense as well as inflammation, which can reactivate a latent infection. TNF-α plays an important role in granulation and the host defense against intracellular pathogens, such as mycobacteria and *Legionella*. Since monoclonal antibodies against TNF-α (infliximab and adalimumab) exert more suppression of macrophage function than a TNF-a receptor-construct fusion protein (etanercept), they are associated with more significant risk of infection. In this presentation, the pathogenesis, diagnosis, and treatment of respiratory infections in patients with rheumatic diseases are to be reviewed.

S6-1

Epidemiology of osteoarthritis in Japanese men and women: The Research on Osteoarthritis/osteoporosis Against Disability (ROAD) study

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Conflict of interest: None

As the proportion of the aging population is expanding in Japan, there is an urgent need for a comprehensive and evidence-based prevention strategy for musculoskeletal diseases, especially osteoarthritis (OA). However, few prospective, longitudinal studies have been undertaken, and little information is available regarding the prevalence and incidence of OA and lumbar spondylosis (LS) as well as pain and disability in the Japanese population. From the beginning, only the estimated number of patients of knee OA (KOA) and LS was not clear in Japan. It is difficult to design rational clinical and public health approaches for the diagnosis, evaluation, and prevention of OA without such epidemiological data. The Research on Osteoarthritis/osteoporosis Against Disability (ROAD) study is a prospective cohort study that aims at the elucidation of an environmental and genetic background for bone and joint diseases, represented by OA and osteoporosis; it is designed to examine the extent to which risk factors for these diseases are related to the clinical features, laboratory and radiographic findings, bone mass and bone geometry, lifestyle, nutritional factors, anthropometric and neuromuscular measures as well as to determine how these diseases affect activity of daily living and quality of life in Japanese men and women. In the present lecture, we clarified the prevalence and incidence of KOA and LS, and risk factors of these disorders in Japan by analysing the baseline and the 3-yr follow-up data of the ROAD study.

S6-2

Biological markers: Possibility as indicators of OA treatment

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Conflict of interest: None

Although the advance of degenerative osteoarthritis (OA) is very gradual progression, decision making of the timing for the starting of a medical treatment is difficult. A thing which delays the advance is that there is no existing of so-called true curative medicine (disease/structure modifying anti OA drugs: DMOADS) in a strict meaning, and this is the major factor which has spoiled the development of the treatment for OA. The internal use of NSAIDs

which expected the relief for clinical symptoms of sharp pain, swelling and the anti-inflammation effect is the major reasons for the treatment. Also the usage of hyaluronan or corticosteroids which expected the anti-inflammation effect or biological lubrication effect for the articular cartilage, is the same meaning of a symptomatic therapy curative medicine (symptom modifying drugs) serves as a main subject of treatment in daily clinical aspects. Although there are some reports which pointed out correlation with the curative effect and some joint markers in the hyaluronan injection treatment, it may be considered in a possibility of the improvement of the synovial membrane inflammation by hyaluronan administration. Moreover, CTX-II (considered to be specific cartilage singularity), COMP (the minor protein which is one of the cartilage composition ingredients), and hyaluronan (contained in a cartilage matrix) show positive correlation in the advance of the radiological stage of OA in large-population-scale Cohort study. And this results leads an expectance for the possibility of the potentiality and role of biological markers as of medical treatment and restoration for OA. These are also considered to be the prime candidate of biological markers about curative effect judging or prediction of prognosis in OA stage progression. We report the possibility of biological markers as indicators of OA treatment with including bibliographic consideration and investigation examination.

S6-3

Possible role of hyaluronan as the disease modifying drugs for osteoarthritis

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Conflict of interest: None

【Introduction】Although joints maintain homeostasis within a physiological range of mechanical loading, overloading has catabolic effects, particularly for the cartilaginous components and leads to osteoarthritis (OA). We have demonstrated the involvement of mitogen-activated protein kinases (MAPKs) in stress-mediated cartilage degradation. Intraarticular HA injection is a treatment for the knee OA with beneficial effects. HA also plays as chondroprotecting on the OA cartilage as the disease modifying drugs for OA, although the underlying mechanisms have not been clear. In the present study, we focused on the Rho GTPases in the stress-mediated cartilage degradation to elucidate the precise role of HA.【Material and Method】We used ATDC-5 cells. Compressive loads were applied to bovine cartilage explants using the FX-4000C.【Result and Discussion】Rho GTPases activator (lysophosphatidic acid, LPA) clearly enhanced the expression of Rho-GTP in ATDC-5 cells. Western blotting showed the MAPKs phosphorylation, including JNK, P38, ERK, with LPA. ROCK inhibitor, Y27632, reversed these MAPKs phosphorylation. LPA inhibited type 2 collagen mRNA and, in turn, enhanced ADAMTS-5 mRNA synthesis. ROCK inhibitor also reversed these alterations, thereby suggesting that the Rho/ROCK play important role as upstream of stress-mediated signal transduction in ATDC-5 cells. Mechanical stress loaded on the cartilage explant enhanced Rho-GTP actity. Simultaneously, MMP-13 synthesis and p38 phosphorylation were also enhanced. ROCK inhibitor reversed stress-enhanced MMP-13 synthesis and p38 phosphorylation. These data suggest that Rho/ROCK is the potential therapeutic application of OA. Our preliminary data demonstrated that HA partially inhibit stress-enhanced Rho/ROCK activity.

S6-4

Effects and limitation of bisphosphonates in OA treatment

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Conflict of interest: None

Patients who are suffering from osteoarthritis is increasing in number. The importance of the bone changes in the initiation and progression of OA is still being debated. Subchondral bone remodeling was suggested to play a role in the progression of osteoarthritis (OA). To test this hypothesis we characterized the changes in the rat anterior cruciate ligament transection (ACLT) model of OA and evaluated the effects of Alendronate (ALN), a potent bone resorption inhibitor, on cartilage degradation and on osteophytes formation. Male rats underwent ACLT or sham-operation in the right knee. The animals were then treated with ALN (0.03 and 0.24 mg/kg/wk, s.c.) and sacrificed at 2- or 10-wk post-surgery. OA changes were evaluated by histologic score. Subchondral bone volume and osteophyte area were measured by histomorphometric analysis. ALN was chondroprotective at both doses as determined by histological criteria and collagen degradation markers. ALN suppressed subchondral bone resorption, which was markedly increased 2-wks post-surgery, and prevented the subsequent increase in bone formation 10-wks post-surgery, in the tibial plateau of ACLT-joints. Furthermore, ALN dose-dependently reduced osteophyte incidence and area. Taken together, subchondral bone remodeling plays an important role in the pathogenesis of OA.

S6-5

The pain management of symptomatic OA -At presnt and in future-

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Conflict of interest: Yes

Osteoarthritis (OA), the most common form of joint disease, represents a major cause of disability, particularly in the senile people. The treatment of OA consists mainly of the improvement of the symptoms (Symptom modifying effect) and the maintenance of cartilage integrity (Structure modifying effect, Disease modifying OA drugs: DMOAD). Although the relationship between the pathology and pain of OA has been still unclear, the new concepts of therapeutic approaches have emerged to overcome the chronic pain in symptomatic OA. The nonsteroidal anti-inflammatory drugs (NSAIDs) have been found to cause significant side effects, which is a concern for the aging population. Therefore the usefulness of NSAIDs for chronic OA symptom could be limited. The use of opioid analgesics for the treatment of symptomatic osteoarthritis began in Japan. It was reported that an improvement in OA pain that did not responded to NSAIDs has been only with strong opioids. If so, the use of opioids must be reserved for exceptional situations, such as patients awaiting planned joint replacement. Also there is a high withdrawal rate of patients treated, because of adverse effects such as nausea and vomiting. The animal model studies have shown that the inhibition of NGF reduces pain. There have been the clinical trials with a monoclonal antibody raised against NGF, named tanezumab. The knee OA study showed that tanezumab reduced pain during walking in symptomatic knee OA. The result suggested the promising future of this drug. However, FDA halted the clinical research of tanezumab because of an unexpected increase in the need for total joint replacement with this drug. It seems likely that drug-induced osteonecrosis and/or an accelerated progression of OA possibly due to pain relief. Now we can realize that the pain management of symptomatic OA is approaching to new generation with various drugs.

S7-1

Current state of gout and hyperuricemia in Japan

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Conflict of interest: None

Hyperuricemia is now fairly common in Japan, the frequency of which reached 30% in men of 30's in 2004 in a certain working place. The frequency decreased somewhat in those older than 40 y. The proportion of individuals receiving anti-hyperuricemic treatment increases in those older than 40 y, probably explaining decreases in the frequency of hyperuricemia in these ages. Therefore, the frequency of hypericemic men including those receiving treatments seems to be near 30% in the ages older than 30 y in Japan. It has been reported that the frequency of hyperuricemia in men began to decrease after 2006, until which time the frequency had continued to be increasing. National survey of people's individual life state in Japan (kokumin-seikatsu-kiso-chousa) showed that the number of individuals who answered yes to a questionnaire "Are you attending a hospital due to gout?" slightly decreased in 2007 compared to 2004. This tendency is striking because the number of individuals who answered yes to that questionnaire had continued to increase by more than a hundred thousand in every survey until 2004 (the survey is conducted every 3 years). Since the number of tablets of urate-lowering drugs sold in Japan continued to be increasing even in 2010, however, the number of individuals with gout or hyperuricemia who are receiving treatment seems to be increasing. The prevalence of gout based on correct diagnosis was most recently reported from a population-based survey conducted in 2003 in Kamitonda-cho in Wakayama prefecture, being 1.7% among men older than 30 y. Since the age distribution of people in that area is similar to total Japanese population, it may be concluded that more than 1 in 60 men develop gout during life-time in Japan. The prevalence of gout in the same area studied 30 years ago was approximately 1/2 of that of 2003. Therefore, the prevalence of gout seems to have been increasing in recent years.

S7-2

Relationship between hyperuricemia and chronic kidney disease

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Conflict of interest: None

Since about 70% of uric acid is excreted from the kidney, hyperuricemia occurs when renal function deteriorates. Until now, it has not been clear whether or not the hyperuricemia seen in such renal diseases plays a role in the progression of renal disease. However, recent clinical studies show that the serum uric acid value is closely associated with hypertension in hyperuricemic patients (a cross-sectional study), and also with the onset of hypertension (a longitudinal study). Furthermore, one interesting report shows that the treatment of hyperuricemia by allopurinol lowers blood pressure in juvenile essential hypertension patients with hyperuricemia. In addition, it is well known that hyperuricemia is closely associated with chronic kidney disease (CKD), is a risk factor for renal insufficiency in general populations, and a poor prognostic factor of renal function in patients who also have IgA nephropathy. On the other hand, in intervention studies on hyperuricemia, the treatment of hyperuricemia by allopurinol in CKD has resulted in a fall in blood pressure and inhibition of the progression of renal damage. Conversely, the cessation of allopurinol treatment in CKD caused a rise in blood pressure and development of renal damage. Furthermore, the rise of blood pressure and development of renal damage induced by the cessation of allopurinol treatment are only seen in patients who are not receiving angiotensin converting enzyme inhibitor (ACEI) or angiotensin receptor blocker (ARB). This suggests that the renin angiotensin (RA) system plays an important role in the mechanism of hypertension development and renal damage by hyperuricemia.

S7-3

Hyperuricemia and Cardiovascular Diseases

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Conflict of interest: None

Uric acid has a simultaneous antioxidant action and marked vasotoxicity, and hyperuricemia has often been reported to be an independent risk factor for atherosclerosis. Recent prospective observational studies demonstrated that serum uric acid level is an independent predictive factor for the development of hypertension. There are many prospective cohort studies to clarify whether high serum uric acid level is an independent risk factor for cardiovascular diseases, which produce conflicting results. Reports on the results that a change in uric acid level in association with the therapy of lifestyle-related diseases has impacts on cardiovascular events are limited to those of sub-analyses, in which serum uric acid level after intervention studies of antihypertensive therapy and lipid–lowering therapy has been set newly as an explanatory variable. It is necessary to wait the results of the randominzed controlled trials that have been conducted to examine the impacts of therapeutic interventions to reduce serum uric acid level on cardiovascular events for concluding that uric acid level is a risk factor for cardiovascular events.

S7-4

Diagnosis and management of gouty arthritis with musculoskeletal ultrasonography

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Conflict of interest: None

Gouty arthritis is an inflammatory arthritis caused by monosodium urate crystal formed in joint capsule due to persistent hyperuricemia. Excess total body urate pool accompanies with the deposition of MSU crystal in joint and various factors cause shedding of the crystal which induce intra/peri-articular inflammation. Treatment of gouty arthritis consists of suppression of joint inflammation, correction of hyperuricemia and dissolution of excess total body urate pool, there novel therapeutic options are now available and expected to improve outcome of gouty arthritis. On the other hand, many clinical questions remain: the risk of gouty arthritis in patients with asymptomatic hyperuricemia, treatment target of serum urate level and duration of medication, appropriate dosing of urate lowering drugs to prevent acute attack. Musculoskeletal ultrasonography (US) can evaluate structural anatomy of the joint by B-mode, and detect active inflammation, especially in synovium, by power Doppler US. In patients with gouty arthritis, synovitis and MSU crystal deposition can be assessed by US, which may indicate the clues to answer clinical questions in daily practice. Topics in diagnosis and management of gouty arthritis are to be reviewed with current US data.

S7-5

Treatment of hyperuricemia (selection of urate-lowering drugs)

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Conflict of interest: None

Hyperuricemia can be classified into the overproduction type, the underexcretion type, and the mixed type. The classification is established by measuring urinary uric acid excretion (Eua) and uric acid clearance (Cua) under water loading with restriction of purine-rich diet. Urate-lowering agents are classified into two categories based on the mode of action; uricosurics and xanthine oxidase inhibitor. In Japan, benzbromarone, probenecid, and bucolome are available as uricosurics. Benzbromarone and probenecid exert their action through inhibition of URAT1. Besides urate-lowering agents, both losartan and fenofibrate inhibit URAT1 and lower serum uric acid levels, thus are useful for the treatment of hyperuricemic patients with hypertention and/or hypertriglyceridemia. Until now, the only available xanthine oxidase inhibitor was allopurinol. Since allopurinol and its active metabolite oxypurinol are excreted from kidney, it is recommended that the dosage should be adjusted based on GFR to avoid lethal adverse event. However, it is often difficult to attain serum uric acid levels below 6.0 mg/dL, according to the recommendation. Febuxostat, a selective non-purine xanthine oxidase inhibitor, received marketing approval on May 2011. The main route of its elimination is urine and feces. Therefore, the pharmacokinetics of febuxostat is unaffected in subjects with mild-to-moderate renal impairment. Febuxostat has been shown to be more effective than allopurinol in attaining serum uric acid levels below 6 mg/dL. Rasburicase, a recombinant uric acid oxidase produced by a genetically modified *Saccharomyces cerevisiae*, is indicated for the prevention and treatment of tumor lysis syndrome. RDEA 594 and JPH367 (selective URAT1 inhibitor), FYX-051 and NC2500 (xanthine oxidase inhibitor), and BCX4208 (PNP inhibitor) are in the pipeline and are expected to be used in the near future.

S8-1

Genetic analysis of Behçet's disease and Rheumatoid arthritis

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Conflict of interest: None

We conducted a genome-wide association study using 500K SNPs in 574 Japanese individuals with Behçet's disease (BD) and 671 controls. We identified two new BD risk loci: chromosome 1p31.3 (*IL23R*/*IL12RB2*; rs1495965, $P = 6.4 \times 10^{-8}$) and chromosome 1q32.1 (*IL10*; rs1800872 and rs1800871, $P = 2.4 \times 10^{-8}$), suggesting *IL23R*/*IL12RB2* and *IL10* play an important pathophysiological role in BD development.

S8-2

Genetics of autoimmune rheumatic diseases: a candidate gene approach.

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Conflict of interest: None

Candidate gene studies provide valuable information on genes strongly implicated in the disease processes. Thus far, we reported a number of susceptibility genes to Japanese patients with systemic lupus erythematosus (SLE), including the first report of association of *FCGR2B* polymorphism with SLE. In this symposium, I will discuss some of our recent findings. Type I IFN plays a crucial role for SLE. Based on a candidate pathway approach targeted at type I interferon related genes, we confirmed association of *IRF5*, *STAT4*, *TNFAIP3* and *TNIP1* with Japanese SLE, and also found new association of a single nucleotide polymorphism (SNP) located in the 3' untranslated region (3'UTR) of *TLR7* in a multicenter collaborative study in East Asia. Furthermore, we reported a new association of a SNP in the 3'UTR of *SPI1* gene encoding a transcription factor PU.1. The risk allele abolishes a binding motif for a miRNA hsa-miR-569, which leads to overexpression of *SPI1*. Recent studies revealed that a number of genes are shared susceptibility genes to multiple complex diseases. We considered SLE- or RA-associated genes as candidates for susceptibility genes to systemic sclerosis (SSc) and ANCA-associated vasculitis (AAV), and conducted association analyses. Thus far, we detected association of *IRF5*, *STAT4*, *BLK* and *UBE2L3* with SSc, and that of *STAT4* and MPO-ANCA positive AAV. These observations implicated that these genes play a role in the common pathways leading to various autoimmune rheumatic diseases. These studies were conducted in collaboration with the members of Molecular and Genetic Epidemiology Laboratory, Faculty of Medicine, University of Tsukuba, as well as a number of co-investigators.

S8-3

Genome-wide association study of systemic lupus erythematosus in Japanese

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Conflict of interest: None

Systemic lupus erythematosus (SLE) is an autoimmune disease with complex etiology whch results in multiple organ damage. Although recent genome-wide association studies (GWAS) in Eueropean populations have discovered multiple SLE susceptibility genes, few studies have been performed in Asian populations. We performed a GWAS for SLE in Japanese examining 891 SLE cases and 3,384 controls and identified significant associations in six gene loci including *HLA, STAT4*, *TNFAIP3*, *HIP1*, *BLK*, and *ETS1* that satisfied the genome-wide significance threshold of $P < 5.0\times10^{-8}$. We also observed significant replications of association in 17 of 26 previously reported SLE susceptibility loci. Of these, significant replications were enriched in the loci identified through the studies in Asian populations (80%; 8 of the 10 loci) compared to those in European populations (56.3%; 9 of the 16 loci). We also performed multi-stage replication studies to evaluate the moderate association signals in GWAS. The association signals were first prioritiezed by the results of expression quantitative trait locus (eQTL) analysis in B-lymphoblastoid cells, and then tested by examining additional 1,387 SLE cases and 28,564 controls, which identified an additional risk locus in the AF4/FMR2 family, member 1 (*AFF1*) gene (rs340630; $P = 8.3\times10^{-9}$, odds ratio = 1.21). The risk A allele of rs340630 demonstrated a cis-regulatory effect on the *AFF1* transcripts with enhanced expression levels. As *AFF1* transcripts were prominently expressed in $CD4^+$ and $CD19^+$ peripheral blood lymphocytes, up-regulation of *AFF1* may cause the abnormality in these lymphocytes. Like the *AFF1* locus, we observed enrichments of cis-regulatory effect positive loci among the known SLE susceptibility loci (30.8%) compared to the genome-wide SNPs (6.9%), suggesting accumulation of quantitative changes in gene expression would accelerate the disease onset of SLE.

S8-4

Genetic risk factors for rheumatoid arthritis

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Conflict of interest: None

Rheumatoid arthritis (RA) is believed to be a complex disease that is influenced by both genetic and environmental factors. There is increasing evidence that genome-wide association study (GWAS) represents a powerful approach to identify genetic markers that are associated with complex diseases including RA. To date, a great deal of genetic data from various ethnic populations has been accumulated, especially from European and East Asian descents. These data show us the evidence that there exists an ethnic-specific genetic background that contributes to susceptibility to RA in each ethnic population. This is why we have launched GARNET consortium made up of Japanese research institutes including RIKEN, The University of Tokyo, Kyoto University and Tokyo Women's Medical University to conduct a large-scale GWAS meta analysis focused on RA susceptibility in Japanese. As a result of GWAS meta analysis using 4,074 patients and 16,891 controls and subsequent replication study with 5,277 patients and 21,684 controls, we found several novel locus that associated with RA susceptibility in Japanese. Though we also tested the effect of RA susceptibility locus on radiographic severity in RA patients using data of 865 patients with Sharp/van der Heijde score (SHS) of the hands at 5-year disease duration, we could detect the effect of radiographic severity on HA-DRB1 and PADI4 but not on novel RA susceptibility locus.

S8-5

Genetic Factors for developing anti-CCP antibody-negative RA

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Conflict of interest: None

Anti-CCP antibody (ACPA)-negative RA, which comprises of ~20% of RA, has been shown to be a distinct subset from ACPA(+) RA clinically and genetically. By the twin studies, ACPA(-) RA development was shown to be influenced by the genetic background as much as ACPA(+)RA. However, almost no susceptibility genes have been detected so far. Most of the susceptibility genes for RA in Caucasian (eg. HLA-DRB1, PTPN22, TNFAIP3) were associated only with ACPA(+) RA but not ACPA(-) RA. First, we suspected whether such results were obtained by the contamination of non-RA arthritic diseases. So, we selected only ACPA(-) RA patients who have typical bone erosions in the X-ray, and performed association analysis for HLA-DRB1 shared epitope (SE). As a result, we found SE is not associated with ACPA(-) erosive RA, which clearly showed ACPA(-)RA is a distinct subset from ACPA(+) RA. Next, we searched associated HLA-DRB1 alleles with ACPA(-)RA. Using 869 cases of ACPA(-)RA and 2,008 healthy controls, HLA-DRB1 was typed and association analysis was performed. As a result, HLA-DRB1*12:01 (p=0.000088, OR 1.72), *04:05 (p=0.0063, OR 1.26) and *14:03 (p=0.0043, OR 1.81) were found to be associated with ACPA-negative RA. We also found that HLA-DRB1*15:02 and 13:02 were protective against ACPA-negative RA (p=0.00010, OR 0.68 and p=0.00059, OR 0.66, respectively). Genome-wide association study (GWAS) of ACPA(-) RA was performed in Caucasian but no genes satisfied the genome-wide significance level of association. We attempted GWAS of ACPA(-) RA using 1,285 ACPA(-) RA and 38,575 controls. I will present the current status of this GWAS study.

S8-6

Rare variants' impact on diseases

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Conflict of interest: None

GWAS, which exhaustively explores disease-related genes in the human genome, has revolutionized medical research. In 2002, our center reported the first GWAS results in the world. Thereafter, the International HapMap project was launched to construct an LD map and select tagging SNPs, which have been used for chips/arrays. This has resulted in a large increase in the number of GWAS, further accelerated by the BioBank Japan project, revealing many genes related to common diseases, cancers, and drug responses. We now face the missing heritability problem; the heritability of diseases has yet to be fully explained by the factors identified by GWAS. For exploring moderate-effect factors with high allele frequencies under the common disease common variants hypothesis, enlarging sample size using disease cohorts, and doing meta-analysis by collaborations would be promising. In addition, it would be necessary to explore lower frequency/rare variations with higher risks under the common disease rare variants hypothesis. Deleterious mutations should have been suppressed and tend to have lower frequencies under natural selection. Also, many researches with candidate gene approach revealed that rare variants could be related to common diseases. In practice, to explore such variants, it is efficient to utilize GWAS results. One of the solutions is to detect synthetic associations; rare variants with large effect size could be detected by near-by common variants through haplotypes. For this, up to 2Mb around each GWAS significant locus are sequenced. Another is imputation, which can be used to explore hidden SNPs, particularly with lower allele frequencies (<0.05). Also, soon it will be practical to analyze lower frequency variations, e.g. SNVs and CNVs, using next-generation sequencing. One of efficient ways is whole exome sequencing. Here, how to collapse rare variants under adequate disease models to avoid the multiple testing problem is critical. I will discuss these.

S9-1

Overview-The status quo and future of the methotrexate therapy for rheumatoid arthritis in Japan

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Conflict of interest: Yes

A recent paradigm shift of the treatment of rheumatoid arthritis (RA) is to aim for remission by the treat to target (T2T) strategy, using DMARDs as early as possible in the disease process. Among the DMARDs, methotrexate (MTX) is considered to be the anchor drug and should be used first in patients with active RA, especially in whom poor prognostic factors are present. Although the limitation of MTX dose has been a longstanding problem 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. Now, 84.2% of RA patients are treated with MTX at Tokai University Hospital, and 38% among these patients are treated in combination with biologics or other DMARDs. Since the results of RCTS comparing different dosage of oral MTX in RA treatment showed dose dependent efficacy between 5mg and 20mg/week, efficacy tends to be reached plateau at 15mg/week. In the dose-escalation study at Tokai University, the population of patients who showed ACR 70 response when MTX used up to 15mg/week was 3 times higher than that obtained by the treatment with 8mg/week of MTX. It remains to be established that treatment with higher dose of MTX results in higher rate of remission/ low disease activity and better structural prognosis. The MTX doses in adult RA patients under 60 years old are distributed in 32.6% for 12mg/week, 25.4% for 10mg/week, and 28.3% for 8mg/week. The appropriate doses in combination with biologics also need to be determined. Regarding safety considerations, fatal cases because of pneumonitis are declining year by year, but considerable cases of serious hematological side effects have been reported. Infection and lympho-

proliferative disorders are showing a tendency to increase during the recent 3 years. It is necessary to elucidate the underlying factors of these serious adverse events.

S9-2

The relationship between doses and efficacy of methotrexate in treatment of rheumatoid arthritis based on the analysis of the IORRA cohort

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Conflict of interest: None

Methotrexate (MTX) is a crucial drug that is not indispensable for treatment of rheumatoid arthritis. Analysis of efficacy and safety of MTX at doses over 8 mg/week in Japanese rheumatoid arthritis cohorts were executed and the maximum dose at 16 mg/week of MTX was approved in February 2011. In this symposium, we will summarize the data of efficacy and safety of MTX using the large observational IORRA cohort database. Total of 5,201 patients who had been treated with MTX but not with biologics or other immunesuppressive drugs were selected from the IORRA database from October 2000 survey to October 2007 survey. The relationship between doses and efficacy and safety of MTX were analyzed. Among patients (n=260) who had been treated with 8 mg/week or less doses of MTX at a certain phase and with increased doses at the following phase, DAS28 was significantly decreased by 0.563 (95 % confidence interval (CI) 0.438-0.688). When dose of MTX at 10 mg/week or less at former phase and increased to over 10 mg/week at latter phase, DAS28 was significantly decreased and so at 12 mg/week, 14 mg/week, and 16 mg/week, respectively. The decreases in DAS28 values were more significant compared to the condition where MTX was stabilized at 8 mg/week. Concerning safety of MTX at dose over 8 mg/week, logistic regression analysis was performed in which the objective variable was existence or nonexistence of self-reported side effects. The results indicated that MTX doses over 8 mg/week did not have any association with self-reported side effects. This analysis is based on the practical rheumatoid arthritis cohort IORRA where MTX was started around 6 mg/week and gradually increased according with the careful inspection for safety and efficacy individually. To make the most of MTX in treatment of rheumatoid arthritis, we should emphasize that appropriate clinical evaluation for each patient is prerequisite in the use of MTX.

S9-3

Efficacy and limitation of methotrexate monotherapy on structural progression of rheumatoid arthritis

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Conflict of interest: Yes

Methotrexate (MTX) is currently the most widely used non-biologic DMARD because of its efficacy and safety profile, and considered the gold standard of treatment of rheumatoid arthritis (RA). Several recent studies supports higher dose of MTX in patients with early arthritis. About 40% of patients will do well with MTX monotherapy with adequate treatment approach, and approximately 15-20% of patients will achieve responses akin to remission when MTX alone is initiated. The result of COMET study showed 80% of patients did not have radiographic progression in MTX monotherapy (rapid dose escalation to 20mg/wk) group. However, the results of TEMPO study MTX monotherapy (up to 20mg/wk) indicates radiographic progression was seen in 43% of patients, and change in mTSS score was 2.8 at 52 weeks. In patients without DAS remission, 58% o patients showed radiographic progression at 3 years. OPTIMA study demonstrated MTX monotherapy (up to 20mg/wk) achieved the good structural prognosis for one year in patients with low disease activity, but rapid progression of the joint destruction was noted in patients do not respond to MTX monotherapy. To date, there is no way to predicting which patient will respond well to MTX monotherapy alone and which truly should have started with the combination therapy. Scores on musculoskeletal US synovial hypertrophy, power Doppler (PD), and MRI synovitis assessments in individual joints at baseline were significantly associated with progressive radiographic damage. A significant population of patients does not respond to MTX monotherapy even with high dose, and failed control of disease activity associates with progression of joint damage. Treat to target approach using high resolution imaging modality would be useful to identify the patients at a risk of joint damage progression, or who can expect better structural outcome.

S9-4

Clinical characteristics and management of infections in rheumatoid arthritis patients receiving treatment with methotrexate

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Conflict of interest: Yes

Background. Infection, bone marrow suppression, and interstitial pneumonia are three main serious adverse events in rheumatoid arthritis (RA) patients given methotrexate (MTX) that led to death. Of 2,502 RA patients who had serious adverse drug reactions (ADRs) related to MTX in Japan, 316 died and infection was the main cause of death in 61 patients (16.9%). These infections encompassed 30 opportunistic infections, 18 pneumonia (including pneumonia, bacterial pneumonia, and Legionella pneumonia), 8 sepsis and septic shock, and other infections. To contribute to proper management of patients receiving MTX, we investigated clinical characteristics of severe infections in RA patients given MTX. **Methods.** We retrospectively enrolled 49 RA patients who were admitted to Tokyo Medical and Dental University Hospital between 2007 and 2010 for treatment of infection and were taking MTX until their admission. Clinical and laboratory data were collected using a standardized case report form. **Results.** Of 49 patients, 37 (76%) were female and mean age was 66 +/- 12 years old. Comorbidities were interstitial pneumonia in 10 patients (20%), diabetes mellitus in 4 (8%), liver disease in 1 (2%), and renal disease in 3 (6%). Mean, maximum, and minimum dose of MTX at the onset of infection was 8.0 +/- 2.7, 16, and 4 mg/week, respectively. Glucocorticoid was used in 69% of the patients and mean prednisolone-equivalent dose was 5.5 +/- 4.7 mg/day. Biologics were used in 18 patients (37%). Main infection sites were lung in 26 patients (53%), kidney and urinary tract in 9 (18%), skin and soft tissue in 8 (16%), and bone and joint in 5 (10%). We had 16 pneumonia (33%), 7 Pneumocystis pneumonia (14%), 5 cellulitis (10%), and 2 herpes zoster (4%). Five patients (10%) were dead at discharge. **Conclusion.** During treatment with MTX, variety of infection can develop with a substantial mortality rate. Rheumatologists should be aware of benefit-risk balance of treatment with MTX.

S9-5

Clinical characteristics of methotrexate-associated lymphproliferative disorders

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Conflict of interest: None

In recent years, the treatment of rheumatoid arthritis (RA) has made a lot of progress by the discovery of biological agents. Nevertheless it is no doubt that methotrexate plays a central role in RA treatment. However, it has been well known some adverse events might occur due to methotrexate and one of these adverse events is the occurrence of lymphoproliferative disorders. Methotrexate-associated lymphproliferative disorders are classified in the term "other iatrogenic immunodeficiency-associated lymphproliferative disorders" in the World Health Organization classification of lymphoid neoplasms updated in 2008. Methotrexate-associated lymphproliferative disorders have some clinical characteristics. It is well known that it has an association with EB virus infection and the discontinuation of methotrexate without any further treatment might result its complete improvement. Therefore, it is very important to understand its clinical features, diagnosis, treatment and prognosis. The aim of this presentation is to figure out methotrexate-associated lymphproliferative disorders through our clinical experiences and bibliographic consideration.

S9-6

The optimum management of the use of methotrexate in rheumatoid arthritis patients in the perioperative period

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Conflict of interest: Yes

Methotrexate (MTX) is a drug widely used on patients with rheumatoid arthritis (RA). Nowadays, no clear consensus exists on whether MTX should be continued or whether this therapy should be discontinued for a few weeks in patients with RA undergoing elective surgery. Continued MTX therapy may impair wound healing and/or increase local infections due to its immunosuppressive effects, but discontinuation of the medicine may increase the risk of flares of the disease. To date, only around 10 studies as to this question have been published, including randomized controlled trials (RCTs) and cohort studies. Especially the use of up to 16 mg/week of MTX in adult RA patients and its first-line use were approved in 2011 in Japan. It is the time for us to reconsider the use of MTX perioperatively. Majority of previous studies concluded that continued MTX therapy appears to be safe perioperatively and seems also to be associated with a reduced risk of flares. According to the RCTs, MTX was not associated with an increasing risk of surgery complications. On the other hand, some of cohort studies revealed that there were more infections in the RA patients who continued MTX perioperatively. The contrasting results may be explained by differences in sample size and study design. However, the mean doses of patients continuing on MTX perioperatively were mostly from 5 up to 10 mg weekly even in the studies conducted abroad. Further study with a larger number of patients should be necessary to better define this important problem in the care of RA patients undergoing surgery. These studies should also include the analysis as to other risk factors for the perioperative complications such as higher dosages of MTX, type of operation, comorbidity, and combination therapy.

S10-1

Can biologics prevent the pregression of cervical lesion in RA patients?

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Conflict of interest: Yes

Cervical lesions are known as a complication of rheumatoid arthritis (RA). The progression of cervical lesions leads to severe pain in the post-cervical lesion and myelopathy, which in turn result in a deterioration in the daily living activities of RA patients with joint damage in the limbs. The biological agents including infliximab have had a major impact on RA treatment. We evaluated radiographic change in the cervical lesions of 47 RA patients receiving continuous infliximab therapy for at least 1 year. Infliximab treatment had been initiated between November 2003 and December 2007. The radiographic evaluations of the cervical lesions were made at the initiation of infliximab treatment and at week 54. The atlanto-dental interval (ADI), the space available for the spinal cord (SAC), and the Ranawat value were measured by plain lateral radiographs with the patient in the flexion position, and the anterior atlanto-axial subluxation (AAS) and vertical subluxation of the axis (VS) were evaluated with the patient bending forward. Patients who were progressive (20 cases) and non-progressive (27 cases) in terms of RA cervical lesions were compared. Matrix metalloproteinase 3 (MMP3) values improved significantly only in non-progressive patients within the 1-year treatment window. Cervical lesion progression was suppressed in 19 of the 23 patients (83%) showing a good response to infliximab treatment and occurred in 16 of the 24 patients (67%) showing a moderate response. This difference was shown to be significant by the Fisher's exact test ($p = 0.002$). In conclusion, the strong suppression of RA disease activity by biologics such as infliximab can provide the beneficial effects on the natural course of RA cervical lesions.

S10-2

Aggravation of Cervical Spine Instabilities due to Rheumatoid Arthritis

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Conflict of interest: None

To clarify the natural course of cervical instabilities, we designed 5-year prospective cohort multicenter study. METHODS Over five years after 634 outpatients with definite or classical RA were assigned, 256 RA patients were followed and eleven patients operated to the cervical spine during the follow-up were also included. Instabilities were classified into anterior atlantoaxial subluxation (AAS) (ADI≥3mm), vertical subluxation (VS) (Ranawat<13mm), and subaxial subluxation (SAS) (translation≥2mm). The aggravations were defined as the changes in ≥2mm of ADI/Ranawat or in ≥1mm of translation. "Severe" instabilities were defined as AAS with ADI≥10mm, VS with Ranawat≤10mm, and SAS with translation≥4mm or at multilevel. RESULTS 52.4% of the patients without any instabilities at the beginning decreased to 29.6% ($p<0.01$), whereas VS and SAS increased significantly ($p<0.01$). The aggravation of VS was observed in 49.1% of initial VS ($p<0.01$). The aggravation of SAS was detected in 47.2% of initial VS and 64.7% of initial SAS ($p<0.01$). "Severe" instabilities were recognized in 33.3% of initial AAS and 75.0% of initial VS ($p<0.05$). Canal stenosis (≤12mm) was observed in 15.8% of initial AAS and 16.7% of initial VS

($p<0.05$). Even the cases without any instabilities at the beginning showed "severe" instability in 12.9% and stenosis in 4.3%. The factors for aggravations were proved to be pre-existing mutilating deformity (odds ratio=21.23), mutilating change starting during the follow-up (13.44), oral corticosteroid (4.65). CONCLUSION Three quarters of VS and a third of AS aggravated to "severe" and 16~17% of them resulted in stenosis with the potential myelopathy. In addition to pre-existing instabilities, pre-existing mutilating deformity and mutilating changes starting during the follow-up were proved to be the important factors for aggravation. RA cervical spine was confirmed to follow the aggravating courses, which might lead to myelopathy.

S10-3

Clinical manifestations and prognosis of severely affected cervical disorders due to rheumatoid arthritis

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Conflict of interest: None

CLINICAL MANIFESTATIONS [Neck-occipital pain] Rheumatoid lesions at C0-C1-C2 joints or neuralgia of C2 (C1?) are the main cause of pain. This type of pain is sometimes a warning bell regarding upcoming fatal problem. Vertical instability at CVJ is a main target for spinal surgeons. [Difficulty in swallowing, Respiratory distress] These life-threatening issues are caused by medulo-high cervical cord dysfunction or abnormal deformity of upper airway/esophagus. [Narrow field of vision] Both pre-op. decreased ROM of the painful cervical spine and post-op. fused vertebrae make the patient's field of vision narrow. [Digestive tract hemorrhage] Histamine H2-receptor antagonist or PPI could not avoid fatal digestive tract hemorrhage in some cases. Endoscopic hemostasis was quite difficult for the patients with deformed or fused neck. [Peripheral vessel lesion] Calcified peripheral vessel's abnormalities were seen. We encountered a few cases whose lower extremities were amputated because of circulatory disturbance. The cause of this lesion is still unknown. For meticulous evaluation of our treatment, we subdivided Ranawat IIIB into two different categories, IIIBa (unable to walk but sit upright) and IIIBb (unable to sit upright, completely bedbound). It was impossible for us to treat IIIBb patients without aggressive surgery. **PROGNOSIS** Fifty-three RA patients who underwent occipito-thoracic fusion for severely destructive cervical spine between 1991 and 2010 were reviewed. Neurological status of all IIIBb patients improved to IIIBa or IIIA. The mean post-op. survival time after surgery was 7.1 years, calculated statistically by Kaplan-Meier method. The survival rate was 60.7% in 5 years after surgery, and 30.8% in 10 years. The survival rate of class IIIBb patients (35% in post-op. 5 years) was extremely shorter than that of other patients. The patients with true severe RA cervical disorders means the patients with extremely poor general condition.

S10-4

Optimal timing for RA patientswith destruction of the cervical spine

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Conflict of interest: None

[Study design] A retrospective study of the surgical outcome of long spine fusion in rheumatoid arthritis. [Objective] To assess the clinical results of occipito-thoracic fusion in RA patients with destruction of the cervical spine. [Summary of background data] There are few reports on the surgical outcome of long spine fusion in RA patients that include an assessment of the activities of daily life (ADL). [Methods] Twenty RA patients with atlantoaxial subluxation, superior migration of the odontoid process into the foramen magnum, and subaxial subluxation underwent occipito-thoracic fusion (C0 to Th5). We used the Ranawat grade for neurological and pain evaluation and subdivided grade IIIB into IIIBa and IIIBb. IIIBa is a patient with objective weakness and long tract signs who can sit, but not walk; IIIBb means IIIBa who cannot sit. [Results] The average age at surgery was 59 years and the follow up averaged 5 years. All cases had preoperative neural involvement: 5 cases were IIIBa and 15 cases were IIIBb. Halo traction was applied 1 month preoperatively in all cases and 12 cases improved to IIIA and 8 cases to IIIBa before surgery. Postoperatively, 6 cases of 12 IIIA improved to II, but 6 cases of IIIA and 6 of 8 IIIBa cases had no improvement but 2cases of them improved to IIIA. In terms of satisfaction of patients in their ADL, 14 cases were extremely satisfied, while three cases were moderately satisfied, due to difficulty of drinking water and compression fracture of lumbar spine. [Conclusion] In the treatment of RA patients with destruction of the cervical spine, preoperative Halo traction was very effective and almost all the patients were satisfied with the results of occipito-thoracic long fusion. We have to pay attention to prevent compression fracture of lumbar spine.

S10-5

Prevention of complications of cervical instrumentation in RA patients

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Conflict of interest: None

Fusion surgery using instrumentation is usually performed for destroyed unstable RA cervical spine. Recent advance in anesthesia, general management, preoperative examination, and surgical techniques, and refinement of instruments reduced perioperative mortality rates and improved the results of surgery. However, instrumentation surgery is known to be susceptible to peculiar serious complications, particularly in RA patients. It is critical to avoid them to achieve high quality of life of RA patients. RA cervical spine has many disadvantages for instrumentation, that is, small and narrow bony structure to which a screw is inserted, distorted anatomy due to bony destruction, and osteoporosis. These factors raise the risk of screw malposition, resulting in possible vertebral artery (VA) injury. VA injury can result in catastrophic consequences such as massive bleeding, cerebellar or brain stem infarction and rarely death. Precise preoperative evaluation of the individual anatomy, the use of recent sophisticated instrumentation system, high surgical skill, and computer assisted surgery, would decrease this complication. RA patients are also susceptive to dysphagia or dyspnea after occipito-cervical fusion. Although temporomandibular joint destruction, laryngeal deviation, laryngeal mucosal abnormalities, and the existence of cricoarytenoid arthriris etc. were suspected to relate to this complication, the real cause has not been known so far. Recently, the reduction of the occipito-C2 (O-C2) angle in the fused position is considered to have a major impact on the oropharyngeal stenosis. To maintain an O-C2 angle not less than the preoperative O-C2 angle in neutral position is important in avoiding inadvertent postoperative dyspnea or dysphagia. The knowledge above would reduce the risk of and improve the result of instrumented cervical fusion in RA patients.

S11-1

Osteoimmunology in bone destruction in RA

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Conflict of interest: Yes

Bone destruction is one of the urgent issues in the treatment of rheumatoid arthritis (RA). How does abnormality of the immune system induce skeletal damage in RA? Although the infiltration of $CD4^+$ T cells in RA synovium is a pathogenetic hallmark and is undoubtedly linked to the bone destruction, it has been unclear what type of and how T cells induce bone-resorbing cells, osteoclasts. We have identified IL-17-producing T helper cells (T_H17 cells) to be the exclusive osteoclastogenic T cell subset. IL-17 induces RANKL, the key cytokine for osteoclastogenesis, on synovial fibroblasts and also stimulates local inflammation leading to overproduction of inflammatory cytokines such as TNF-a, IL-1 and IL-6. These cytokines further enhance RANKL expression on the synovial fibroblasts and activate the osteoclastogenic signals in the osteoclast precursor cells by promoting the sensitivity to RANKL. It has been also shown that the development of Th17 depends on IL-6 and TGF-b. These mechanisms provide a molecular basis for novel therapeutic strategies including the antibodies against IL-6, IL-23 and IL-17.

S11-2

The RANKL/RANK system is a therapeutic target for bone destruction

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Conflict of interest: None

Receptor activator of nuclear factor-kB ligand (RANKL) is a pivotal osteoclast differentiation factor. Discovery of RANKL has opened a new era in the understanding of mechanisms in osteoclast differentiation over the last decade. The discovery results in the development of a fully human anti-RANKL neutralizing monoclonal antibody (called denosumab). It has been approved for postmenopausal osteoporosis (Prolia®) and for the prevention of skeletal-related events in patients with bone metastases from solid tumors (XGEVA™) in Europe and the US. It has been filed for approval for bone disorders stemming from bone metastases in Japan. Clinical trial for osteoporosis (phase 3) and rheumatoid arthritis (phase 2) are currently underway in Japan. Previous studies showed that inhibition of RANKL by denosumab or osteoprotegerin prevented markedly osteoclast differentiation and function in vivo. RANKL inhibition cannot prevent inflammation but abrogate bone destruction. The mechanism of denosumab is different from those of biologics targeting inflammatory cytokines such as TNF and IL-6. Denosumab would work for nonresponders to the abovementioned biologics. Here I report our recent data on RANKL-related research. We established a novel rapid bone loss model with GST-RANKL (Shinohara *et al.* Cell 2008, Tomimori *et al.* JBMR 2009). Pharmacologic studies of candidates for the treatment of osteoporosis with this model can be done in short periods such as 3 days or so although it took several months in the conventional methods with ovariectomized rats. Recently we reported that one injection of anti-mouse monoclonal RANKL antibody (OYC1) to mice significantly increased bone mineral density (BMD) in two days. Continuous increase in BMD and decrease in osteoclast activity were observed after 4 weeks from the injection and RANKL function was almost perfectly blocked by the injection (Furuya *et al.* JBC 2011). These models are useful for acceleration of research in bone biology.

S11-3

Rheumatoid synovial fibroblast as a new therapeutic target

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Conflict of interest: None

Rheumatoid arthritis (RA) is supposed to be induced by autoreactive T cells that are restricted by HLA DRB shared epitope. Following activation of macrophages and other lymphocytes in synovial tissues induce massive secretion of the inflammatory cytokines. These cytokines promote proliferation of synovial fibroblasts (SF), leading to formation of the pannus tissue. These processes result in destruction of the bone and cartilage of the affected joints. Recently developed biological agents target inflammatory cytokines and cell surface molecules of lymphocytes. However, we still have patients refractory to these expensive agents and/or suffering from severe adverse events, especially infections. Alternative strategies we have been pursuing were to suppress SF. First, we observed that intraarticular gene transfer of cyclin-dependent kinase (CDK) inhibitor to suppress CDK4/6 and thus to inhibit synovial cell growth was effective in treating animal models of RA, proliferation of SF in vitro and also the animal models of RA without affecting lymphocyte functions. Small molecule CDK 4/6 selective inhibiters exerted the same effect and inhibited MMP-3 expression by SF. They worked collaboratively with anti-IL-6 receptor antibodies. Next, we focused on triggering receptor expressed on myeloid cells (TREM)-1 expressed by macrophages and neutrophils. Its activation augments multiple inflammatory cytokine production, which lead to SF proliferation. Its inhibition suppresses pathological inflammation with maintaining minimal inflammatory cytokine production for anti-microbial defense. We reported that TREM-1 blockade ameliorated an animal model of RA. We have identified the TREM-1-ligand and raised monoclonal antibodies, administration of which ameliorated the animal model. Anti-TREM-1 treatment will be a new anti-rheumatic therapy that is not associated with a increased risk of serious infection.

S11-4

Immune disorder and bone destruction in the pathogenesis of rheumatoid arthritis

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Conflict of interest: None

Introduction Osteoclasts (Oc) play a vital role in bone destruction in the pathogenesis of rheumatoid arthritis (RA). We reported 6 findings regulating joint destruction in RA. **1.** In 1996, we showed that IL-6 and soluble IL-6 receptors (sIL-6R) in synovial fluids from RA patients are responsible for Oc formation and that authentic Oc are present in synovial tissue of RA patients. **2.** In 1999, for the first time, we showed that sufficient IL-17, a T-cell-derived cytokine, is detected in synovial fluids from RA patients using conventional ELISA and that IL-17 induces osteoclastogenesis via PGE2 expression of in osteoblastic cells. IL-17 induces osteoclastogenesis in a culture of monocytes alone (Yago et al. 2009) **3.** In 2001, we demonstrated using human T cells and monocytes that human T cells induce osteoclastogenesis from peripheral human monocytes through their RANKL expression. We also demonstrated that CD4+ T cells in synovial tissues from RA patients express RANKL, and that the ratio of RANKL to OPG in synovial fluids is elevated. In 2005, we reported that human IFN-γ-

producing T cells (Th1 cells) induce human osteoclastogenesis from monocytes via RANKL production from Th1 cells, and that T cells expressing both IFN-γ and RANKL are elevated in the peripheral blood of RA patients. **4.** In 2005, we demonstrated that GGA, an anti-ulcer drug, inhibits human osteoclastogenesis and prevents bone loss in tail-suspended rats and ovariectomized rats (Nanke et al.). **5.** In 2009, we reported that a novel peptide from T-cell leukemia translocation-associated gene (TCTA) protein inhibits human osteoclastogenesis and the function of mature Oc, preventing cellular fusion by TCTA protein and a putative counterpart molecule. **6.** In 2010, we detected a novel ionchannel on the plasma membrane of human Oc. Antibodies against the ion-channel inhibit human osteoclastogenesis. **Conclusion** We are now trying to make further findings of human Oc to develop novel therapies.

S11-5

Anti-cytokine therapy and bone metabolism in rheumatoid arthritis

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Conflict of interest: None

Loss of bone mass in patients with rheumatoid arthritis (RA) causes decreases in ADL. In a total of 344 patients with RA (40 male and 304 female; mean age, 63 years; mean duration of RA, 13 years), bone mineral density (BMI) was measured and the annual rate of change was assessed. BMD at the femoral neck (both neck area and total area) and lumber spine (average of L2-4) was significantly decreased. Especially the average reduction of BMD at the neck area was 2.8%. To determine factors affecting changes in BMD of this area, the univariate analysis was firstly performed. Eighteen items were selected as an explanatory variable, including age, sex, BMI, duration of RA, CRP, anti-CCP antibody, serum osteocalcin, urinary NTX, presence of lumber compression fractures, HAQ score, having working or not, frequency and the kind of exercise, hospitalization for one month or more, average amount of daily steroids, average amount of weekly MTX, administration of bisphosphonate, and administration of biologic agents. The result showed significant association with 7 items including HAQ score, having working or not, frequency of exercise, the presence of lumber compression fractures, amount of steroids, and administration of infliximab (IFX). Assuming these 7 factors for explanatory variables and increase or decrease in BMD for dependent variable, logistic regression analysis was performed. The result showed that low HAQ scores, the absence of lumber compression fractures and administration of IFX were significantly associated with increase in BMD. Based on these findings, bone metabolism markers were measured in these IFX-treated RA patients. During the treatment of IFX, a bone resorption marker, urine NTX decreased markedly and the serum osteocalcin, bone formation marker, increased significantly. In conclusion, anti-TNF therapy with IFX inhibits bone resorption and promotes bone formation, thus preventing the decrease in BMD and osteoporosis in rheumatoid arthritis patients.

S12-1

Mechanisms that regulate specific autoimmune responses in patients with connective tissue disease

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Conflict of interest: None

Autoantibodies to various nuclear, cytoplasmic, membrane, and plasma proteins are detected in patients with connective tissue diseases. Pathogenic activities of autoantibodies to nuclear and cytoplasmic proteins are still matter of debates, but antibodies to organ-specific antigens such as platelet membrane glycoproteins are known to be involved in the pathogenic process. Autoantibodies in patients' sera usually have high affinity and are of IgG isotype, indicating a critical role of T-cell dependent process. We have analyzed autoreactive $CD4^+$ T cells by focusing on those reactive with topoisomerase I, platelet GPIIb/IIIa, β2-glycoprotein I, and myeloperoxidase, and have found that (i) autoreactive $CD4^+$ T cells recognize 'cryptic' epitopes, which are generated at a subthreshold level by the processing of native autoantigens under normal circumstances; (ii) their recognition is restricted by HLA class II alleles associated with the disease susceptibility; (iii) they mainly produce Th1 cytokines; and (iv) they have capacity to promote autoantibody production from B cells. In fact, we have shown in a mouse model that transfer of a single autoreactive $CD4^+$ T cell clone can elicit production of autoantibodies and resultant expression of disease phenotype. Autoreactive T cells are also detected in healthy individuals, but they are activated *in vivo* only in the patients. These findings strongly suggest that autoantibody responses depend not only on the presence of autoreactive $CD4^+$ T cells, but also on mechanisms that facilitate presentation of cryptic peptides by antigen-presenting cells. This determines the specificity of the autoimmune response, which is further promoted by genetic predisposition and dysfunctional regulatory function. Studies examining processes that induce presentation of autoantigenic cryptic peptides would be useful in clarifying mechanisms for initiation of pathogenic autoantibody responses and in identifying novel therapeutic targets.

S12-2

Differentiation of T helper cell and autoimmunity

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Conflict of interest: None

CD4 positive T cells (T helper cells, Th cells) regulate the immune response by differentiating into various effector subsets. Th1 and Th2 cells enhance cellular and humoral immunity, respectively. Thus, it has been proposed that the abnormality of Th1/Th2 balance is closely related to the pathogenesis of autoimmune diseases. Accumulating evidence that cannot be explained by this dichotomy, however, has led to the identification of novel Th subsets, among which Th17 cells are being especially vigorously investigated. Th17 response is reported to be important for the eradication of bacteria and fungi, mainly through the activation of neutrophils. Th17 cells also play an important role in mouse collagen-induced arthritis. Monoclonal antibodies to interleukin (IL-) 17, which is a critical cytokine produced by Th17 cells, are now under clinical testing as drugs towards human inflammatory diseases including rheumatoid arthritis. Th-subset differentiation is defined by the immediate environments around the Th cells, especially the cytokine profile. In the course of Th-subset differentiation, transcription factors that are specific to each Th subset are induced that lead to the expression of various effector molecules. **"**Master regulator transcription factors", which have a key role in effector Th-cell differentiation, have been identified in each subset. Transcriptome analysis of Th1/2/17 cells showed that the transcription factor c-Maf is significantly induced in Th17 cells. We have been engaged in clarifying the role c-Maf plays in Th-cell differentiation by performing an analysis of T-cell specific c-Maf transgenic mice and the development of bone marrow chimera in which the T-cells lack c-Maf. We also will present our data on human Th cells and discuss the network of transcription factors in Th-cell differentiation and its implication in the pathogenesis of autoimmune diseases.

S12-3

Regulation of the development of autoimmune disorders by the control of transcription factors expression specific for Th cell differentiation

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Conflict of interest: None

CD4+T cells play a critical role in the generation of rheumatoid arthritis (RA). Recent studies reported the pathogenicity of IL-17 producing Th-17 cells in RA. However, the regulatory mechanism of CD4+T cell differentiation in the development of arthritis is not clarified. Collagen induced arthritis was induced in T cell specific T-bet transgenic (T-bet Tg) mice, and significant suppression of CIA was observed in T-bet Tg mice compared with wild-type C57BL/6 (WT) mice. In vitro experiments revealed that IL-17 production from type II collagen (CII) reactive T cells was not detected inT-bet Tg mice, and that overexpression of T-bet and down-regulation of RORγt in CII reactive T cells in T-bet Tg mice. Although CD4+T cells from naïve WT or T-bet Tg mice were cultured in the condition favoring Th-17 differentiation, IL-17 production and RORγt expression were inhibited in T-bet Tg mice. T-bet Tg x IFNγ$^{-/-}$ mice were generated by crossing T-bet Tg mice and IFNγ$^{-/-}$ mice. In vitro experiments of Th-17 differentiation revealed that IL-17 production from CD4+T cells was also inhibited in T-bet Tg x IFNγ-/- mice. These results showed that overexpression of T-bet in T cells suppressed the development of autoimmune arthritis by the inhibition of CII reactive Th-17 differentiation via IFNγ-independent mechanisms. Next, we generated T cell specific RORγt transgenic (RORγt Tg) mice, and induced CIA. Unexpectedly, CIA was significantly suppressed in RORγt Tg mice compared with WT mice. IL-17 production from type II collagen (CII) reactive T cells was elevated in RORγt Tg mice. However, anti-CII antibody in sera was lower in RORγt Tg mice than that in WT mice. We are currently doing adoptive transfer experiments to clarify the regulatory mechanism of RORγt overexpression. In conclusion, the generation of autoimmune arthritis was regulated by the expression of transcription factor T-bet and RORγt.

S12-4

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. Recently, 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. Interestingly, 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. In contrast, CD4+CD25+ Treg from MRL/+ mice failed to exhibit therapeutic effect in MRL/lpr mice. In addition, in NP-OVA immunized RAG1 deficient mice transferred with B cells and OVA specific OT-II cells, co-transfer of CD4+CD25-LAG3+ Treg suppressed anti-NP antibody production. In in vitro analysis, CD4+CD25-LAG3+ Treg from OT-II mice suppressed anti-NP antibody production in co-culture of B cells and helper T cells from NP-OVA immunized C57/B6 mice. Notably, CD4+CD25-LAG3+ Treg from B6.lpr mice showed reduced capacity to suppress in vivo antibody production, suggesting that Fas-Fas ligand system plays role in the functional development of CD4+CD25-LAG3+ Treg. 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.

S12-5

Regulatory B cell in autoimmunity

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Conflict of interest: None

B cells play critical roles in the pathogenesis of autoimmune diseases including systemic lupus erythematosus and rheumatic arthritis. Indeed, B cell-targeted therapies including mAbs to CD20, CD22, and BAFF are currently under evaluation in the treatment of human SLE patients. However, the results of these clinical studies also elucidate the complexity of B cell functions. SLE is a prototypic multisystem autoimmune disease characterized by the production of autoantibodies and the involvement of most organ systems. Recent studies have revealed that B cell is not just an antibody-producing cell but has more diverse functions in the immune system. These functions include antigen-presentation, production of various cytokines, lymphoid organogenesis, differentiation of T effector cells, and influence of antigen-presenting dendritic cell function. Recently, “regulatory B cells” have been identified. Murine regulatory B cell is a phenotypically unique subset of spleen that share phenotypic markers with both B-1 and marginal zone B cells, and is competent for IL-10 production. Regulatory B cells suppress inflammation and autoimmune disease in mice, including contact hypersensitivity, experimental autoimmune encephalomyelitis, inflammatory bowel diseases, and arthritis. The complexity of B cells in autoimmune diseases is due to this double-edged role of proinflammatory and anti-inflammatory functions.

S12-6

Innate lymphocytes and autoimmunity

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Conflict of interest: None

Innate lymphocytes abundantly exist in mucosal tissues and play an important role as a first line defense against various endogenous and exogenous stimuli. Innate lymphocytes include NK cells, gdT cells, iNKT cells, natural helper T cells. Mucosal-associated invariant T (MAIT) cells are a subset of innate-like lymphocytes which are restricted by MHC class 1b molecule, the MHC-related molecule-1 (MR1). MAIT cells express an invariant TCRa chain: Va7.2-Ja33 in humans and Va19-Ja33 in mice with a limited set of Vb chains. MAIT cells express NK markers such as NK1.1 in mice and CCD161 in human, and therefore are a subset of NKT cells. In this symposium, the data related to innate lymphocytes including iNKT cells and MAIT cells in human autoimmune diseases and their animal models will be presented.

S13-1

Immunosuppressive therapy for systemic lupus erythematosus

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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, 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. Five patients presented with International Society of Nephrology/Renal Pathology Society (ISN/RPS) class I, 63 with II, 21 with III or III+V, 73 with IV or IV+V and 25 with V. 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. Mycophenolate mofetil (MMF) was reported to be usuful for inducing lupus remission and maintenance as well. In this presentation, the successful treatment of MMF will be shown in our patients with active systemic lupus erythematosus.

S13-2

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 based on the partial amino acids sequence of the affinity purified protein from porcine spleen in the University of Fukui. Syk is activated by various physiological stimulations, and is required for the activation of immune cells, such as mast cells, macrophages, osteoclasts, and B cells. In addition, Syk is involved in the pathogenesis of leukemia (M3). Recently, novel Syk inhibitors (R112, R406, R788) were developed and its usefulness has been evaluated in the treatment of allergic rhinitis, rheumatoid arthritis, and idiopathic thrombocytopenic purpura. Moreover, association of Syk in systemic lupus erythematosus has been reported. In this session, I will introduce the structure and function of Syk, and then review the novel Syk inhibitors and their current status.

S13-3

Anti-BAFF antibody and TACI-Ig

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Conflict of interest: None

Efficacy of B-cell-targeting therapy in autoimmune diseases highlights a pivotal role of B cells in the pathogenesis of autoimmunity. Systemic lupus erythematosus (SLE) is the prototypic systemic autoimmune disease that is characterized by the production of a plethora of autoantibodies. In contrast to our expectations, however, almost all trials testing novel therapeutic agents for SLE have been failed. B-cell activating factor (BAFF) and a proliferation-inducing ligand (APRIL) are the TNF family cytokines and are expressed on monocytes, DCs, activated T cells and some malignant B-cells. BAFF interacts with transmembrane receptors BAFF-R, TACI and BCMA, the latter two of which are also bound with APRIL. Stimulation of all three receptors promotes B-cell survival and differentiation. SLE patients have elevated serum levels of BAFF that correlates with the anti-dsDNA antibody titers. Belimumab is a fully human mAb that binds BAFF, thus inhibiting its activities on B cells. Belimumab entered two Phase III trials, termed BLISS-52 and BLISS-76, evaluating the drug's efficacy, safety, and tolerability in seropositive SLE patients at 52 weeks and 76 weeks. Notably, these trials used a newly designed SLE responder index (SRI) to measure an individual patient's improvement from baseline. At 52 weeks, both trials met their primary end points, and statistically significant improvement versus the placebo group was observed. Atacicept is a recombinant fusion protein made of the extracellular ligand-binding portion of TACI fused to the Fc portion of a human IgG. It is a soluble receptor that binds BAFF and APRIL. Although a Phase II/III lupus nephritis trial in SLE patients gave disappointing results and the study was discontinued due to the development of severe infections in some patients, a new Phase II/III trial of atacicept in generalized SLE is underway. We hope to manage this devastating disease with a novel B-cell-targeting approach in the near future.

S13-4

Anti-CD20 and anti-CD22 antibody therapy for patients with refractory systemic lupus erythematosus (SLE)

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Conflict of interest: None

SLE is a systemic autoimmune disease induced by overproduction of auto-antibodies by activated B cells and tissue injury by immune complex. Therefore, B cells are a potent therapeutic target for SLE. Although CD20 antibody rituximab shows obvious efficacy in some patients, foreign clinical trial of rituximab for patients with SLE such as EXPLORER have been failed. We investigated the phenotypic changes of peripheral lymphocytes in patients with SLE after rituximab. Rituximab rapidly depleted naïve and memory B cells from the peripheral blood. In the patients with prolonged remission, the memory B cells remained depleted while naïve B cells recovered, and the expression levels of CD80 remained down-regulated for 6 years. There was also a decrease of memory T cells relative to naive T cells, and the expression of CD40L and ICOS on $CD4^+$ T cells rapidly decreased and remained down-regulated for 6 years. In two patients, increase in the number of memory B cells with up-regulation of CD80 expression was noted just before relapse. In other two patients with relapse, however, recovery of $CD4^+$ memory T cells with up-regulation of ICOS expression was noted with no change in the number of memory B cells. These results suggest that the phenotypic changes of the peripheral B cells results in the inhibition of T cell differentiation and activation mediated by B cells and thereby, long-term remission of SLE. Activated memory B cells or $ICOS^+$ $CD4^+$ memory T cells reappeared in association with relapse, probably reflecting the heterogeneity of SLE. Meanwhile, clinical trial of anti-CD22 antibody epratuzumab has been conducted and confirmed its efficacy for refractory SLE. A main mode of action by epratuzumab is believed to be the down regulation of the BCR signaling through ITIM mo-

tif, differing from rituximab. These B cell targeting therapy by biological product could be promising new therapeutic agents for the treatment of SLE.

S13-5

Anti-interferon antibody in SLE

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Conflict of interest: Yes

Systemic Lupus Erythematosus (SLE) is a prototype autoimmune disease characterized by a multi-system clinical manifestations. Glucocorticoids and immunosuppressing agents such as cyclophosphamide, azathioprine, mizoribin, tacrolimus have used for the management of SLE. Although the short-term prognosis has been improved by these treatments, middle to long-term prognosis of SLE is still graved and unsatisfactory. Enormous effort has been paid for identifying the appropriate target molecules through the comprehensive approach such as mRNA expression analysis. Among those, type I interferon (IFN) and type I IFN-induced molecules have been demonstrated to be up-regulated in peripheral blood from the SLE patients, facilitating the clinical development of biological agents against interferon-α. Focusing on human monoclonal antibodies against IFN-αsuch as sifalimumab and humanized anti-IFN-α (rontalizumab), the disease type, criteria for inclusion and exclusion, and the trial design will be introduced. IFN-γis similarly attracted attention for the researchers for the pathogenesis of SLE and the possible candidates as the molecular intervention. Fully human monoclonal antibody against IFN-γ (AMG-811) is now on phase 2 dose ranging study. I would like to summarize the information and discuss the potential benefit from the new biologics targetinginterferon in the treatment strategy in SLE.

S14-1

New Horizons of Molecular Targeted Therapies in Rheumatoid Arthritis: an Overview

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The advent of biologic therapies in rheumatology marked a distinct change in the development of therapeutics from mostly empiric clinical analyses of broadly immunosuppressive molecules such as methotrexate and cyclosporine A in the 1980s and 1990s to the specific selection of therapies designed to have biological effects that directly target key cytokines or important lymphocyte subsets in the 1990s and since the year 2000. Thus, blockers of TNF, IL-1, and IL-6 as well as B-cell depleting and T-cell modulating treatments have all been introduced into the practice of rheumatology in the past 15 years. Experience with such drugs is rapidly accumulating, and it is clear that rheumatologists continue to learn how better to use these agents for the individual patient, while for some of these targets additional biologics are being tested with specific distinguishing features. More biologics with other molecular targets are already in use for other indications (e.g., anti-BAFF for SLE, anti-IL12/23 for psoriasis, anti-α4-integrin for multiple sclerosis), or are being developed for various rheumatological indications (anti-IL17 and others). In parallel, there has been a major focus in pharmaceutical development towards small molecular compounds with efficacy at the same level as biologics, hoping to achieve such efficacy with the convenience of oral dosing and the potential for more favorable cost effectiveness. For many years these developments proved unsuccessful, but in recent years promising results from clinical trials have been reported. Thus, the inhibitors of several protein kinase enzymes, most notably Janus kinase (JAK) and spleen tyrosine kinase (Syk) have demonstrated meaningful clinical benefits. Finally, completely novel targets are also being explored today as well as non-pharmacological methods of immunomodulation such as vagal nerve stimulation.

S14-2

Anti-rheumatic effect of small-molecule drugs

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Conflict of interest: None

Biologics targeting inflammatory cytokines has opened the gate of the new world of treating rheumatoid arthritis (RA). Treatment with biologics on methotrexate (MTX) background has made it possible to not only induce remission but also biologic free and drug free remission. However, ~30% of patients poorly respond to treatment and due to parenteral administration and expense, difficulty in induction and continuation of biologics can be experienced. Small-molecule drugs targeting Janus kinases (JAK) and Spleen tyrosine kinase (Syk) has gathered attention since they are orally available and highly effective in RA patients resistant to MTX or anti-TNF inhibitors with a short half-life. JAK and Syk are kinases activated in the cytoplasm immediately after extracellular signals (ie cytokines, immunoglobulins, MHCs) that binds to their unique receptors expressed on the cell surface. Recent results from the clinical trials with a JAK-inhibitor (tofacitinib) and a Syk-inhibitor (R788) has gathered attention with its high anti-rheumatic effect similar to biologics. At the ACR 2011, efficacy and safety of tofacitinib were reported to be maintained up to 36 months and was also shown to possess inhibitory effect on bone destruction. Notably, the phase II study conducted in Japan for patients resistant to MTX resulted in over 90% achieving ACR20 and over 30% achieving ACR 70 with tofacitinib. As a matter of fact, number of compounds targeting JAK is now under clinical trials. For instance, INCB28050 specifically targeting JAK1/2 was also reported to be as effective as tofacitinib. Depending on the process of synthesis of these small-molecule drugs, it is expected to be less expensive compared to biologics. Therefore, small-molecule compounds are expected as a problem-solver of biologics and trigger another paradigm shift in treatment of RA. In this symposium, recent advance in JAK inhibitors will be reviewed and discuss on the possible mechanism of action.

S14-3

Current concept of anti-TNF therapy for rheumatoid arthritis

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Conflict of interest: Yes

Inhibitors of TNF represent important treatment advances for rheumatoid arrhtitis (RA). TNF inhibitors offer a targeted strategy that contrasts with the non-specific immunosuppressive agents traditionally used to treat the disease. Information on the benefits from these agents and on their adverse effects are being collected through clinical studies. Infliximab has been used since 2003 in Japan, followed by other antibody agents such as adalimumab, golimumab and certolizumab. Etanercept, a soluble TNF receptor fusion protein, is as usuful as anti-TNF drugs. In terms of the efficacy and safety, there are no great differences among the agents. Anti-TNF has been used not only for remission-induction

but also for improving the quality of life for the affected patients. In this symposium, we are going to discuss how to use infliximab in the high dose. We have evaluated the efficacy of the dose-escalation infliximab (IFX) protocol for RA since 2009. Nineteen patients were treated with this protocol (Group C) and their outcomes were compared with those of 31 historical controls treated with the dose fixed IFX before 2006 (Group A), or 27 patients between 2007 and 2008 (Group B). No significant differences were found in the backgrounds between the group B and C. Seven (36.8%) in group C achieved clinical remission during the first 6 months, though the remission rate of group C were not significantly improved than that of group B (p=0.428). The differences in the incidences of adverse events were not shown between group B and C. Therefore, the dose-escalation IFX therapy is well tolerated for the patients with active RA. In addition, high dose of methotrexate was approved in 2010, and consequently we have a number of options in the treatment for rheumatoid arthritis in Japan. We are exploring the efficacy of the combination of high dose MTX and the anti-TNF agent in early RA with poor prognosis.

S14-4

New anti-cytokine therapies in RA

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Conflict of interest: Yes

Substantial progress has been made to identify net molecular targets for intervening systemic autoimmune diseases such as Rheumatoid Arthritis (RA). Among those candidates, I would like to first focus on IL-17A for RA in this symposium and introduce updates for clinical information. The pre-clinical information, background how Th17 and IL-17 is important in inflammation and immunology for understanding of the pathogenesis of RA will be reviewed. Based on the pre-clinical knowledge, the clinical trial and their design are shown and discussed. Next, two monoclonal antibodies including IgG4 humanized anti-IL-17 (LY2539821) and IgG1 human anti-IL-17A (secukinumab) has been reported to show efficacy and safety in the phase II clinical trials. Now, the additional clinical trials have been carried out. I would like to summarize these information and discuss the potential benefit from the new biologics targeting IL-17A in the management of RA. Finally, the possible positioning of these new agents in treatment algorithm for RA will be discussed.

S14-5

T cell targeted therapies for rheumatoid arthritis

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Conflict of interest: Yes

The association between certain polymorphisms of major histocompatibility complex (MHC) class II alleles and rheumatoid arthritis (RA) suggests antigen presentation to CD4+ T cells is crucial in the pathogenesis. In fact, the presence of CD4+ T cell infiltration within rheumatoid synovial tissues is prominent. In animal models, a crucial role for antigen-specific CD4+ T cells has also been reported. Several lines of evidence suggest that T cells should play important roles in the pathogenesis through production of proinflammatory cytokines, promotion of autoantibody production by B cells, and activation of synoviocytes and osteoclasts. Although anti-cytokine therapies are generally accepted as important strategies for improvement of RA, some patients may exhibit inadequate response. Cytotoxic T lymphocyte-associated antigen 4 (CTLA4) is an inhibitory receptor on the T cell surface that binds with CD80 and CD86 on antigen presenting cells. Abatacept (CTLA4-Ig) is a fusion protein that consists of the extracellular domain of CTLA4 and the Fc portion of IgG1. Abatacept binds to CD80 and CD86 on antigen presenting cells, and it thus prevents the second activation signal in T cells. Abatacept has been reported to be effective in treating patients with RA. Inhibition of structural damage of the joints was also significant. Abatacept has an acceptable safety profile and is well tolerated in patients with RA.

S14-6

B cell-targeting therapy in rheumatoid arthritis

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Conflict of interest: Yes

Rheumatoid arthritis (RA) is a representative inflammatory autoimmune disease thought to involve disturbances in T- and B-cell functions and recent research has highlighted the role of B cells in joint inflammation and led to RA trials for rituximab. Rituximab, a chimeric monoclonal antibody that selectively targets and depletes CD20-positive B cells, has demonstrated clinical efficacy and long-term safety in patients with active RA and it was approved in USA and EU for the treatment of RA with inadequate response to TNF-inhibitors. Ocrelizumab is a humanized monoclonal antibody that also selectively targets and depletes CD20-positive B cells. Ocrelizumab was clinically effective therapies to improve signs and symptoms in a difficult-to-treat patient population, having failed one or more TNF-inhibitors. However, ocrelizumab revealed higher rates of serious infections than placebo that was consistently observed throughout the program in all patient populations. The overall evaluation of clinical efficacy and safety led the conclusion that further development and an application for regulatory approval of ocrelizumab in RA were not warranted. Thus, B cell-targeting therapies have not been approved in Japan. However, the following three appears to have a potential for the treatment of RA, which are currently under the clinical examination in Japan; 1) a CD20-small molecule immunopharmaceutical (SMIP) SBI-087, 2) anti-BAFF antibody belimumab which inhibits co-stimulatory signaling in activated B cells, 3) a small molecule compound of spleen tyrosine kinase (Syk) fostamatinib, which inhibits B cell receptor and Fc receptor-mediated activation signals in B cells. Future perspective of B-cell targeting therapies will be documented.

S15-1

Overview of cohort studies for rheumatoid arthritis in the world

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Conflict of interest: None

Rheumatoid arthritis is a chronic and systemic inflammatory disease that affects joints and extraarticular organs. The treatment for rheumatoid arthritis has been dramatically improved by introduction of biologics and potent immunosupressants. It must be preferable that the effects of treatment should be evaluated not only by short-term outcomes such as disease activity and physical dysfunction but by long-term outcomes such as comorbidities (infection, cardiovascular diseases and malignancies) and mortality. The observational cohort studies are appropriate methods to evaluate long-term outcome. In western countries, there are many population-based, hospital-based or inception cohorts established for long time ago. Norfolk Arthritis Register (NOAR) was started in 1989 in England and population-based cohorts in Sweden in 1964,

in Finland in 1987 and in Olmsted in the United States in 1955. Numerous reports dealing with trends of disease activities and physical function, cardiovascular events, infections and mortality have been derived from these cohorts. After the introduction of biologics to treatment for rheumatoid arthritis, so called biologics registers such as BSRBR in England, BIOBADASER in Spain, RABBIT in German, ATIS in Sweden and DAMBIO in Denmark had been established in accordance with each country's own circumstances including medical economy. Most of those countries have national databases of hospitalization, cancer and death and they could link to those databases, which are impossible in Japan. It is important to know the difference between cohorts in the criteria of entry and between counties in the criteria for administration of biologics.

S15-2

NinJa cohort

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Conflict of interest: None

NinJa (National Database of Rheumatic Diseases by iR-net in Japan) is the only nationwide multicenter prospective cohort database in Japan since 2002. Thirty facilities have been participating in NinJa. The number of RA patients registered each year has been increasing and exceeded 7,000 since 2009. In recent years, drug therapy for RA has been remarkable advanced. Furthermore, based on advances in drugs, more aggressive treatment strategies are being introduced with early diagnosis and tight control. It's a welcome development, while there remain issues to be resolved. These problems are extra-articular lesions or complications caused by therapeutic interventions, such as interstitial lung diseases, malignant lymphomas, infections and osteoporosis. In addition, expensive therapies could cause dysfunction of universal coverage system in selecting treatment in Japan. This is also a major problem to be solved. We have been analyzing NinJa every year. As a result, the current situation and problems become apparent, as shown below. 1) DAS28 (ESR) has been improving over time, although 50-60% of patients still showing moderate or high disease activity in 2010. 2) RA-related surgery has decreased. A marked reduction has been shown in synovectomy and first joint replacement. 3) The frequency of administration of biologics has been increasing linearly since 2003, showed a slowdown in 2010 with 18.6%. 4) The frequency or dose of MTX has increased over time. 5) The reasons for serious adverse events other than treatment of RA are infections, interstitial lung diseases and osteoporosis-related diseases. 6) The cost of anti-rheumatic drugs in one RA patient per year continues to increase over time, which reached about 38 million-yen in 2010. NinJa is just observational epidemiological study. However, it shows the current situation and problems, namely, that plays an important role in validating the results of therapeutic interventions continue to change.

S15-3

Nagasaki cohort

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Conflict of interest: Yes

Cohort study is indispensable to investigate the diagnosis, therapeutic efficacy and prognosis of rheumatoid arthritis (RA). Our department has started the cohort study of early arthritis at 2003. Our study is a prospective clinical investigation that includes MRI of both wrist and finger joints and recently, US. We have summarized the results obtained from our Nagasaki cohort study. 1. Establishment of Nagasaki score: Nagasaki score is a classification criteria of RA from early arthritis patients. The subjects are evaluated for their positive or negative status with respect to 3 objective measures at entry: anti-CCP Abs and/or RF, MRI-proven symmetrical synovitis and MRI-proven ostitis and/or bone erosion. The patients who are positive for at least 2 of these measures classified as RA with around 80% PPV. Furthermore, in early arthritis patients positive with both autoantibodies and MRI-proven ostitis, PPV of RA claasification is almost to 100% Also, there is a close correlation of Nagasaki score with 2010 RA classification criteria. 2. Evaluation of joint prognosis: We have found that MRI-proven ostitis at entry is a very strong predictor of plain radiographic progression at 2 years in early RA patients. 3. Evaluation of therapeutic efficacy: We have found that significant improvement of MRI-proven ostitis score (RAMRIS ostitis score declined less than 33% as compared with the baseline) indicates the protection of structural damage in early RA patients with the tight control approach. 4. The role of US in early arthritis: We have found that active articular synovitis, determined as PD grade $\geqq$ 2 by EULAR definition, is specific in early RA patients. The combination of 2010 RA classification criteria with PD grade $\geqq$ 2 role is very useful to differentiate RA from non-RA. 5. Importance of anti-CCP Abs in palindromic rheumatism, anti-CCP Abs and MRI-proven ostitis in Sjögren's syndrome have been also reveled by Nagasaki cohort.

S15-4

Registry of Japanese rheumatoid arthritis patients for long-term safety (REAL)

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Conflict of interest: Yes

Background. The introduction of tumor necrosis factor (TNF) inhibitors for treatment of rheumatoid arthritis (RA) is a major therapeutic breakthrough. Because biologics, including TNF inhibitors, have become indispensable and widely used clinical armament for treatment of RA, assessment of their safety is important. We therefore established the Registry of Japanese Rheumatoid Arthritis Patients for Long-term Safety (REAL) database in 2005 to compare the safety of treatment between biological DMARD and non-biological DMARD. **Methods**. We enrolled patients meeting the 1987 American College of Rheumatology criteria for RA and starting treatment with biologics (the exposed group) or non-biological DMARD (the unexposed group) at the time of study entry. In addition, patients receiving treatment with non-biological DMARD at the time of study entry are also enrolled as the unexposed group until 2007. As of December 2011, 1,920 RA patients were enrolled in the REAL from 27 hospitals. **Results**. Analysis of serious infection in the first year after enrollment in the REAL database revealed that the use of TNF inhibitors is a significant independent risk factor for serious infection (relative risk 2.37, 95% CI

1.11–5.05, p = 0.026). Analysis of serious infection during three years revealed time-dependent increased risk: the relative risk (95% CI) of continuous use of TNF antagonists for SIs after adjusting for baseline and time-dependent covariates were significantly elevated for over all [1.97 (1.25-3.19), p =0.0045] and for the first year [2.40 (1.20-5.03), p =0.0157], but not for the second and third years combined [1.38 (0.80-2.43), not significant]. **Conclusion**. The nation-wide, multi-centered REAL database has provided unique evidence for the safety of TNF antagonists in clinical practice. Nation-wide registry for RA patients should be maintained to assess mid- to long-term effectiveness, safety, and benefit-risk balance for new treatments that will emerge in the next decade.

S15-5

IORRA cohort

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Conflict of interest: None

The management of rheumatoid arthritis (RA) has been dramatically altered with the introduction of new DMARDs and biologics. There was a significant change in the goal of treatment, from short-term to long-term improvement in quality of life during the past decade, with the fact that achieving "remission" or "low disease activity state" is a realistic therapeutic goal nowadays based on these recent developments in RA treatment. However, it is extremely difficult to quantitatively evaluate such changes in daily practice. The results from randomized controlled trials (RCT) are considered to have a higher evidence level, however, we should be aware that RCTs include strict selection criteria, thus, the patients registered into RCT are usually selected patients but not the representative of patients in daily practice. Furthermore, it is hard to evaluate long-term outcomes in patients with RA using RCT since RA is a chronic disease. Therefore, to understand what is going on in real world, the importance of the observation cohort study that verifies a long-term outcome and safety is emphasized. There was no prospective observational cohort study in Japan until the establishment of IORRA (Institute of Rheumatology Rheumatoid Arthritis) study, just when treatment strategy of RA faced to a rapid change or evolution. Eleven years have passed since IORRA study was launched in our institute. By accumulating information from more than 5,000-6,000 RA patients using patient self-report questionnaire biannually, analysis has conducted to find the way for the better outcome of patients, and many scientific papers have been published. The concept of IORRA is transplanted into all PMS studies of biologics, and IORRA stimulated the establishment of other registry studies of RA in Japan, indicating that importance of cohort study in rheumatology has become greater and greater. In this session, IORRA system and the evidences produced through IORRA will be discussed.

S16-1

The timing of the surgical treatment to introduce from internal medicine to orthopedist

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Conflict of interest: None

Orthopedic surgery was regarded as a surrogate marker for joint destruction in RA. A recent paradigm shift has occurred dramatically in RA therapy after the use of biologics. The pharmacotherapy plays a key role of RA treatment, and the surgical treatment for RA patients is decreasing. However, continuing joint problem may still occur even after reaching clinical remission treated with MTX and/or biologics. In addition, there are some patients who never responded to pharmacotherapy or could not adapted because of their complications. Considered for QOL in some RA patients, surgical management is conducted prior to pharmacotherapy. Therefore, non-pharmacological and surgical interventions are commonly utilized in conjunction with systemic management strategies using MTX and/or biologics. In Japan, most of rheumatologist in internal medicine and orthopedics treat each RA patient separately. And the system that treats one patient comprehensively is not established. At this symposium, we consider about cooperation with rheumatologist in internal medicine and orthopedics for RA treatment from the situation of the internal medicine. We often hesitate to consult with orthopedist in some cases. We experienced some cases as follow; ①the case that we should consult to orthopedist earlier, ②the case that the patient had not indication of surgery although we referred to orthopedist, ③the case that was able to tight control by surgery combined with pharmacotherapy, ④the case that required surgery with therapeutic progress. We did not discuss about cooperation among each rheumatologist enough until now. Therefore RA patients may not receive adequate treatment. The indication of surgery is changing in the dramatic progress of RA treatment and realization of the more tight control. In order to contribute to improvement of QOL with RA patients, we suggested to the formulation of team medical care system by medical staff including rheumatologist in internal medicine and orthopedics.

S16-2

Timing of surgical treatment for RA: Consultation with orthopedists from the internists' viewpoint

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Conflict of interest: None

Rheumatoid arthritis (RA) treatment has advanced remarkably in recent years. Previously treatment was only able to control symptoms; however, improved diagnostic technology for RA has made its early diagnosis and treatment possible. The time has now come to realistically aim at remission of RA by tight control for treat-to-target (T2T). However, internists encounter many RA patients who are forced to undergo surgical treatment, and it is important for internists not to miss the timing of surgical treatment for RA. Internists should know the following about RA treatment: (1) For what types of RA is surgery indicated?; (2) When should internists consult with orthopedists regarding the timing of RA surgery?; and (3) How should internists follow-up patients with RA so as not to miss the timing of surgical treatment? In this symposium, taking the above into consideration, I would like to speak about the timing of surgical treatment for RA with respect to consultation with orthopedists from the internists' viewpoint. This will be illustrated with some actual case examples.

S16-3

Timing of the surgical treatment for the patients with rheumatoid arthritis

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Conflict of interest: None

Treatment of rheumatoid arthritis changed dramatically with

biologics, however, not all the cases showed the improvement of symptom and joint destruction. Thus, the surgical treatment for the advanced cases has an important role in the management of the patients with rheumatoid arthritis. In this symposium, we like to focus on the follow-up method and the indication for the surgery. Plain X rays of the key joints such as shoulder, elbow, cervical spine and large joints in the lower extremities are recommended to be taken for the comparison. "Progressive joint destruction and loss of function in spite of modern tight control" is a gold standard of indication for the surgical treatment. We like to emphasize it through case presentations.

S16-4

The collabolation with orthopaedic surgery and interanal medicine for patients with rheumatoid arthritis If you introduce the patient involved severe knee pain

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Conflict of interest: None

It is often recommended that the operative timing of total knee arthroplasty for knee involvement in RA is their dysfunction such as severe pain and remarkable range of motion limit, severe difficulty in walking. In A-P X ray, Larsen grade4 are generally consensus before falling in large bone defect, severe instability by dysfunction of collateral ligament, severe osteoporosis. However, I think even if the knee involvement is Larsen grade3, severe pain and/or instability with severe extension lag exist subchondral bone breakdown, I recommend the total knee arthroplasty. Because it is impossible the reproduction of articular cartilage involved severe synovitis even if makes full use of biological DMARDs, and the orthopedist or rheumatologist have to recognize it is as an irreversible change. Some patients say they have no pain if they keep still to make a remark to escape from the thought, however we must recommend the knee arthroplasty. However, contribution degree to QOL can finally include the age, life background, we must judge the operation. In this current symposium, I would like to ask decision of treatment strategy about some cases with severe knee involvements for these past several years after it was used biological DMARDs in daily practice in Japan. (Case1) 62 years old woman with 28years RA duration by medication of oral MTX 6mg a week had left knee mild pain. Her A-P X-ray revealed Larsen grade4, however she can walk smoothly. (Case 2) 48 years old woman with 18years RA duration by medication of oral MTX 6mg and subcutaneous injection etanercept 50mg a week had left knee moderate pain and extension lag 20 degree. Her A-P X-ray revealed Larsen grade3 with secondary osteoarthritis change. (Case 3) 65 years old woman with 8years RA duration by medication of oral MTX 8mg a week by orthopedist in another hospital suffered bilateral knee pain and swelling with severe gait disturbance. She was introduced to our hospital for induction of biological DMARDs. Her A-P X-ray revealed Larsen grade4. (Case 4) suffered bilateral knee pain and severe knee flexor contracture. By various medical institutions, She had only conservative treatment by conventional DMARDs for a short term period. It is both knees flexion contracture extension -90 degrees for several years and could not walk. (Case 5) 61 years old woman complicated with RA+SSc, IP/PH with 10 years duration suffered right knee pain and medicated Tacrolimus in our hospital by orthopedist, division of collagen disease in internal medicine and dermatology. She fell in her garden and complicated with tibial plateau fracture nearby knee involvement Larsen grade4. Her left elbow pain is revealed intraarticular calcification.

S17-2

Management of rheumatoid arthritis patients with malignancy

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Conflict of interest: None

Background. Several novel targeted therapies as represented by biologics have been developed for treatment of rheumatoid arthritis (RA) during the past decade along with better strategies to apply these therapeutic armaments into clinical practice. Patients with RA, however, still have to spend long years with the disease and may develop various types of comorbidities including malignancies. Although recommendations or guidelines for the treatment of RA provide some treatment options in patients who developed malignancy in the past, it is sometimes quite difficult to apply them to individual patients presenting with malignancy. We investigated how rheumatologists manage RA with malignancy in clinical practice. **Methods**. We identified 26 RA patients who were enrolled in the REAL or SECURE cohort from Tokyo Medical and Dental University Hospital and developed malignancy. **Results**. Mean age at the diagnosis of malignancy of these patients were 71 +/- 9.5 years old and 15 (58%) of them were female. Twenty patients had solid malignancy; 3 prostate, 2 stomach, 2 lung, 2 colon, 2 uterine cervix, 2 liver and gall bladder, 2 kidney, 1 uterus, 1 thyroid, 1 pancreas, 1 urinary bladder, and 1 oral cavity. Five had malignant lymphoma and 1 had leukemia. Of 26 patients, 10 used biologics, 19 used disease-modifying antirheumatic drugs, 12 used methotrexate, 13 used prednisolone, and 10 used non-steroidal anti-inflammatory drugs. After the diagnosis of malignancy, less intensive treatments were provided in 17 patients. The remaining patients were not receiving intensive treatment due to low disease activity of RA at the diagnosis of malignancy or gave priority to RA treatment due to patients' or their families' preferences. **Conclusion**. Details of the treatment before and after the diagnosis of malignancy will be presented and better management of RA patients with malignancy will be discussed.

S17-3

Infection (mainly non-tuberculous mycobacteia infection)

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Conflict of interest: None

Many drugs administrated to RA patients suppress their immune system and may cause a lot of infectious diseases. Particularly, patients using anti-tumor necrosis factor (TNF) compounds are at increased risk for mycobacteriosis. TNF-α is secreted by macrophages or lymphocytes and plays an important role in phagocytosis and bactericidal action of macrophages with interleukin 12 and interferon γ. TNF-α is integral to granuloma generation and maintenance and vital to host defense against mycobacterial infection. The increased clinical use of TNF antagonists has been accompanied by increased reporting of granulomatous infectious diseases, such as tuberculosis, non-tuberculous mycobacteria (NTM) infection, and several less common conditions. Takayanagi et al reported 59 NTM cases including 50 cases with *M. avium* complex (MAC) infection. Most of them had underlying lung diseases and 8.5% of them died. Winthrop et al (2009) reviewed the US FDA MedWatch database for reports of NTM disease in patients receiving anti-TNF-α therapy. One hundred and five cases, including 73 RA patients, met ATS/IDSA pulmonary NTM disease criteria.

Most were in women (65%), and the median age was 63 years. The anti-TNF-α agents reported for these patients included infliximab (n=73), etanercept (n=25), and adalimumab (n=7). MAC was the most common etiologic organism reported (n=52), followed by rapidly growing maycobacteria (n=20). Nine patients died. Anti-TNF-α agents caused serious illnesses and poor prognosis. It is generally difficult to treat MAC and rapidly growing mycobacteria and get a complete recovery of them. Anti-TNF agents should be stopped when RA patients had these NTM and may not be resumed after NTM infection treatment. Biologics are able to be resumed in *M.kansasii* infection because it is a treatable NTM. The resumption of biologics is dependent on whether NTM is treatable. However, further study and accumulation of cases will be needed because of a few RA infected with NTM.

S17-4

Infection (Chiefly non-tuberculous mycobacteria)from the viewpoint of the rheumatologist

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Conflict of interest: None

In the past decade, the introduction of biologic DMARDs (biologics) and MTX have caused a paradigm shift in the treatment of rheumatoid arthritis (RA). It is important for clinicians to appropriately manage pulmonary complications such as MTX-associated pneumonia, tuberculosis (TB) infection and pneumocystis pneumonia (PCP) in treating RA. The IORRA cohort, which is a large observational cohort established in 2000 at the Institute of Rheumatology, Tokyo Women's Medical University, revealed that the major causes of death were malignancies and respiratory involvement among patients with RA. These findings suggest that RA with pulmonary complications should definitely be managed by both rheumatologists and respiratologists in collaboration. Although the complication of TB was induced at the beginning of the administration of biologics, the testing and treatment of latent TB could prevent the reactivation of TB. Although the mortality rate was approximately 10-20%, early diagnosis and appropriate treatment have recently improved the prognosis of PCP in RA treated with biologics. Non-tuberculous mycobacteria (NTM) is widely distributed in the environment, particularly in wet soil and rivers. Pulmonary NTM can be found in immunocompromised hosts or those with respiratory diseases. The frequency of complication with NTM infection is approximately 0.1-0.2% in RA treated with biologics. The treatment with biologics is contraindicated in RA complicated with NTM according to the guidelines established by Japanese College of Rheumatology, because there is no effective agent with which to cure NTM infection. Previously, it was not known how NTM infection should be managed during the administration of biologics in RA. Recently, a multi-institutional collaborative study conducted in Japan investigated NTM complicated by RA in patients receiving biologics. We will describe the clinical practice and management of NTM in patients with RA by reviewing several previous studies.

S17-5

Interstitial Pneumonia associated with Rheumaotid Arthiritis <From the Standpoint of a Respirologist>

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Conflict of interest: None

Pulmonary complications in Rheumatoid Arthritis (RA) patients are easier to understand if they are classified as lung diseases directly associated with RA, lung infection, drug-induced pneumonia, lung cancer, etc. Lung diseases directly associated with RA include rheumatic nodules, pleuritis, interstitial pneumonia, bronchiectasis, bronchiolitis, and pulmonary vascular lesions. Interstitial pneumonia is classified into categories such as UIP (usual interstitial pneumonia), NSIP (nonspecific interstitial pneumonia), OP (organizing pneumonia), and DAD (diffuse alveolar damage). Many reports written by rheumatologist have put these categories together such as rheumatoid lung or rheumatoid arthritis related interstitial lung disease. We previously reported the clinical characteristics and prognoses of 144 cases of lung diseases directory associated with RA (Eur Respir J. 2011 Jun;6:1411-7). Frequency was UIP>NSIP>OP=DAD. Furthermore, more than 80% of cause of death of lung diseases directory associated with RA were due to pulmonary lesions. For interstitial pneumonia associated with RA, caution is required regarding its progress, lung cancer, and chronic lung infection. The next issue is regarding treatment strategy for interstitial pneumonia and RA itself. We would like to describe that the treatment strategy differs depending on the clinical category of interstitial pneumonia and present some cases. The biggest problem in RA treatment is whether MTX can be used or not. A prospective study must be curried out in order to resolve this. At least, MTX should not be used in cases with dyspnea. At this symposium, we would like to summarize the frequency, clinical categories, diagnosis, treatment, and prognosis of interstitial pneumonia associated with RA, and treatment for RA itself with interstitial pneumonia. And we would like to present cases of UIP with complications, which also require care regarding complications by lung cancer and chronic lung infection.

S17-6

RA-related interstitial lung diseases (RA-ILD) from the viewpoint of a rheumatologist

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Conflict of interest: None

Rheumatoid arthritis (RA) is a systemic autoimmune disease characterized by poly-articular synovitis and subsequent joint destruction, with extra-articular organ involvements. Interstitial pneumonia (IP) or interstitial lung disease (ILD) is the most frequent and potentially fetal extra-articular manifestation in RA. "Interstitial pneumonia" should be recognized as a term that comprehensively represents a series of pulmonary involvements with interstitial shadow on radiologic imaging. Rheumatoid arthritis-related interstitial lung disease (RA-ILD), which arise as a specific extra-articular manifestation of RA with disease activity of arthritis, has various histological subtypes including UIP, NSIP, or OP pattern, with different therapeutic efficacy or prognosis. It is essential for making diagnosis of RA-ILD to distinguish other pulmonary disorders including drug-induced hypersensitivity pneumonitis, pulmonary infection, or concurrent combination of those conditions. Rapid and precise anti-rheumatic therapy against RA is often required for the treatment against RA-ILD as well. We had cases of RA-ILD with worsening disease activity of RA, in whom both of pulmonary and articular lesions were ameliorated with intensification of treatment by biologics. We examined clinical, radiological, and physiological efficacy of tacrolimus on 26 patients with RA-ILD for six months, and revealed general improvement in 42%, and radiological improvement in 50%. It should be avoided to provide insufficient treatment for RA, fearing pulmonary event

excessively. Moreover, after application of our criteria for prophylaxis, development of Pneumocystis pneumonia was almost completely inhibited with SMX/TMP in patients treated with biologics. In the symposium, overview of several problems in RA-ILD and our approach against pulmonary involvement in RA will be presented.

S18-1

The value and use of remission criteria in RA

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Over the years many different remission criteria have been used. The ACR remission criteria were one of the oldest but limited by the fact that fatigue was one of the components. Subsequently, remission criteria were developed based on disease activity scores such as the DAS, DAS28, CDAI and SDAI. In addition to the remission criteria definition also definitions for low disease activity (LDA) have been developed. Most recently, the ACR and EULAR came up with a new definition: the ACR/EULAR remission criteria. There are two versions: one is based on the SDAI, the other is a Boolean expression including swollen joint count, tender joint count, patient global level of disease activity and CRP. This ACR/EULAR criterion is a very strict criterion. Overall, the DAS28 remission criteria are the least stringent. However, if you take the patients in remission and in LDA together all definitions include more or less the same amount of patients. Remission and LDA are used for the treat-to-target and management recommendations. Therefore, it is important to know what the performance of the various criteria sets are with respect to the effect on physical function and radiographic damage. This has been assessed in various studies which will be reviewed.

S18-2

The validity of criteria for clinical remission of rheumatoid arthritis based on the analysis in IORRA cohort

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Conflict of interest: None

By the introduction of biologics to treatment of rheumatoid arthritis, we need to treat patients aiming remission for patients with early diseases stages. However, it became elucidated that it is not enough to keep patients in DAS28 remission for achieving structural remission. More stringent criteria for remission was proposed by EULAR/ACR in 2010, and this criteria should be validated by evaluating the long term outcome such as prevention of physical dysfunction. We evaluated these new remission criteria in the point of prevention of physical dysfunction by using the large observational Institute of Rheumatology, Rheumatoid Arthritis (IORRA) cohort database. In this symposium, we will summarize the results of the analysis and validate the new clinical remission criteria. A total of 915 RA patients with DAS28 remission in IORRA survey in April 2008 were selected and these patients were evaluated whether or not they achieved remission criteria at consecutive data collection from April 2008 to October 2010 (six data collections). Functional disability was assessed by the validated Japanese version of Health Assessment Questionnaire (J-HAQ) score. The patients who achieved new remission criteria (Boolean Trial or Boolean Practice) for 6 consecutive surveys were less aggravated physical function than the patients who achieved CDAI, SDAI or DAS28 remission criteria. The 30-60 % of patients who achieved either remission criteria only once were aggravated physical function within following 2 years. The more frequently the patients achieved the remission criteria, the less patients got disabled. From the view of preventing physical function in daily rheumatoid arthritis cohort IORRA, the new remission criteria were validated as useful criteria.

S18-3

Validation of the clinical remission criteria in rheumatoid arthritis at Keio Immunotherapy Center

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Conflict of interest: None

Objective: Remission has become the realistic goal in rheumatoid arthritis (RA). In 2011 ACR/EULAR has developed new definition of remission in RA which can presumably reflect the residual disease activity more accurately. However there is little information regarding the validity and the feasibility of the new definition in clinical practice. To clarify the performance we investigated the prevalence and agreement between remission definitions at Keio Immunotherapy Center Cohort. Methods: RA patients treated with biologic agents for more than two months at KIC as of April 2011 were cross-sectionally included in this analysis. Remission rates were calculated based on 4 definitions: DAS28<2.6, SDAI≦3.3, CDAI≦2.8 and ACR/EULAR (Boolean) which requires the complete fulfillment of the follwings; TJC≦1, SJC≦1, patient global (PtGH)≦1 on a 10cm VAS scale and CRP≦1mg/dl. It was also examined which variable was more attributed the cause of not-fulfillment of ACR/EULAR remission. Results: A total of 319 subjects were analyzed; 85% were female, mean age was 56 years old, mean disease duration was 124 months and mean treatment duration with the current biologic agents was 18 months. Most were RF positive (76%) and anti-CCP antibody positive (72%). One hundred twenty three patients were treated with infliximab, 86 with etanercept, 30 with adalimumab, 66 with tocilizumab and 17 with abatacept. Remission was identified in 56% using DAS28, 47% by SDAI, 43% by CDAI, 33% by ACR/EULAR remission. The mean (max) swollen joint count in remission patients was 0.55 (5) by DAS28, 0.23 (2) by SDAI, 0.19 (2) by CDAI, and 0.17 (1) by EULAR/ACR remission. When three variables in ACR/EULAR remission were≦1, the other variable was PtGH in 77%, SJC in 18%, TJC in 3% and CRP in 2%. Out of patients whose PtGH was ≦1, 33% reported their PtGH <2. Conclusion: In daily clinical practice ACR/EULAR remission was the most stringent among other clinical remission definitions and an achievable goal.

S18-4

Reliability of ACR/EULAR definitions of remission in patients of RA treated biologics in our institute

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Conflict of interest: Yes

Purpose: Recently, ACR/EULAR definitions of remission is recommended to assess clinical outcome for RA treatment. Here, comparison in DAS28, CDAI, SDAI and Boolean-based definition for remission rate in the patients treated by biologics was investigated and especially analyzed in drug-free remission cases. Methods: 919 cases of RA treated with biologics were investigated the remission rate of DAS28 (CRP), CDAI, SDAI and Boolean-based definition for remission. In infliximab group, 11 cases has accomplished drug-free remission, 1 male and 10 female, mean age of 55.7 years old, mean disease duration of 57 months. Clinical data including DAS28, CDAI, SDAI and Boolean-based definition for

remission was analyzed for prediction of drug-free remission. Results: 24 weeks after using biologics DAS28 remission were 154/388 in infliximab, 69/197 in etanercept, 79/208 in tocilizumab, 23/73 in adalimumab, 19/53 in abatacept. CDAI remission was 42/388 in infliximab, 19/197 in etanercept, 25/208 in tocilizumab, 5/73 in adalimumab, 5/53 in abatacept. SDAI remission was 69/388 in infliximab, 31/197 in etanercept, 42/208 in tocilizumab, 11/73 in adalimumab, 7/53 in abatacept. Total remission rate of DAS28, CDAI, SDAI and Boolean-based definition were 37.4%, 10.4%, 17.4% and 15.2% in biologic treatment. The ratio of bio-free remission of infliximab was 16%. Drug-free remission cases showed that mean DAS28, CDAI and SDAI were 1.96, 1.71 and 1.79 satisfied Boolean-based definition in all drug-free cases. Flare-up cases 2 years after drug-free remission showed long disease duration and high titer of rheumatoid factor. Conclusion: ACR/EULAR definitions of remission were more stringent than DAS28 remission criteria. In cases of drug-free remission of infliximab, DAS28, CDAI and SDAI were all under 2.0. Tight control by using biologics for treatment RA by using ACR/EULAR definitions of remission was suitable for clinical assessment to attain true remission toward bio-free remission.

S18-5

ACR/EULAR new remmision criteria

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Conflict of interest: None

It may be said that ACR/EULAR new remission criteria is effective outcome evaluation by clinical trial and a cohort study, but may it be said that it is a useful when we evaluate the individual patient in daily practice? In my own experiments, drug medication is successful in one patient with RA, and is good results in views of the objective which TJC/SJC/CRP is below 1, and "is well-conditioned at all" from patient ego; when "pain is free", is said, and a line is pulled in a place more than 1cm, and Pt GA VAS is done in remission and the state that can judge clinically unless with that alone satisfy remission. On earth what varies without exceeding it when PGA is beyond 1cm? We inspect validity of Pt GA VAS and speak a personal opinion from a skeptical viewpoint about ACR/EULAR new remission critera. (Methods) Public welfare labor science study NinJa (National Database of Rheumatic Diseases by iR-net in Japan) where I belongs to was used. Among 7,254 RA patients registered with in 2010, TJC/SJC/CRP below 1 for 2,703 patients; and 1,084 lower than PGA1cm group, group 1,609 more than PGA1cm for a sex / age / disease duration/SDAI/CDAI / DMARDs/ total joint arthroplasy / m-HAQ/NSAID /Steroid / operation of joint surgery / height / weight /Stage/Class/DAS28CRP/ hospitalization with multivariable analysis of logistic-regression analysis weighed it (Results) By logistic-regression analysis, we satisfied less than PGA1cm, and, as a factor for achievement of remission, odds ratio 1.0 of use of (gold sodium thiomalate, bucillamine, SSZ) was higher than, and was significant was found in only height, weight, classical DMARDs ($P < 0.05$). In addition, there were age, disease duration, Stage, Class, DAS28-CRP, mHAQ, total joint arthroplasty, hospitalization of the past one year, surgical operation, NSAID use, Steroid use, DMARDs combination therapy were significant below odds ratio 1.0 ($P < 0.05$). (Discussion) What remission cannot achieve (social demographical factor, psychologic pain, a coexistence disorder, RA disease duration) was reported by some variables that the case that does not reach remission criteria by Pt GA VAS as for the new remission criteria by RA cohort, QUEST-RA in ACR2011, and is not associated with many things, disease activity. In this current study, the factor that Stage, Class were not associated with disease activity at the point in time for (hospitalization, operation history) age with much coexistence disorders, disease duration was given as the factor which prescribed Pt GA.

S18-6

The validity of the 2010 ACR/EULAR remission criteria of rheumatoid arthritis in clinical practice

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Conflict of interest: None

The term "Complete remission" of rheumatoid arthritis (RA) implies the total absence of all articular and extraarticular inflammation and immunologic activity related to RA (Pinal RS, 1981). Various definitions of remission criteria have been proposed since 1981 ACR remission criteria. EULAR advocated the remission criteria using Disease Activity Score (DAS). They proposed DAS $\leqq$ 2.6 as the definition of RA remission. And it has been adopted in the current number of clinical trials. However, there have been reported some cases remaining swollen joints even if DAS $\leqq$ 2.6. In recent years, advances in anti-rheumatic drugs and biological products, we can aim the remission in RA therapy. More stringent definitions of remission have been needed. In 2010, ACR / EULAR proposed a new remission criteria, ①TJC $\leqq$ 1, SJC $\leqq$ 1, CRP $\leqq$ 1, PtGA $\leqq$ 1 (definition based on Boolean) or ②Simplified Disease Activity Index (SDAI) $\leqq$ 3.3 in clinical trials, and ①TJC$\leqq$1, SJC $\leqq$ 1, PtGA $\leqq$ 1, or ②Clinical Disease Activity Index (CDAI)$\leqq$2.8 in clinical practice. Felton et al. examined the predictive validity of the new RA remission criteria defined by ACR / EULAR. They reported that if the definition of remission in RA are SDAI $\leqq$ 3.3 or on Boolean, it shows the statistical significance on both the structural and functional stability. In the recommendations of the international task force, the goal is to improve patient outcomes in RA, to that the main goal of RA treatment should be the clinical remission. The question for us engaging in the clinical practice of RA in Japan is whether to meet the new remission criteria can prevent structural destruction and functional impairment, and can lead to improvement of QOL in RA patients. We will discuss the validity of the new remission criteria using the data in our hospital.

S19-1

RANKL and bone destruction

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Conflict of interest: None

RANKL and its receptor RANK are key regulators of osteoclastogenesis. Aberrant expression of RANKL explains why autoimmune diseases, cancers, and periodontal disease are associated with systemic and local bone loss. In particular, RANKL is the pathogenic factor that causes bone and cartilage destruction in arthritis. Inhibition of RANKL function by the neutralization antibody prevents bone loss in postmenopausal osteoporosis, cancer metastasis and arthritis. RANKL induces osteoclastogenesis through activating a transcriptional program mediated by the master transcription factor, NFATc1. RANKL has been postulated to be

mainly expressed by osteoblasts, bone marrow stromal cells and T cells, but there has been no genetic evidence regarding the major cellular source of RANKL in the bone microenvironment. We show that osteocytes embedded within the bone matrix are the critical source of RANKL in bone remodeling. Osteocytes, the most abundant cell type in bone tissue, are thought to orchestrate bone homeostasis by regulating both bone resorption and formation, but *in vivo* evidence and the molecular basis for the regulation has not been sufficiently demonstrated. 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. Thus, 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.

S19-2

Rheumatoid arthritis and bone destruction

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Conflict of interest: None

Rheumatoid arthritis (RA) is a disease characterized by chronic inflammation and continuous joint destruction. RA causes sever joint damage and pain, and limits patients' daily living activities. However, how inflammation and joint destruction are sustained chronically, remain largely unknown. In this study, we identified that signal transducer and activator of transcription 3 (STAT3) is the key factor that medicates both chronic inflammation and joint destruction in RA. STAT3 is activated by major pro-inflammatory cytokines that highly expressed in RA such as IL-1, TNF and IL-6 either directly or in-directly. Activated STAT3 further induces expression of IL-6 family cytokines and receptor activator of nuclear factor kappa B ligand (RANKL), which is an essential cytokine for osteoclastogenesis. Inhibition of STAT3 by gene disruption or STAT3-inhibitor resulted in a significant inhibition of the expression of both IL-6 family cytokines and RANKL induced by IL-1, TNF or IL-6 *in vitro*. Pharmacological inhibition of STAT3 was also effective in inhibiting IL-6 family cytokine and RANKL expression in a RA animal model, collagen induced arthritis (CIA) model, and that STAT3 inhibition was effective in preventing both chronic inflammation and joint destruction in CIA model *in vivo*. Thus our data provide new insight into the pathogenesis of RA, and demonstrate that inflammatory cytokines trigger a cytokine auto-amplification loop via STAT3 that promotes sustained inflammation and joint destruction. From our data, STAT3 is considered a potential target for treating RA.

S19-3

RANKL-targeting in rheumatoid arthritis

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Conflict of interest: Yes

Rheumatoid arthritis (RA) is a representative inflammatory disease characterized with systemic, chronic and destructive synovitis and subsequent bone destruction that causes severe disability and mortality. Since joint destruction occurs from the early disease, its diagnosis and treatment have to be done timely. However, functional disabilities due to bone and joint damages are often irreversible unless appropriate treatments from early stage of the disease course are undertaken in each patient. Bone and joint manifestation in RA is accompanied with 1) bone and cartilage destruction induced directly or indirectly by synovial inflammation, 2) peri-articular localized osteoporosis influenced by synovitis and 3) systemic osteoporosis caused by aging, menopause, immortalization, the synthetic glucocorticoid and many factors. Total management of such bone and joint destruction has become the aim that should be accomplished in treatment of RA. Recent clinical examinations document that an anti-RANKL antibody denosumab inhibits bone erosion, periarticular osteoporosis and systemic osteoporosis without influencing disease activity in patients with RA. Namely, A significant difference in the radiographic modified Sharp erosion score of the hands/wrists and feet was also observed as early as 6 months in the 180-mg denosumab group as compared with placebo, and at 12 months, both the 60-mg and the 180-mg denosumab groups were significantly different from the placebo group. Based on these results, a double-blind controlled trial of denosumab in patients with RA is ongoing in Japan.

S19-4

Intravital imaging study of bone-resorbing osteoclast function regulated by interactions with inflammatory cells in situ

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Conflict of interest: Yes

During the last decade, multi-photon microscopy has launched a new era in the field of biological imaging. The near-infrared excitation laser for multi-photon microscopy can penetrate thicker specimens, enabling the visualization of living cell behaviors deep within tissues and organs without thin sectioning. The minimized photo-bleaching and toxicity contributes to the visualization of live and intact specimens for extended observation periods. By using this advanced imaging technique we have established a new system for visualizing in situ behavior of osteoclasts and their precursors within intact bones. Osteoclasts are bone-resorbing multinuclear giant cells that differentiate from mononuclear macrophage/monocyte-lineage hematopoietic precursor cells. Although previous studies have revealed key molecular signals, how the bone-resorptive functions of mature osteoclasts are controlled in vivo remains less well characterized. Here, we have visualized fluorescently-labeled mature osteoclasts in intact bone tissues using intravital multiphoton microscopy, identifying two different populations of mature osteoclasts, 'static - bone resorptive (R)' and 'moving - non-resorptive (N)'. We found that rapid RANKL injection changed the osteoclast status from N to R, providing a direct evidence showing that RANKL in controlling mature osteoclast function. Furthermore, we showed that Th17, a bone destructive CD4+ T cell subset expressing RANKL, could induce rapid N to R transition of mature osteoclasts via cell-cell contact, revealing one mechanism by which Th17 has a potent effect on controlling bone resorption in vivo. These findings provide new insights into the activities of mature osteoclasts in situ and identify novel actions of RANKL expressed by Th17 that may be promising as a new therapeutic target in inflammatory bone-resorptive diseases, such as rheumatoid arthritis.

S20-1

Mechanisms of Inflammatory arthritis via TIARP deficiency

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Conflict of interest: Yes

The prognosis of patients with rheumatoid arthritis (RA) has improved significantly with the recent availability of biologics TNFa and IL-6. However, the exact mechanisms of action of these agents remain largely unknown. In Glucose-6-phosphate isomerase (GPI)-induced arthritis, clear therapeutic benefits from TNFa was observed, suggesting similar etiology to RA. Using our GeneChip analysis, we have demonstrated the upregulation of TNFa-induced adipose-related protein (TIARP, other name TNFAIP9) in GPI-induced arthritis, thus we examined the role of TIARP in mice and humans. TIARP was expressed on $CD11b^{+}$ splenocytes in early induction phase of arthritis, and clearly downregulated by TNF antagonist. We have recently generated TIARP deficient ($TIARP^{-/-}$) mice in C57/BL6 background. $TIARP^{-/-}$ mice developed spontaneous arthritis in 12 months of age, and collagen-induced arthritis (CIA) was clearly exacerbated in $TIARP^{-/-}$ mice. Pathophysiology of arthritis in $TIARP^{-/-}$ mice is due to IL-6 overproduction, increased numbers of macrophage/neutorophil, aberrant signal by STAT3, and dysregulation of apoptosis and overexpression of chemokines. Human TIARP counterparts such as six transmembrane epithelial antigen of prostate 4 (STEAP4) were also highly expressed in synovial $CD68^{+}$ cells of patients with RA. STEAP4 was expressed on monocytes and neutrophils in peripheral blood in RA. Migration of neutrophil-like HL60 was downregulated by overexpression of STEAP4. Moreover, STEAP4 overexpression in fibloblast like synoviocytes suppressed IL-6 and IL-8 expression, inhibited cell proliferation, and induced apoptosis, while STEAP4 downregulation by siRNA enhanced the expression of IL-6 mRNA. Expression of STEAP4 mRNA was significantly decreased after infliximab treatment in patients with RA, especially in good responders. These findings suggest that STEAP4/TIARP is induced by TNFa and regulates IL-6 expression, might be linked to pathogenesis of RA as a new regulator.

S20-2

Identification of the TREM-1 ligand as a therapeutic target of arthritis

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Conflict of interest: None

Triggering receptor expressed on myeloid cells (TREM)-1 is expressed by macrophages and neutrophils. Its activation augments inflammatory cytokine production triggered by Toll-like receptor engagement. In a mouse sepsis model, blockade of TREM-1 by administration of a TREM-1 extracellular domain/Ig Fc domain fusion protein (TREM-1-Ig) prolonged survival of the affected mice. This indicated that TREM-1 blockade suppressed pathological inflammation with maintaining minimal inflammatory cytokine production for anti-microbial defense. We reported previously that TREM-1 is expressed on synovial macrophages in the rheumatoid joints and that TREM-1 blockade ameliorated mouse collagen (CII)-induced arthritis (CIA), which is an animal model of rheumatoid arthritis. However, since a ligand for TREM-1 was unknown, physiological roles of TREM-1-ligand and interactions between TREM-1 and TREM-1-ligand remained to be clarified. The present study was conducted to identify the TREM-1-ligand molecule for discerning its involvement in arthritis. To search for cells expressing the TREM-1-ligand, various types of cells were incubated with TREM-1-Ig. It bound to mouse B cells and A20 B-cell lymphoma cells. Expression cloning using A20 cell cDNA library led us to identify a gene encoding the TREM-1-ligand. Furthermore, we raised anti-TREM-1-ligand blocking monoclonal antibody (mAb). Administration of this antibody to CIA mice, before or after the onset of arthritis, ameliorated the disease. Anti-TREM-1-ligand mAb treatment exerted no apparent effects on T and B cell responses to CII. Thus, in analogous to the effect of TREM-1-Ig, this effect appeared attributable to attenuation of the inflammatory responses rather than inhibition of the adaptive immune responses. Identification of the human TREM-1-ligand in the future study will warrant establishment of a new anti-rheumatic therapy that is not associated with a risk of serious infection.

S20-3

Arthritis Pathogenesis and Potential Therapeutic Strategy at RNA Level

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Conflict of interest: None

MicroRNAs (miRNAs) are a family of ~22-nucleotide (nt) noncoding RNAs that are evolutionarily conserved and regulate gene expression by posttranscriptional mechanisms. The major role of miRNAs is to control development and tissue homeostasis through the 'fine-tuning' of the gene expression. Several miRNAs exhibit a tissue- or developmental stage-specific expression pattern and have been associated with diseases such as cancer and cardiovascular disorders. miR-140 is highly expressed in chondrocytes, however its function has not yet been elucidated. To examine the role of miR140 in vivo, we generated miR140 null mice. In null miR140 mice knee articular cartilage we observed spontaneous onset of osteoarthritis at the age of 8 months. To test the function of miR-140 in articular cartilage, we performed microarray for mRNA expression with articular cartilage from wild type and miR-140 null mice and on chondrocytes transfected with miR-140. Among the mRNAs most highly increased in miR140 null mice was ADAMTS-5, a critical cartilage degradation enzyme in osteoarthritis pathogenesis. ADAMTS-5 is also a strong miR-140 candidate as predicted from Target scan bioinformatics data-base. ADAMTS-5 expression is significantly increased in chondrocytes from miR-140 null mice. Consistent with this, GAG loss in articular cartilage was significantly increased in miR140 null mice. Overexpression of miR-140 in chondrocytes from miR-140 null mice decreased the expression of ADAMTS-5. Furthermore, reporter construct carrying ADAMTS-5 3' UTR was also inhibited by miR-140 overexpression. These data indicate that ADAMTS-5 is directly inhibited by miR-140 and that loss of miR-140 causes catabolic effect on cartilage homeostasis and subsequent osteoarthritis, at least in part, via regulating ADAMTS-5.

S20-4

The IL-6 amplifier, an inflammation inducer, and arthritis

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Conflict of interest: None

The IL-6 amplifier is an inflammation inducer that causes the expression of various chemokines in mesenchymal cells via the activation of NFkB and STAT3. The amplifier was originally identified as an IL-17-triggerred positive feedback system of the IL-6 signal in type 1 collagen+ cells like endothelial cells and fibro-

blasts, and has proven essential for the development of arthritis in the F759 mouse model and multiple sclerosis in the EAE mouse model. We have further established a four-step model that can explain the tissue specificity for MHC class II associated autoimmune diseases and IL-6 amplifier activation. Indeed, activated CD4+ T cell accumulation, which can be both dependent and independent of tissue-specific antigens, induces autoimmune diseases via activation of the IL-6 amplifier. Here we describe the molecular mechanism of the IL-6 amplifier activation and direct links between this activation and various human diseases and disorders. We employed a new method, which consists of genome wide screens followed by GWAS comparisons. We performed two genome wide screens, one functional and one expression-based, that resulted in identifying about 1400 genes involved in IL-6 amplifier activation. After careful investigation using GWAS database, we found over 10% of these genes associated with human diseases and disorders including rheumatoid arthritis. We have since been analyzing over 30 genes whose deficiency can significantly suppress IL-6 amplifier activation not only in vitro, but also inhibited cytokine-induced arthritis in vivo. Moreover, several soluble factors in the list increased in the sera of several disease patients including those with rheumatoid arthritis. Thus, we concluded that IL-6 amplifier activation is indeed associated with human diseases and disorders and that our new method is effective for investigating direct links between disease model studies and human diseases and disorders.

S20-5

TIM-4 has two different functions in mouse models of arthritis

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Conflict of interest: None

T cell Ig and mucin domain (TIM)-4 is a member of the TIM family, which has been implicated in the control of T cell-mediated immune responses. However, the effect of TIM-4 binding to T cells has not been clarified and much remains to be determined regarding its activity in vivo. The role of TIM-4 in various disease models has not been clarified yet. In this study, we investigated the effects of anti-TIM-4 mAb in a collagen-induced arthritis (CIA) to determine whether TIM-4 contributes to the joint inflammation. Administration of anti-TIM-4 mAb at the induction phase exacerbated the development of CIA. The anti-TIM-4 mAb treatment significantly enhanced CII-specific CD4 T cell proliferation and IFN-γ and IL-17 production at the priming phase. TIM-4-Ig could bind to CD4 T cells in the LN cells from CIA-induced mice, which did not express the known receptors (TIM-1, PtdSer, or LMIR5) of TIM-4. These results suggest that CD4 T cells bind to TIM-4 through an unidentified receptor, which may mediate an inhibitory signal into CD4 T cells at the priming phase of CIA. In contrast, notably, therapeutic treatment with anti-TIM-4 mAb just before or after the onset or even at later stage of arthritis significantly suppressed the development and progression of CIA by reducing pro-inflammatory cytokines in the ankle joints without affecting T or B cell responses. We also examined the effect of anti-TIM-4 mAb on collagen antibody-induced arthritis (CAIA), which is not mediated by T or B cells. Consistently, clinical arthritis scores were significantly reduced in anti-TIM-4-treated mice with a concomitant decrease of pro-inflammatory cytokines in the joints, further substantiating the anti-inflammatory effect of anti-TIM-4 mAb. These results indicate that TIM-4 has two different functions depending on the stage of arthritis, and suggest that TIM-4 is an appropriate target for the therapeutic treatment of human arthritis.

S20-6

C1qTNF is an endogenous regulator of the complement system that plays an important role in the development of arthritis

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Conflict of interest: None

Rheumatoid arthritis (RA) is a systemic, chronic and inflammatory autoimmune disease with almost 1% world's population being affected. We have established two RA models both of which spontaneously develop autoimmune arthritis resembling RA in humans; one is the HTLV-I transgenic mouse and the other is the IL-1 receptor antagonist knockout (KO) mouse. Excess IL-1 signaling was involved in the development of arthritis in both models, causing IL-17A production in joints. In addition to proinflammatory cytokines, we identified *C1qtnf6* (gene product: CTRP6) as one of the commonly activated genes in the affected joints of both models by microarray analysis. CTRP6 is a soluble protein of a C1qTNF family member, having a C1q globular domain in the C terminus and a collagen domain in the N terminus. We generated *C1qtnf6* KO mice and found that these mice were highly susceptible to the induction of collagen-induced arthritis (CIA). On the contrary, transgenic mice with *C1qtnf6* developed milder arthritis upon induction of CIA. We found that the active fragments of complement components (C3a and C5a) in the serum and C3b deposition in the joints were increased in these KO mice after CIA induction. Furthermore, the intra-articular injection of recombinant human CTRP6 could cure CIA. These observations indicate that CTRP6 is an endogenous regulator of the complement system and can be a good candidate for an anti-rheumatoid arthritis drug in humans.

S21-1

Success story of tocilizumab clinical development

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Conflict of interest: Yes

New technology, materials, and ideas that are owned by companies and universities are called "Seeds". "Seeds-orientated" marketing is likely to produce innovative products that ensure long-term market. On the other hand, "Needs-oriented" marketing attempts to meet the consumers' needs and the balance of "Seeds" and "Needs" is very important for the success. In medical research, basic medicine is likely to "Seeds-orientated" and clinical medicine to "Needs-oriented". The convergence of both basic and clinical medicine is required especially for the development of new treatments including new drugs. In the clinical development of tocilizumab, achievements of basic research about IL-6 by Osaka University and others and bio-technology owned by Chugai Pharmaceutical Company are the "Seeds". The need for novel therapies in clinical practice and the preferable treatment such as dosages and prediction of efficacy is "Needs". The convergence of both led to the success of tocilizumab. It is needless to say that the pathological roles of IL-6 playing in the inflammatory diseases and technology to develop therapeutic antibodies were important as "Seeds". On the other hand, the protocols of clinical trials made the pharmacological features of both IL-6 and tocilizumab stand out. It is also notable that they also best reflected the needs of clinicians and their patients. For example, the protocols to rescue patients assigned to the placebo group and long-term extension studies to continue tocilizumab were welcome in clinical practice, and greatly contributed to the shortening of the period to recruit the subjects. In addition, long-term extension studies lead to the accumulation of safety data of a maximum of eight years and total of

2188 patient-year exposure at the approval. Osaka University not only reduced the risk of failure in drug development but also emphasized the benefit of tocilizumab.

S21-2

Investigator-initiated clinical trial in myositis-associated interstitial pneumonitis: to share our experience and to review various hurdles encountered

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Conflict of interest: Yes

Interstitial pneumonitis (IP) is a common and serious complication of polymyositis (PM) and dermatomyositis (DM). Fifty percent of cases are unresponsive to corticosteroids (CS), an only approved drug for this disease, but evidence suggesting that the early use of immunosuppressive drugs could improve its prognosis has accumulated. Small market due to its low prevalence, however, discourages manufacturers from investigating their products for this disease. Favorable experiences with tacrolimus reported by ourselves and by other institutions prompted us to investigate it for a potential new drug, and we thus designed and carried out an investigator-initiated multi-center clinical trial that was in full accordance with Japanese Good Clinical Practice and was designed to obtain data necessary for applying for product approval. Our work was funded and supported by the Japan Medical Association Center for Clinical Trials (JMACCT). Our study aimed to compare the combination of CS and tacrolimus against CS alone in PM/DM patients with new-onset IP. Randomization into CS-alone group was considered ethically unacceptable due to the high short-term mortality of this disease, and thus we used historical control consisting of those who fulfill the same inclusion criteria as the prospective interventional group and received initial treatment consisting of CS alone, and compared data from both groups using propensity score matching. Eleven institutions participated in our study. The prospective investigational part reached its planned cohort size after extending its enrollment period for an additional year due to slow recruitment. The historical control cohort size, however, remained too small for propensity score matching due, primarily, to the fact that very few patients in general practice have received initial treatment of CS alone in recent years. We will share our experience with and to review various hurdles encountered in conducting investigator-initiated clinical trials.

S21-3

Clinical research in connective tissue diseases - from a standpoint of a rheumatologist working for a pharmaceutical company

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Conflict of interest: Yes

Clinical research mainly consists of registration trials, other trials with intervention, and non-interventional observational research. In the symposium, as an in-house physician, I will try to introduce problems as well as the present situation of clinical research chiefly in the rheumatology area in Japan. Recently, clinical development strategy in our country has changed from what they call 'bridging' to active participation in global trials with the same protocol, so the drug lag may shorten or hopefully disappear in the near future. Japanese patients are, however, rarely able to take part in the early exploratory studies such as those of First-in-Human and Proof-of-Concept. In cooperation with other East Asian countries, running Asian studies from the early-stage clinical study through the confirmatory trials under the control of Japan could be, ideally, an option to demonstrate qualities of leadership, although we need to work out a solution to the problems, e.g., a possible pharmacokinetic difference. Since Apr. 2009, we have had much more difficulty in conducting clinical research including an observational study from ethical points of view. Regarding rheumatoid arthritis, it is said that the results of the large observational cohort studies by Japanese rheumatologists were of great help in acquiring the approval of an increase in methotrexate dosage (i.e. 16 mg/w) in Feb. 2011. The analyses of Japan-specific postmarketing surveillance data on every patient with rheumatoid arthritis, who was prescribed the biologics in question, demonstrate several lines of novel knowledge together with safety and effectiveness. In order to present more valuable evidence to the world, it is desirable that well-designed investigator-initiated interventional studies be also implemented. I would like to emphasize that we must devote all of our energies to respecting for the welfare of all the patients when we plan and conduct any clinical study.

S21-4

Drug development for rheumatic diseases: Clinical concerns as medical reviewers at PMDA

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Conflict of interest: None

PMDA (Pharmaceuticals and Medical Devices Agency) is Japanese regulatory agency, working together with Ministry of Health, Labour and Welfare. PMDA conduct reviews of marketing authorization application of pharmaceuticals and medical devices, monitoring of their post-marketing safety. We also provide consultations on clinical trials of new drugs, where we check whether a proposed clinical trial properly complies with the requirements for regulatory submission, and also give advice to facilitate the improvement of the clinical trial. The advent of biologics has changed the treatment of rheumatic diseases, dramatically. At present, at least seven biologics are available in Japan, which is approved either for rheumatoid arthritis, juvenile inflammatory arthritis, ankylosing spondylitis, Behcet disease, and Cryopyrin-Associated Periodic Syndrome. Still, new biologics, bio-similar, and kinase inhibitors against rheumatic diseases are under development. As global studies become popular also in this field, clinical concerns have raised especially how we manage safety issues. Since most of the rheumatic disorders are rare and have diverse clinical symptoms, hurdles remain in collecting participants and designing appropriate endpoints for clinical trials. In this talk, clinical concerns about studies for rheumatic diseases from the standpoint of medical reviewers at PMDA will be presented.

S22-1

Total shoulder arthroplasty vs Humeral head replacement in patients with rheumatoid shoulder

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Conflict of interest: None

Various surgical treatment were reported on rheumatoid shoulder. However, there were no recommended surgeries in the Japanese 2nd basic published text of rheumatoid disease. We had performed total shoulder arthroplasty and humeral head replacement in patient with Rheumatoid shoulder from 1992. In first study of comparing outcome after total shoulder arthroplasty and humeral

head replacement showed almost same results. Recovery of shoulder elevation was not able to have a satisfaction in both groups. (Total shoulder replacement; 110 degree, Humeral head replacement; 102 degree) Also, a lucent line around the glenoid component in total shoulder group was found in all cases. The second study of midterm results after humeral head replacement showed deteriorated results in elevation angle (96 degree) due to medial migration of the artificial humeral head. From 2004, we are able to use 3rd generation type of total shoulder arthroplasty system. The short term results after 3rd generation of total shoulder arthroplasty revealed improved range of shoulder motion after surgery. (Elevation; 130 degree) And also, the rate of the lucent line around the peg of glenoid component was very low. Now almost of the rheumatoid shoulder cases which has intact rotator cuff and enough glenoid bone amount were performed 3rd generation of total shoulder arthroplasty. However, we perform humeral head arhroplasty with or without Pectoralis Major muscle transfer or Latissimus dorsi muscle transfer in cases which massive rotator cuff tear.

S22-2

Intermediate- and Long-term Results of Total Ankle Arthroplasty for Rheumatoid Arthritis

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Conflict of interest: None

Total ankle arthroplasty (TAA) or arthrodesis is the last resort for severe damaged ankle with rheumatoid arthritis (RA). Bony ankylosis is frequently observed in the RA tarsal joints. Arthrodesis may lead to pantalar fusion, which caused remarkable limitations of activity of daily living. The advantage of TAA is to maintaining joint movement. Therefore we tried TAA for the RA ankle. Our prosthesis (TNK ankle) was made of alumina ceramic coated with alumina beads. TAA was performed for 53 ankles in 43 patients from 1991 to 2008. Subtalar arthrodesis was combined for 16 joints. Artificial total talar prosthesis was replaced in one ankle. Duration of follow up ranged 3 years to 19 years, with mean of 8.7 years. The JSSF ankle-hindfoot scale improved from 30 points preoperatively to 66 points at the follow-up. Total ranges of motion (ROM) of the ankle was decreased from 27 degrees to 23 degrees. Revision surgery was performed for 4 ankles. 3 ankles were with collapse of the talus, and 1 ankle with deep infection. Total talar replacement was performed for 1 ankles and arthrodesis for 3 ankles. Revision rate was 7.5%. Although improvement of ROM was not expected, retaining of ROM of the ankle was very important for RA patients. TAA may be indicated in patients who have marked destruction, and particularly in patients in whom osteoarthritis changes are seen in the subtalar or midtarsal joints. The results of TAA for RA were worse than for patients with osteoarthritis. Therefore we recommend to use bone cement for patients with severe osteoporosis. Because revison rates of TAA with TNK ankle were low, TAA is a promising procedure for the RA ankle. Since biologics inhibit the progression of ankle joint deterioratin and improve erosions of small joints, it is expected to expand the indication of TAA.

S22-3

Indication and timing of surgical intervention for cervical lesions in rheumatoid arthritis: based on the results of long-term survival patients after surgery.

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Conflict of interest: None

Purpose: To know appropriate indication and timing of surgery for RA cervical spine lesion based on the prognosis after surgery. Materials and methods: Out of 196 patients who underwent primary surgery from 1979 to 2000, 80 patients (11 men, 69 women) who had lived more than 10 years after surgery (Group A) and 86 patients (30 men, 56 women) who had lived shorter than 10 years (Group B) were compared retrospectively (85% of all cases). 1) The average ages at surgery, 2) sex ratio, 3) Steinbrocker's stage and functional classification, 4) the location of RA lesion (upper cervical, lower cervical and both level) 5) duration of RA disease, 6) surgical indication, 7) pre- and post-operative severity of myelopathy, 8) postoperative improvement of myelopathy, 9) the age at death, 10) survival rate by the Kaplam-Maier method were investigated. Results: In group B, the average age at surgery was older and there were more male, advanced stage and worse function patients and more patients with lower cervical lesion and severer myelopathy than in group A. Five year survival rate was 77% in total patients (group A & B) and 55% in group B. The later was similar to that of pre-operative non-ambulant patients. But there were no difference between those of ambulant and non-ambulant patients in group B, 59% and 52% respectively. Discussion: The prognosis of severe myelopathy cases is poor, and it may be also influenced by severity of RA in itself. Surgery improves ADL of patients and avoids the comorbidities and then the prognosis of patients may be improved. We think surgery may be recommended if spinal cord is at risk for myelopathy by progressive or severe instability. Conclusion: the prognosis of RA patients after cervical spine surgery is affected by both severity of myelopathy and RA disease, but aggressive surgical therapy should be considered in the case of severe instability to prevent the aggravation of myelopathy, maintain of the QOL and improve the prognosis.

S22-4

Clinical outcome of the surgery in patients with rheumatoid arthritis in the long term follow up Total elbow arthroplasty: linked vs. unlinked

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Conflict of interest: None

Biologic agents as well as positive use of methotrexate have dramatically changed the treatment of rheumatoid arthritis (RA) over the past decade. Biologic agents can reduce the disease activity of RA, and prevent the joint destruction. On the other hand, some patients cannot use the biologic agents due to primary, or secondary failure, patient's complication, or economic reason. Artificial joint replacement is a reliable procedure for the joint that has seen an irreversible joint destruction as the means for pain relief and functional reconstruction. Prosthesis of total elbow joint arthroplasty (TEA) is divided into two types, linked type and unlinked type. The axial stress transmitted to the component is partly absorbed by the soft tissue, therefore unlinked type prosthesis is thought to have advantages of loosening of stem and wear of polyethylene. Linked type prosthesis is applied to unstable RA elbows that have bone defect and ligamentous dysfunction because linked type prosthesis has intrinsic stability in itself, although the risk of loosening of linked type prosthesis might be much higher than that of unlined prosthesis. Since 1997, 102 patients (115 elbows) with

rheumatoid arthritis (RA) were managed with J-alumina ceramic elbow (JACE) prosthesis with bone cement. The clinical and radiographic data were available from 77 patients (80 elbows) who had been followed for more than 1 year. The average JOA score improved from 50.1 to 90.2 points. No dislocation was seen, and revision surgery had done in one elbow (1.7%) due to massive loosening and in one elbow (1.7%) due to deep infection. A JACE total elbow arthroplasty with bone cement provides excellent clinical outcome, especially in pain relief and good functional return in patients with rheumatoid arthritis. In this symposium, we would like to review the other elbow prosthesis including both linked and unlinked types and discuss about the indication and limitation of prosthesis.

S22-5

Figer implant arthroplasty: Silicone implant vs surface implant

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Conflict of interest: Yes

Although nearly half century has passed since first finger implant developed, silicone finger implant still has position of major stream. Many papers reported as the silicone finger implant had fairly good results. However, several efforts have been carried out during these period such as; twice materials changes and addition of the grommets in most famous silastic finger implant of Swanson, and preflexed design in Neuflex and others which latest line of the Sutter's finger implant. On the other hand, hinged type, boll and socket and surface type finger implant have also been developed at the same time. Unfortunately almost all these finger implant failed and disappeared. Difficulties of precise bone resection and cementing technique compared to hip and knee, and major manufactures retraction of investment towered finger implant are believed to slow down the development of this field. Cementless surface finger implant (Self Locking Finger Joint, S.L.F.J, Nakashima Medical Corp. Okayama Japan) have been used since 1999 and reached over 1500 joints in 750 cases. Loosening of the implant was very low (less than 10%). Firm fixation of the stem (joint anchor) to the bone were found within one year when proper size of the implant are used. Good fixations were obtained for the cases of failed silicone and other implant with bone graft. Because of the surface design, palmer dislocation was the major concern for MP implant in Ulnar drift, however, post-operative dislocation seldom occurred even for the cases of severe palmer dislocation. In long term follow up, number of dislocation secondary to ligament attenuation and muscle weakness increased. Recurrences of ulnar drift were found fairly high in different degrees. Newer and stronger techniques of radial collateral ligament reconstractions and realignment of flexor tendon were under process. Results of the PIP joints are very successful and cases in different institutions are increased.

S22-6

Clinical results of the total hip arthroplasty in reumatoid arthritis.

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Conflict of interest: None

【Introduction】Cases of rheumatoid arthritis associated with acetabular bone deficiencies and poor bone quality of femur are not rare, which distresses surgeons. There is no consensus on whether or not reinforcing materials such as support rings or metal mesh should be used, as well as on whether or not the acetabular and femoral components should be fixed with cement. We present results on primary total hip arthroplasties (THAs) with the bone-grafting technique, an uncemented or cemented in patients with rheumatoid arthritis.【Subjects and methods】The subjects were 68 patients (70 hips) consisting of 65 women (67 hips) and three men (three hips) with a mean age of 61.4 years (range: 42-80 years). In hips with rheumatoid arthritis with a defect that could be filled with an autograft from ipsilateral femoral heads, we used fresh autogenous bone. In the case of rheumatoid arthritis with severe destruction of femoral head, which cannot be filled with autograft from ipsilateral femoral heads, we used fresh-frozen allograft, defrozen and sterilized. Uncemented or cemented component was implanted with or not reinforcing devices. The duration of follow-up ranged from 5 years to 30.5 years, with a mean duration of 11.6 years.【Results】The radiographic evaluations of the hips were good or excellent at the time of final follow-up in 69 hips. Revision arthroplasty was performed in one case.【Discussion】Gerber et al. demonstrated that absorption of the grafted bone was noted in 20% of hips with acetabular defects treated by primary cemented acetabular reconstructions using autograft at an average of 7 years after surgery. Non-structural morselized bone grafts have been shown to provide excellent improvement.【Conclusion】Total hip arthroplasties with cemented and uncemented compoments had satisfactory results immediately after the operation and at final follow-up. Revision arthroplasty was performed in one case.

S23-1

Differential diagnosis of elderly onset RA- Osteoarthritis-.

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Conflict of interest: None

Now, aggressive intervention for patients with the earlier stage of rheumatoid arthritis (RA) is very critical for good clinical response for the treatment and prevention of functional loss. However, the classification of RA defined in 1987 is based on characteristics of patients with long disease duration established, RA. ACR/EULAR proposed new classification of rheumatoid arthritis in 2010. The important point of the new classification criteria is differential diagnosis of RA with other diseases. The 2010 ACR/EULAR criteria allow more rapid identification of patients requiring methotrexate compared with the 1987 ACR criteria when applied at baseline. However, overdiagnosis is an important issue to consider if these criteria are to be used in very early disease (Cader et al, 2011). One of the most important diseases for differential diagnosis is osteoarthritis, which is very common joint disease in elderly patients. First of all, we have to detect chronic synovitis based on physical examination, US, and MRI. It is actually difficult to diagnose RA on OA. Radiographic subchondoral sclerosis and osteo spur could mask radiographic change of RA such as bone atrophy and erosion. It should be helpful to understand clinical features of elderly onset RA. Elderly onset RA has been reported to differ from younger-onset RA by a more balanced gender distribution, a higher frequency of acute onset often associated with systemic features, more frequent involvement of the shoulder girdle and higher disease activity (Bajpcchi et al, 2000). Elderly patients often have co-morbidity, or risk for adverse events for aggressive treatment while there is a possibility that delayed intervention could cause rapid physical function loss. Finally, proper decision, which is not based on overdiagnosis of the arthritic condition, should be needed for successful treatment of elderly onset RA.

S23-2

Systemic connective tissue diseases

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Conflict of interest: None

Rheumatoid arthritis (RA) is a systemic autoimmune disease characterized by persistent and erosive arthritis. Early therapeutic intervention is required to prevent the development of joint destruction and the consequent dysfunction, therefore, early diagnosis is critical in the management of RA. Systemic connective tissue disorders that cause inflammatory arthritis should be excluded to diagnose early RA. In addition to musculoskeletal examination, general and extra-articular symptoms and signs should be checked. Anti-nuclear antibody (ANA) test is useful for screening connective tissue disorders, and then disease-specific antibodies are tested due to clinical symptoms and the staining pattern of ANA. Non-erosive arthritis that mostly improves within several days is frequently seen in patients with systemic lupus erythematosus (SLE). Clinical features, such as malar rash, discoid rash, photosensitivity and cytopenia, are important to diagnoze SLE. Jaccoud's arthropathy, a non-destructive arthritis with ulnar deviation, may be observed in SLE and other connective tissue diseases. Arthralgia and skin involvement often cause reduced mobility of hand in systemic sclerosis. Anit-amynoacyl tRNA synthetase antibodies are associated with specific clinical features, including arthritis. Erosive arthritis may occur in patients with mixed connective tissue disease. To distinguish systemic connective tissue diseases from early RA is sometimes difficult. Systemic examination, having clear clinical pictures of each disease, is required.

S23-3

Spondyloarthritides

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Conflict of interest: None

Spondyloarthritides (SpA) is a family of rheumatic diseases that occurs with many concomitant conditions, and is considered nearly equivalent to rheumatoid arthritis (RA) in Europe and America. The prevalence of SpA was reported as 0.2% among the inhabitants of Wakayama prefecture in Japan, and was equal to the prevalence of RA in this population. In addition, even when using FDP/PET in health screening for healthy people, polyenthesitis was reported in eight cases (0.8%) out of 1000 people. [Symptoms and diagnosis] Ascertaining inflammatory back pain (IBP) is essential to diagnose SpA. It is important to obtain information about pain and stiffness in the extremities and trunk. Most patients complain of neck, back, buttocks and limb pain, and have suffered from stiffness and such pain since youth. These pains tend to be reinforced when resting or maintaining the same posture, and are reduced after mild physical activity. The diagnosis of SPA is established by the Amor diagnostic criteria, or the classification criteria of the European Spondyloarthropathy Study Group. Furthermore, the axial spondyloarthritis classification criteria has been recommended since 2009; leading to the diagnosis of axial SpA by STIR of MRI. Some of the undifferentiated SpA (uSpA), subclass of SpA, are diagnosed as axial SpA, and enter the category same as AS. [Laboratory findings] ESR and CRP are insufficient indices of disease activity. Therefore, BASDAI (the Bath ankylosing spondylitis disease activity index) or ASDAS (ankylosing spondylitis disease activity score) is used today. [HLA] The HLA-B locus is an important problem in the diagnosis and prognosis of SPA. However, the frequency of HLA-B27 positive patients is very low in Japan. We have assessed the frequency of the HLA-B locus, with only one HLA-B27 positive case (0.3%) out of 306 cases with SPA. [Conclusion] SPA should be noticed by all medical personnel in Japan.

S23-4

Differential diagnosis of early RA- polymyalgia rheumatica, arthritis associated with infection-

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Conflict of interest: None

Recently, the treatment of RA accomplished dramatic progress by methotrexate and biologics. With therapeutic progress, we could induce many RA patients into remission by early treatment intervention. However, Traditional criteria (ACR 1987 criteria) had some limitations to diagnose early RA. It is hoped that ACR/EULAR classification criteria proposed in 2010 contribute to diagnose early RA. In Japan, this new criteria was validated, and it was confirmed that diagnostic sensitivity was better than ACR 1987 criteria. However, differential diagnosis is very important because diagnostic specificity was inferior to traditional criteria in some cases. At this symposium, we describe PMR and arthritis associated with infection those are difficult to distinguish form early RA.PMR is inflammatory disorder that develops in a patient with 65 year old or over. Generally in PMR, the pain from trunk and large joint involvement are mainly. In RA patient, small joint are involved commonly. PMR could be distinguished from RA at the point of involved joint distribution. However, it is difficult to discriminate PMR from elderly-onset RA (EORA). Disease onset of EORA is often abrupt with constitutional symptoms and large joint involvement, with a PMR-like presentation. Imaging techniques (MRI, US, and FDG-PET) may be helpful. It is necessary to discuss in this symposium. Arthritis associated with infection is composed of bacterial or viral arthritis and ReA. It is difficult to discriminate between sustained viral arthritis and RA. In the clinical examination, the patients with viral arthritis have symmetric swelling with small joint and morning stiffness similar to RA. ReA is characterized by negative RF, asymmetric arthritis and /or tendinitis. Most of ReA patients have HLA-B27 and preceding urinary tract or enteric infection. Due to differentiation with RA, we need detailed interviews and physical examinations. We discuss about the point of differential diagnosis with early RA.

S23-5

Differential diagnosis for early rheumatoid arthritis: gout, pseudogout, and pigmented villonodular synovitis

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Conflict of interest: Yes

The differential diagnosis for early rheumatoid arthritis includes gout, pseudogout, and soft tissue tumors at the joints. Approximately 80% of gouty arthritis shows acute onset of monoarthritis often at the base of the big toe (70%), but other joints such as knees and ankles are also commonly affected. Acute gout attacks are characterized by a rapid onset of severe pain with swelling, redness and marked tenderness. They usually subside in hours to several days, and symptoms disappear until the next attack. Most patients with gout will experience repeated attacks within a year, and may develop chronic arthritis over the years if it left without any medication for hyperuricemia. In chronic (tophaceous)

gout, nodular masses of uric acid crystals (tophi) deposit in various soft-tissue areas of the body are found around the fingers, achilles tendon, or at the tips of the elbows. Pseudogout commonly involves the knee joint and the attacks of joint inflammation are characterized by acute joint pain, swelling, redness, and local heat. As inflammatory signs such as serum CRP or ESR are exaggerated, differential diagnosis includes another crystal-induced arthritis or infection in the joint. On radiography, abnormal calcifications are seen around meniscus or cartilage, so called chondrocarcinosis. The diagnosis of pseudogout is confirmed when the calcium pyrophosphate crystals are identified in joint fluid under a polarizing microscope. Pigmented villonodular synovitis (PVS) is a benign proliferative form of monoarthritis with unknown etiology, often affects knee joint, but shoulder, ankle, and hip joints are also affected less commonly. The appearance of joint fluid from affected joint is usually bloody. Typical MRI findings are proliferative nodular synovitis margined with thick low signal band. The diagnosis can be pathologically confirmed with hemosiderin deposits and multinuclear giant cells and foamy cells.

S23-6

RA-mimicking diseases: RS3PE and SAPHO syndrome

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Conflict of interest: None

Early diagnosis and treatment with DMARDs is important in achieving control of disease and prevention of disability in rheumatoid arthritis (RA). However, in patients with early disease, joint symptoms are often difficult to distinguish from other forms of inflammatory polyarthritis. Remitting seronegative symmetrical synovitis with pitting edema (RS3PE) and the peripheral arthritis of SAPHO syndrome are sometimes difficult to differentiate from early RA and differ in both management and prognosis. I will review several cases of RS3PE and SAPHO syndrome and describe several distinct features that are useful in daily practice to differentiate these from RA.

S24-1

Overview of anti-citrullinated protein antibody (ACPA) in rheumatoid arthritis

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Conflict of interest: None

New ACR/EULAR classification criteria for rheumatoid arthritis (RA) includes anti-citrullinated protein antibody (ACPA) together with rheumatoid factor (RF) as an important serological test for RA. ACPA is usually evaluated by measuring anti-citrullinated peptide (CCP) antibody. However, ACPA is not equally to anti-CCP antibody and “anti-CCP antibody” is diverse because of different antigenic peptides and measuring systems. This talk will present an overview of studies on ACPA and anti-CCP antibody. 1. History of studies on ACPAs in RA. Identification of target antigen (citrullinated filaggrin) for APF (anti-perinuclear factor) and AKA (anti-keratin Ab). Discovery of importance of “citrullination” for RA-specific antigens. 2. Physiological roles of citrullination, mechanisms of ACPA production and pathological roles of ACPA in RA. 3. Identification of citrullinated proteins in RA. 4. Changes in measuring methods for anti-CCP antibody. Increase in sensitivity by cyclic antigen (peptide). Improvement of antigenic peptides (2nd and 3rd generation). Changes in detection methods: ELISA → automated chemiluminescence enzyme immunoassay→ easy immunochromatographic assay kit 5. Development of measuring methods for ACPAs. 6. Clinical importance of measuring anti-CCP antibody and ACPAs.

S24-2

Correlations between the titer of rheumatoid factor / anti- CCP antibodies and clinical manifestation in rheumatoid arthritis

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Conflict of interest: None

Rheumatoid Factor (RF) and anti-CCP antibodies are both markers for diagnosis of rheumatoid arthritis (RA). In the 2010 ACR/EULAR classification criteria for RA, RF and anti-citrullinated protein/peptide antibodies (ACPA) were included for serological markers. Presence of these autoantibodies can contribute substantially to diagnosis of RA, for which ≧ 6 points are required; it yields 2 points when RF or ACPA was positive but lower than 3 times of the normal upper limit, and yields 3 points when it was higher than 3 times. But it remains unclear whether the titers of RF and anti-CCP Abs were important or not. We followed 98 patients for two years, who visited to our hospital during less than 12 months after the first episodes of articular manifestation, and all the patients fulfilled the ACR 1987 revised criteria in two years. RF or Anti-CCP Abs at the first visit were measured and patients were classified to 3 groups according to RF or anti-CCP Abs titer; in RF, Group N (RF-N): lower than 11.7 IU/mL, Group L (RF-L): 11.7 - 100 U/mL, Group H (RF-H): higher than 100 IU/mL, and in anti-CCP Abs, Group N (CCP-N): lower than 4.5 U/mL, Group L (CCP-L): 4.5 - 100 U/mL, Group H (CCP-H): higher than 100 U/mL. In this cohort, DAS28-ESR levels at two years were higher in H groups than in N groups with both autoantibodies. However, yearly progression of Larsen score (YP) showed different characteristics between RF- or anti-CCP Ab- positive patients. Regarding RF, YP score was not different between negative and positive patients, while RF-H showed higer YP score than the other group of patients. Regarding anti-CCP Abs, positive patients showed higer YP score than negative patients, although it was almost comparable between CCP-L and CCP-H. These results suggested that RF and ACPA may have the different clinical significance for erosive arthritis, and especially it should be evaluated in the future investigation whether RF and ACPA were equally contributed to RA diagnosis or not.

S24-3

Anti-citrullinated GPI antibodies in rheumatoid arthritis

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Conflict of interest: Yes

In general, anti-citrullinated protein antibodies (ACPA) are essential for diagnosis of RA, sometimes detected before the onset of arthritis, however their relevance to pathogenecity is mostly unclear. Glucose-6-phosphate isomerase (GPI) in mice can provoke arthritis directly, and indeed GPI is reported to be increased in RA serum, whereas human anti-GPI antibodies (Abs) are detected in

few RA patients with high disease activity. Thus, we examined the immune reaction to citrullinated GPI, and explore the mechanisms of pathogenesis with those Abs. Nine cyclic citrullinated peptides spanning whole lengths of GPI were constructed (CCG-1-9) and the levels of anti-CCG Abs were measured in RA, systemic lupus erythematosus, Sjögren's syndrome and healthy subjects by ELISA. The Abs were also compared to anti-circulated citrullinated alpha-enolase peptide (CEP-1), CCP Abs. HLA-DRB1 genotyping was performed and the numbers of SE alleles were calculated. In addition, the titers of anti-CCG and CEP-1 Abs were compared before and after treatment of RA patients with TNF antagonists. Three of nine peptides specifically reacted to RA serum, especially specificity and positivity of anti-CCG-2 Abs were, 99.7%, 26.0%, respectively. Anti-CCG-2 Abs were correlated with anti-CEP-1, CCP Abs, and also correlated with the presence of HLA-DRB1 SE allele. Treatment with TNF antagonists significantly reduced anti-CCG-2 Abs titer, but not anti-CCG-1, 3, CEP-1 Abs. We identified the presence of anti-CCG Abs in RA patients. Specifically, anti-CCG-2 Abs were highly specific for RA patients and correlated with SE and their titers were sensitive to TNF antagonists, suggesting that anti-CCG-2 Abs could be considered as a marker for the diagnosis of RA and its disease activity. In this synposium, we will also discuss and compare to the other ACPAs.

S24-4

Association between anti-citrullinated protein antibody production and immunity against BiP in rheumatoid arthritis

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Conflict of interest: Yes

Anti-citrullinated protein/peptide antibodies (ACPAs) are highly specific to rheumatoid arthritis (RA) patients and are thought to have a close relationship with the pathogenesis of arthritis. Several proteins, including fibrinogen, vimentin, and alpha-enolase, were reported as ACPAs-target antigens, and their importance in RA pathogenesis was widely proposed. However, antibodies against naïve-form of these proteins are less frequently detected in RA. BiP is a member of the heat shock protein 70 family and is expressed in the endoplasmic reticulum and anti-BiP antibodies showed similar sensitivity and specificity as RF. We have found that anti-citBiP antibody levels were higher than anti-BiP antibody levels in 72% of RA patients and the serum levels of anti-CCP antibodies were correlated with those of anti-citBiP antibodies in RA patients. Several citBiP citrulline residues were determined to be major epitopes of anti-citBiP antibodies. Immunization of DBA/1J mice with citBiP induced several kinds of ACPAs, including anti-CCP and pre-immunization with citBiP exacerbated CIA. These results suggest that citBiP is a newly described ACPA target that may play a pro-inflammatory role in arthritis. Recently other group described that ACPAs enhance NF-kB activity and TNF-alpha production in monocyte/macrophages via binding to surface-expressed citBiP and this report also suggest the contribution of citBiP. to the RA pathogenesis. Moreover, we also found that an epitope derived from BiP induced the strongest proliferation of peripheral blood mononuclear cells (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 specific for the BiP epitope in RA. This extraordinary expansion of BiP–specific $CD4^+$ T cells strongly suggested continuous active immunization with BiP in RA. These facts show the possible contribution of BiP-specific T cell response to ACPAs production.

S24-5

Citrullination and PADI4 in rheumatoid arthritis

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Conflict of interest: None

Rheumatoid arthritis (RA) is a common inflammatory disease with autoimmune features that affected 0.5-1% of the world's population including Japanese. Previous studies indicated that genetic factors were important in RA susceptibility. The only conclusively associated locus is the HLA DRB locus, which accounts for about one third of the genetic component. To identify non-HLA genes associated with RA, we performed whole-genome association study using single nucleotides polymorphisms (SNPs) as genetic markers. Previously, we reported that peptidylarginine deiminase type4 (PADI4) is one of the non-HLA genetic factors in RA. The association of PADI4 with RA was replicated by many studies. The enzymatic function of PADI4 is citrullination, which is one of the post-translational modifications. In particular, autoantibodies to a part of citrullinated filaggrin and its circularized form (cyclic citrullinated peptide: CCP) are remarkably specific and sensitive in RA patients and this autoantibodies can also use as an early diagnositic markar and a prognostic factor of joint destruction. We identified that expression level of mRNA from susceptible haplotype was higher than that from non-susceptible haplotype. We suggested that PADI4 gene was related with the development of RA, resulting the increment of the PADI4 expression. However, physiological roles of PADI genes, its products and citrullinated proteins/prptides are not clear. We summarize about the relationship between RA and PADI4 from the aspect of genetics and discuss about citrullination and anti-citrullinated peptides/proteins antibodies in RA.

S25-1

Effect of glucocorticoid on bone

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Conflict of interest: None

Glucocorticoid (GC) is necessary for the treatment of collagen disease and autoimmune disease because of its potent anti-inflammatory and immunosuppressive effects. Chronic use of glucocorticoid causes various adverse effects such as glucocorticoid-induced osteoporosis. The pathogenesis of glucocorticoid-induced osteoporosis includes 1) direct effect of GC on bone, 2) secondary hyperparathyroidism in response to change in calcium metabolism by GC, and 3) inhibitory effect of GC on sex hormones secretion, and direct effect on bone, especially on osteoblast, is considered to be most important regarding inhibition of bone formation by GC. Physiological concentration of GC is indispensable for differentiation and proliferation of osteoblasts to promote bone formation. However, pharmacological dose of GC suppresses bone formation through 1) inhibition of DNA and protein synthesis in osteoblasts, 2) inhibition of mesenchymal stem cells (MSC) to osteoblasts by suppression of Cbfa-1 expression and promotion of MSC to adipocyte by enhancement of PPARγ expression, 3) induction of apoptosis in osteoblasts, and suppression of bone formation signals such as Wnt or AP-1/IL-11 signaling pathway. Furthermore, pharmacological dose of GC promotes bone resorption. GC induces RANKL expression and suppresses osteoprotegerin in osteoblasts, which

results in promotion of osteoclasts. GC also suppresses osteoclast apoptosis. We have reported that GC suppresses Wnt signal in cultured human osteoblasts, which may be involved in pathogenesis of glucocorticoid-induced osteoporosis. In this symposium, we will discuss the effect of GC on bone in regard to glucocorticoid-induced osteoporosis.

S25-2

Treatment of Glucocorticoid-induced osteoporosis

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Conflict of interest: Yes

Glucocorticoids is the most common drugs prescribed by rheumatologists. Glucocorticoids are used not only for rheumatoid diseases but also other systemic inflammatory diseases. Therefore Glucocorticoid-induced osteoporosis (GIOP) is the most common cause of the secondary osteoporosis and lead to the bone fractures which were the most common adverse effect of glucocorticoids. Since the mid-1990s when the drugs for osteoporosis were developed, treatments for GIOP have been tried actively. Large scale randomized control studies were reported in Europe and United States, whereas therapeutic effects were studied in the longitudinal cohort in Japan. The authors had two longitudinal cohort studies of GIOP. In the first study of two-years longitudinal Japanese cohort, authors have reported that risk factors for incidental vertebral fracture were low bone mineral density at the base line, mean dosage of glucocorticoids, prevalent fracture, and age. Bisphosponate (Bis) and menatetrenone (K2) were effective in preventing bone fracture. In the second new cohort, the authors examined the risk factors for the incident fracture in the 136 patients with rheumatic diseases (without rheumatoid arthritis). The mean of age, %YAM, rate of prevalent fracture, prednisolone dosage were 60, 81%, and 8.2 mg/day, respectively at the baseline. The incident fracture was seen in 25% in Bis 80% in D3, 50% in K2, and 62% in the non-treated group. Multivariate analysis showed independent factors for the incident fractures were Bis (odds ratio 0.03), K2 (0.08), prevalent fracture (5.9), prednisolone dose (2.2/5 mg), age (1.3/5years), and BMD (1.3/5%). In conclusion, the rate of fracture was high in GIOP. Other than dosages of glucocorticoids, prevalent fracture, age, BMD were contributed to incident fracture. Active intervention is necessary for preventing fractures of GIOP.

S25-3

Guideline for the prevention and treatment of Glucocorticoid-induced Osteoporosis

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Conflict of interest: Yes

Glucocorticoids (GC) were widely used for the treatment of various disorders. Therefore, the management of glucocorticoid-induced osteoporosis (GIOP) is referred to doctors who take care of underlying diseases. Since GC-induced bone loss is most rapid during the initial 3 – 6 months, and fracture risk also increases during the first 6months of GC therapy, primary prevention of bone loss is especially important. The Japanese Society of Bone and Mineral Metabolism have devised a guideline for the management of GIOP in patients in whom oral GC therapy is considered for 3months or longer. The guideline showed the principals of management by 3-step flow chart according to fracture risk factors, prevalent fragile fractures, low bone mineral density (BMD) less than 80% of YAM, and more than 5mg/day of prednisolone. Bisphosphonates play a central role for the primary and secondary prevention of GIOP in the guideline. In the recent advances in the treatment of osteoporosis, the efficacy of human parathyroid hormone (1-34) (teriparatide) has been reported for secondary prevention of GIOP and is possible another beneficial drug. In 2010, the American College of Rheumatology (ACR) revised the guideline for prevention and treatment of GIOP. The guideline classified the facture risks into 3 categories: high, moderate, and low, guided in part by the FRAX risk assessment tool. Both bisphosphonates and teriparatide are the principal drugs. Although the guideline of Japan and Western countries show the principle of the management of GIOP, the percentage of GC-treated patients who is undergoing the drug therapy based on the recommendations is as low as 30%. In this symposium, the recent recommendations for the prevention and treatment of GIOP and the future direction would be reviewed and discussed.

S25-4

Relationship of glucocorticoid-induced vascular endothelial cell dysfunction and bone necrosis

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Conflict of interest: None

The failure of microcirculation is a major factor in the pathogenesis of glucocorticoid (GC)-induced osteonecrosis of the femoral head. We have aimed to clarify the mechanism of GC-induced vascular endothelial dysfunction as follows. A clinical study showed that endothelium-dependent vasodilation was attenuated by GC and that anti-oxidant vitamin C almost normalized the responses. 3-nitrotyrosine, a marker for elimination of NO by superoxide, was increased in arterioles of GC-treated patients, and oxidative stress markers were increased in arterioles of femoral bones obtained from patients with GC-induced osteonecrosis of the femoral head. Flow-mediated vasodilation, urinary excretion of NO metabolites, and expression and activation of endothelial NO synthase (eNOS) were reduced and superoxide production was increased in C57BL6/J male mice treated with dexamethasone (DEX), a synthetic GC receptor (GR) agonist. Pitavastatin, an HMG-CoA reductase inhibitor, ameliorated these GC-induced vascular dysfunctions. In DEX-treated endothelial cells, pitavastatin increased eNOS expression through enhancement of transcriptional activity and mRNA stability and suppressed superoxide production through inactivation of Rac-1. These effects of pitavastatin were exerted by inhibiting the production of intermediates in the synthesis of isoprenoids and cholesterol. GC could also activate the mineralocorticoid receptor (MR) because the expression level of 11β-HSD 2, which inactivates GC, was low in vascular endothelial cells. Selective MR blockers also ameliorated oxidative stress and NO production attenuated by cortisol and methylprednisolone, natural and synthetic GC, respectively. These findings suggested that GC excess causes osteonecrosis of the femoral head through vascular endothelial dysfunction induced by enhanced oxidative stress and attenuated NO production. An HMG-CoA reductase inhibitor and an MR blocker may prevent GC-induced osteonecrosis of the femoral head.

S25-5

Pathogenesis of steroid induced osteonecrosis: an MRI-based clinical and experimental study

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Conflict of interest: None

Idiopathic osteonecrosis of the femoral head (ION) is an intractable disease that is pathophysiologically characterized by ischemic necrosis of the femoral head and deterioration of hip joint function, and these changes significantly affect patient quality of life. More than half of ION develops in association with systemic steroid administration. Pathogenesis of ION is not fully elucidated yet. Much knowledge have acquired by using clinical MRI system, and pathophysiological features of steroid-induced ION are: (i) it develops at a very early stage during steroid treatment, (ii) large necrotic lesion makes preservation of the femoral head difficult and (iii) there is a long gap of time between the occurrence of the disease and onset of symptom. Earliest clinical detection of ION using conventional MRI is reported 4 weeks after steroid administration. Recently, it is reported that ION could be induced by oxidative stress. It is also said that oxidative stress can be induced within several hours after steroid administration. Experimental high magnetic field MRI system is expected to bring a new knowledge of pathogenesis of ION in its very early stage. We present a recent result from 7.04T experimental MRI system using steroid induced ION animal model.

International Rheumatology Symposium

IS1-1

The microenvironment around total hip replacement (THR) prostheses

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A cadaver study of well-fixed cemented THR implants shows a 3-phase reaction: a marginal rim of necrotic bone trabeculae is seen at the cement-host interface up to 3 wk post-op. This attracts osteoclast precursors to fuse to osteoclasts, which up to 2 yrs lyse damaged bone and produce coupling stimuli recruiting/activating osteoblasts to form woven bone. Finally, bone is remodeled to lamellar bone, forming a neo-cortex around the implant, attached to the original bone cortex with trabecular struts. A thin fibrous membrane is probably necessary to enable micromotion at the implant-host interface. In uncemented implants a good initial contact with host bone is primarily achieved using implant shape (e.g. wedged, threaded) and surface (rough for press/friction/scratch/interference fit), secondarily stabilized by bone ingrowth. Bone remodeling rather than recruitment of MSCs/enchondral osteogenesis assure integration. All THRs (M/CoP, MoM, CoC) produce wear, but only a few patients develop adverse responses. Poor initial positioning of the implants (gliding surfaces) and biomechanical loading (e.g. recurrent traumatic loading) lead to micro- and macromotion: much of the wear is secondary to loosening, not its prime cause. In healthy tissues M-CSF-induced M0 macrophages (mac) clean tissues of apoptotic/ECM rests and low particle numbers. Upon increasing particle load, IL-4 produced by local mast cells induces formation of M2 mac, which move rapidly and phagocytose effectively, but maintain status quo. If instead danger-associated molecular patterns (DAMP): pathogen (PAMP) or necrosis (alarmins) associated, together with locally produced a) IFN-γ and IL-12 or b) IL-6, IL-21 and IL-23 from e.g. dendritic cells polarize anti-inflammatory (M0/M2) mac to a) M1 or b) M17 mac, respectively, osteoclastogenesis and peri-implant osteolysis are also initiated. Host responsiveness rather than particles per se lead to implant loosening.

IS1-2

New imaging for implant loosening and molecular diagnosis for periprosthetic infection

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Conflict of interest: Yes

The preoperative differentiation of aseptic and septic loosening following a total hip arthroplasty (THA) remains a challenging issue for clinicians to which several novel diagnostic tools have been applied. It is often difficult to identify the etiologic agent especially in low-grade infection cases. We have utilized ^{18}F-fluoride PET to evaluate THA cases with stable, septic or septic loosened implants to assess the possibility of differentiating these clinical settings using a novel uptake type classification approach. Furthermore, we have utilized an ultrasonication approach to enable a simple DNA release directly from tissues, and then subsequently performed a simultaneous real-time PCR assay for both MRS and broad-range bacterial infection. ^{18}F-fluoride PET has great potential as a method for diagnosing aseptic and septic loosening after THA, and in the establishment of a novel uptake pattern classification system. In addition, quantification analyses with this method using SUVmax

values revealed that differences between aseptic and septic loosening could be objectively determined. On the other hand, the simultaneous detection of MRS and broad-range bacterial infections would be invaluable for the informed selection of antibiotics and also the subsequent treatment strategy for the patient itself, i.e. one-stage or two stage revision. In addition, preoperative assess ment of major uptake of ^{18}F-fluoride PET markedly improves the accuracy of tissue sampling for micobiologic culture, pathology, real-time PCR, and the sensitivity of subsequent tissue examination. This combination, the preoperative imaging diagnosis by ^{18}F-fluoride PET and intraoperative diagnosis using real-time PCR, may be valuable alternative tool for the clinical evaluation of implant loosening and infection after THA.

IS1-3

Diagnosis of Periprosthetic Joint Infection

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Distinguishing septic from aseptic failure in total joint arthroplasty (TJA) is essential in implementing the appropriate management for the patients. There are many challenges in diagnosis of PJI, most important of which relates to the lack of an absoulte diagnostic test. In addition, presenattion of PJI can mimick aspetic failure in many cases. Recently a workgroup convened by the American Academy of Orthopedic Surgeons proposed evidence based algorithmic approach for diagnosis of PJI. I will discuss the AAOS approach. In addition the role of routine tests (serum ESR and CRP) in work up of patients with painful PJI will be discussed. In recent years the importance of synovial neutrophil count and percentage has been highlighted. The absoulte count and percentage of neutrophils for diagnosis of chronic and acute PJI has been defined and will be presented. Our center and many others have also identified molecular markers in the synovial fluid that can be utilized for more accurate diagnosis of PJI. Some of the potential arkers include synvoial CRP, interlukins, macroglobulins, and VEGF. In addtion we have prposed the use of leukocyte esterase tests for diagnosis of PJI. During my presentation I will discss some of the molecular startegties that can be used to isolate infecting organism(s) in cases of culture-negative PJI. Finally the diagnostic criteria developed by the Muscloskeletal Infection Society (MSIS) and adopted by major organizations will be presented.

IS1-4

The Pathology of Septic and Aseptic Loosening

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Regardless of the composition of the articular surfaces, there are several different mechanism of arthroplasty failure. Those mechanisms include, among other things: 1) mechanical loosening caused by the failure to achieve adequate initial fixation or fatigue failure of an inadequate interface, 2) particle-induced bone resorption, 3) infection, and 4) other adverse local tissue reactions. The histology of tissues around failed implants can often provide clues about the dominant mechanism of failure. For example, tissue around implants that failed to achieve adequate initial fixation contains proliferating blood vessels as a reaction to motion. Tissue around implants that failed due to implant wear contains macrophages and giant cells with particles. The diagnosis of infection may require several different laboratory tests, but more than five neutrophils per microscopic field in at least three fields usually indicates infection. Recent controversies about metal-on-metal hip arthroplasty have focused our attention on a pattern of histologic findings that suggests an immune reaction. Sometimes called "ALVAL" (aseptic lymphocyte-dominant vasculitis-associated lesion), this reaction can be associated with soft tissue masses (inflammatory pseudotumors), bone destruction, neuropathies and poor results of revision arthroplasty. The individual histologic features of ALVAL, such as perivascular lymphocytes, are not specific for failed metal-metal implants, but the combination of necrosis, diffuse lymphocytes and plasma cells is characteristic of an immune reaction to metal debris or ions. Further studies that define the phenotype of lymphocyte populations are needed to help distinguish this reaction from other types of inflammatory arthropathies and from infection.

IS1-5

In vivo analysis of polyethylene wear particles after total joint arthroplasty

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Polyethylene (PE) wear particles induce macrophages to release cytokines, which can lead to osteolysis and aseptic loosening of total joint prostheses. The generation of PE wear particles is one of the most important factors that affect the midterm and long-term clinical results associated with total joint arthroplasty (TJA). The generation of PE wear particles is correlated with the activity level of the patient, and greater demands are placed on total joint prosthesis when it is implanted in a younger, more active patient. Therefore, to achieve better long-term results for patients who have higher activity levels, modifications of materials and design have been developed to reduce PE wear after TJA. The number, size, and shape of PE wear particles have been reported to be critical factors in the development of osteolysis. Greater volume, submicrometer size, and an elongated shape of polyethylene wear particles all stimulate an increased macrophage response. Although *in vitro* study such as wear simulator test provides important information about PE wear, we have often encountered the discrepancy between the *in vitro* results and *in vivo* results. Thus we have performed *in vivo* PE wear particle analysis. We isolated PE wear particles from periprosthetic tissue of a failed total hip arthroplasty. Highly cross-linked polyethylene (HXLPE) generated fewer, rounder, equivalently sized particles compared with conventional PE. We also isolated PE wear particles from joint fluid of the well-functioning patients after total knee arthroplasty. Medial pivot (MP) design, alumina femoral component, and HXLPE generated fewer PE wear particles. Mobile-bearing design generated larger particles. HXLPE generated smaller articles. Alumina MP and HXLPE generated rounder particles. Our results showed that modification of TJA materials and designs resulted in different PE wear particle characteristics. These differences may be important factors in the long-term development of osteolysis.

IS2-1

Immunological Memory in Chronic Inflammation

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A new understanding of immunological memory postulates that memory cells survive in dedicated niches of bone marrow and other lymphoid organs, resting in terms of proliferation and migra-

tion, and maintained by survival signals from stroma cells and accessory cells. While memory B and T cells form the reactive memory, memory plasma cells provide humoral memory. The concept also implies a new role for immunological memory in chronic inflammation, and asks for new therapeutic strategies. A major challenge are memory plasma cells secreting antibodies to autoantigens. Memory plasma cells are resistant to conventional immunosuppression, such as radiation, glucocorticoids, anti-TNF or anti-CD20 antibodies. Memory plasma cells secreting autoantibodies thus can be a motor of chronic inflammation refractory to state-of-the-art therapy. New therapeutic strategies targeting critical survival signals of memory plasma cells underline their central role in driving chronic inflammatory diseases. As for the reactive memory, T helper (Th) lymphocytes are critical, since they control memory as such. Memory Th lymphocytes of protective immune responses, where the antigen has been eliminated, are maintained as resting cells by dedicated stromal cells of bone marrow, expressing IL-7. In contrast, Th cells of the pathogenic memory found in chronic rheumatic autoimmune inflammation are constantly confronted with their antigens and have a history of repeated restimulation. We have identified the transcription factors twist1 and hopx, which are specifically upregulated in pro-inflammatory Th1 cells and are selectively expressed in Th cells isolated from inflamed tissue of patients suffering from chronic inflammatory diseases, like rheumatoid arthritis, reactive arthritis or colitis. These memory/effector Th cells are refractory to conventional therapies and constitute a new challenge for the development of therapeutic strategies.

IS2-2

Immunological mechanisms in autoimmune arthritis via ubiquitous autoantigens

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Conflict of interest: Yes

Rheumatoid arthritis (RA) is a systemic autoimmune disorder, characterized by inflammation and destruction of multiple joints. Prognosis of RA patients has significantly improved with the recent use of biologics, although the etiology of them is mostly veiled. From the clinical evidences, fundamental three axes leading arthritis are inflammatory cytokines, autoreactive T cells and autoantibodies (Abs). They are interacted and collaborated with each other for the generation of arthritis. We identified that autoimmune reaction to glucose-6-phosphate isomerase (GPI) solely provokes arthritis using K/BxN mice. Anti-GPI Abs in this model can transfer arthritis, and mechanisms of "autoantibody-induced arthritis" are intensively investigated by their Abs. We and others also developed GPI-induced arthritis model that can induce arthritis with GPI immunization to genetically unaltered mice. In this model, autoreactive T and B cells are essential, and similar therapeutic effectiveness has been confirmed with TNF and IL-6 antagonists and CTLA-4Ig. T_H-17 was crucial $CD4^+$ T cell lineage for GPI-induced arthritis, and blockade of IL-6R significantly suppressed the arthritis by inhibition of T_H-17 differentiation, auto-reactive T cell proliferation and autoAb production. We also developed peptide-induced arthritis model that was induced by single immunization with 15mer T cell epitope ($hGPI_{325-339}$) in DBA/1 mice, and it is very advantageous to reproduce arthritis development and to chase autoreactive T cells. These findings highlight the potential role of systemic autoreactivity to certain ubiquitous antigens in the pathogenesis of RA. We have investigated autoreactive T and B cell response to GPI including citrullinated form in RA as well. We will discuss and compare the etiological contribution of autoreactivity to certain ubiquitous antigens in arthritis between mice and humans.

IS2-3

Pathogenesis of rheumatoid arthritis

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Rheumatoid arthritis (RA) ranks among the most common inflammatory disease of the musculoskeletal system. It shows frequently systemic involvement but primarily affects the joints, where chronic synovial inflammation and subsequent destruction of articular cartilage and bone are the main characteristics of disease. The accumulation of inflammatory and immune cells, particularly macrophages B-cells and T-cells, is one of the hallmarks of human RA. These inflammatory cells release a variety of cytokines that result in the stimulation of neighboring cells and contribute to the specific environment in the rheumatoid joint. The resulting pathological correlate is a massive hyperplasia of the synovial membrane that not only causes the majority of signs and symptoms of RA but also determines the outcome of disease in the majority of individuals affected by the disease. Special stromal cells, termed rheumatoid synovial fibroblasts, are able to react both on stimulation with cytokines, chemokines and growth factors are also able destroy the articular structures independently, owing to their transformed phenotype. A novel observation is the synthesis of a group of cytokines, the so-called adipokines. Experiments demonstrated that rheumatoid synovial fibroblasts are major sources for distinct adipokines including adiponectin, visfatin and resistin, and that these adipokines act highly proinflammatory and – via the synthesis of collagenase – also prodestructive. In addition, distinct epigenetic changes add to the proinflammatory and prodestructive activity of the fibroblasts as well as of other cells of the RA synovium. Novel animal models have also helped to elucidate the pathophysiology of RA even further, especially the SCID mouse co-implantation model of cartilage destruction. Using this model, it could be found that that rheumatoid arthritis synovial fibroblasts contribute to the spreading of the disease from one joint to another through migrating to distant joints.

IS2-4

Genetics and immunology of Sjögren's syndrome

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Conflict of interest: None

Today, there is no specific drug for treatment of primary Sjögren's syndrome (pSS). In this lecture, I will try to reconcile pathogenesis and treatment by focusing on the crucial pathogenic steps, that could be targeted by emerging therapies. The main new insights into the pathogenesis of the disease are represented by the accumulating data on the involvement of type-I interferon and the triggers of B lymphocyte activation in pSS. First, I will summarize the pathogenic involvement of type-I interferon (IFN) and B-cell-activating-factor of the TNF family (BAFF) in B-cell activation. Interestingly, these recent genetic and pathogenic studies evidenced number of similarities between pSS and lupus, and pSS could be considered as a sort of lupus of mucosa. I will subsequently discuss the different therapeutics that could target such an IFN-BAFF-B lymphocyte axis.

IS2-5

Seed and soil model of autoimmunity-Lessons learned from a new polymyositis model of mice-

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Conflict of interest: None

Polymyositis (PM) is an autoimmune inflammatory myopathy with the clinical manifestation being progressive muscle weakness. Its pathology is characterized by infiltration of inflammatory mononuclear cells in the muscles as well as degeneration and regeneration of muscle fibers. Recently, we established C protein-induced myositis (CIM) as a murine model of PM. It is the first animal model that represents CD8 T cell-mediated muscle injury, which is involved reportedly in PM. It is induced readily by a single immunization of a recombinant fragment of the skeletal muscle C-protein in various strains of mice, including C57BL/6 mice. This model allowed us to dissect various pathological aspects of autoimmune myositis. CIM is similar to PM in many aspects except that it undergoes spontaneous remission. To investigate the regression, we re-immunized CIM mice and found no tolerance established. Interestingly, intradermal injection of complete Freund's adjuvant (CFA) at footpads alone re-induced myositis. Moreover, myositis was inducible only in the legs treated with CFA. Thus, the regression should be attributable to attenuation of the CFA-induced local immune activation. Indeed, the disease course was not altered by absence of CD25 regulatory T lymphocytes or IL-10. Requirement of the local immune activation was confirmed by the adoptive transfer model, where T cells from CIM mice provoked myositis only when transferred to recipients treated with CFA or other toll-like receptor (TLR) ligands at the footpads. Conditioning by the TLR ligand increased intramuscular macrophages producing inflammatory cytokines. Anti-cytokine antibody treatment of the transfer model revealed that IL-1 and TNF-α account for the muscle tissues activation. Myositis development requires activation of autoagressive T cells and conditioning of the muscle tissues. It reminds us of the seed and soil model of disease development that has been proposed as a model of tumor metastasis.

IS3-1

T cell targeted therapies

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Conflict of interest: Yes

Considering the pathogeneses of rheumatoid arthritis (RA), the association between certain polymorphisms of major histocompatibility complex (MHC) class II alleles and RA has been reported. This suggests antigen presentation to CD4+ T cells is critical. In fact, the presence of CD4+ T cell infiltration within rheumatoid synovial tissues is prominent. In animal models, a crucial role for antigen-specific CD4+ T cells has also been reported. Several lines of evidence suggest that T cells should play important roles in the pathogenesis through production of proinflammatory cytokines, promotion of autoantibody production by B cells, and activation of synoviocytes and osteoclasts. Although anti-cytokine therapies are generally accepted as important strategies for improvement of RA, some patients may exhibit inadequate response. Regarding T cell targeted therapies, early clinical trials using anti-CD4 monoclonal antibodies in RA appeared to be promising. However, subsequent randomized, double-blind, placebo-controlled trials turned out to be negative. This lack of efficacy could partially come from the fact that naive T cells are more susceptible with the therapy than activated pathogenic T cells. On the other hand, attempts to inhibit the second signal in T cells by manipulating the costimulatory system have been recently reported to be successful. Cytotoxic T lymphocyte-associated antigen 4 (CTLA4) is an inhibitory receptor on the T cell surface that binds with CD80 and CD86 on antigen presenting cells. Abatacept(CTLA4-Ig) is a fusion protein that consists of the extracellular domain of CTLA4 and the Fc portion of IgG1. Abatacept binds to CD80 and CD86 on antigen presenting cells, and it thus prevents the second activation signal in T cells. Abatacept has been reported to be effective in treating patients with RA. Inhibition of structural damage of the joints was also significant. Abatacept has an acceptable safety profile and is well tolerated in patients with RA.

IS3-2

B cell-targeting – What can we achieve? How do we best achieve it? What are the risks?

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In the late 1990's Prof. Jonathan Edwards suggested, based on *in vitro* observations, but contrary to prevailing opinion, that B-cell targeted therapies could be efficacious in rheumatoid arthritis (RA). Subsequent clinical trials proved this hypothesis to be correct, and rituximab (RTX; anti-CD20) was approved as a treatment for patients who had failed anti-TNF. The clinical trials results have been confirmed in practice-based registries, including 12 European registries that are now joined in the Collaborating European Registries for the study of Rituximab in RA (CERERRA). It is clear that efficacy at par with anti-TNF treatment can be achieved, including clinical disease control and a marked reduction of radiographic damage. Additional data from randomized trials have suggested that retreatment at 6-monthly intervals may be more effective than an 'on demand' schedule. Data both from trials and registries suggest that a dose of 500 mg twice, rather than 1000 mg twice, may be (almost) equally effective, increasing the cost-effectiveness of this therapeutic. Data from CERERRA show that in European countries a significant number of RA patients who are naïve to anti-TNF are treated with RTX, often in connection with specific comorbidities and individual risk factors. Other recent data from CERERRA show that the combination of rituximab with leflunomide may be even more effective than with methotrexate. Treatment with RTX, even when given for many years, has been associated with a remarkably benign side-effect profile, despite profound and sustained B-cell depletion. The one major concern has been the occurrence of progressive multifocal leukoencephalopathy in some patients, but the absolute risk of this fatal complications is currently estimated to be less than 1 in 10,000. Studies of other B-cell targeting biologics have not led to other RA treatments, but bio-equivalents of rituximab are currently being tested in phase III clinical trials.

IS3-3

Personalizing strategy for anti TNF therapy in RA

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Conflict of interest: Yes

Biological agents targeting a specific molecule provide an effective means for therapeutic management of rheumatoid arthritis (RA) due to their specificity and powerful functional capabilities, which has resulted in a paradigm shift in the treatment strategy of this disease. Until now, nine biological agents are approved in RA worldwide and six of them are available in Japan. A treatment strategy that uses tightly controlled doses of administered biologics, targeting clinical remission or low disease activity, and followed by discontinuation of the biologics may be advantageous from both a health and economical point of view. This strategy is

now being examined in several clinical studies and trials in Japan for several biologics, including infliximab, etanercept, tocilizumab, and abatacept. It is ideal to personalize medical treatment for individual RA patients by predicting efficacy and safety of a given biologic. In order to identify predictive factors, enormous amounts of efforts have put forth. Although several clinical variables have been associated with efficacy and safety, they are often unrealistic in clinical practice. We found that the baseline circulating TNF levels and Fc gamma 3B polymorphism are important predicting factors for response to infliximab in RA patients. In addition, monitoring concentration of biologics and according adjustment of the dose or intervals, may maximize the potential of the agents. Given such data, I will discuss the role of these markers in real world. Further clinical studies using biomarkers and molecular expression pattern should provide a clue to find the appropriate predicting markers or even new therapeutic targets. In the near future, the information accumulated from these studies may allow selecting the best biological agents in individual patient.

IS3-4

Advanced therapeutic strategy using anti-IL-6 receptor antibody, tocilizumab, in RA

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Conflict of interest: Yes

IL-6 plays pathological roles in RA and IL-6 targeting therapy has been developed. Tocilizumab (TCZ), an anti-IL-6 receptor antibody, even in monotherapy, frequently induces DAS28 remission in patients with RA refractory to synthetic DMASDs or anti-TNF agents and suppresses the radiographic joint damage. Current issues are to find patients who indeed require TCZ, and to know whether or not TCZ-free remission is achievable. TCZ more significantly reduced radiological progression in patients with risk factors for rapid progression (i.e. high urinary C-terminal crosslinking telopeptide, high urinary pyridinoline/deoxypyridinoline ratio, low body mass index, and presence of joint space narrowing at baseline) than patients without those risk factors. Thus such high risk patients need TCZ. Furthermore, early decreases in serum type IIA procollagen amino terminal propeptide, CRP, and/or matrix metalloproteinase 3 (MMP-3) within 12 weeks can correlate with the preventive effects of TCZ on radiological joint damage for one year. To test the possibility of TCZ free remission, DREAM study was conducted. A total of 187 patients, who had received TCZ in the previous clinical trials (the mean treatment duration was 4.3 years), were enrolled, and discontinued TCZ. Remission, defined as DAS28 less than 2.6, was maintained in 10% of the patients without any drug over 52 weeks. In addition, low serum IL-6 ($\leqq$ 12.9 pg/mL) and MMP-3 normalization at cessation of TCZ were identified as independent predictive markers for the longer duration of TCZ free remission. Furthermore, TCZ retreatment in the patients who experienced loss of efficacy after cessation of TCZ, was well tolerated and showed excellent efficacy equivalent to the initial TCZ treatment. These evidences may establish TCZ personalized therapy for RA patients. Efficacy prediction based on the genome wide association study results, and blood gene expression profiles will be available in the future.

IS3-5

Kinase Inhibition in rheumatoid arthritis - what do we know in 2012?

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The treatment of patients with rheumatoid arthritis is challenging, both for the patient and the physician. Historically, the use of aspirin and later, other non-steroidal anti-inflammatory drugs, helped control symptoms of disease but did not prevent the long term ravages of disease. The introduction of corticosteroids was initially thought to be the answer to the treatment of RA, but, it was quickly evident, that although very helpful with clinical symptoms, its toxicity limited its use. The development of DMARDs, such as gold, were helpful in some patients, but the risk:benefit ratio and long term efficacy, were disappointing. The introduction of DMARDs such as methotrexate late in the last century was a significant advance, as methotrexate can limit disease progression as well as help control symptoms. Its toxicity and the fact that it is of significant benefit in only one-third of patients, even if used early and aggressively, and that there are many patients who cannot tolerate methotrexate, has spurred the search for other medications of value in the treatment of rheumatoid arthritis. This century, the introduction of biologic mediations, has been a major advance in the treatment of RA, as they do help control symptoms, improve patient function and inhibit radiographic progression, but they are not effective in all patients, have a unique side effect profile, are injectable and expensive. There are several medications in development which act by a different mechanism of action – inhibiting kinases ultimately involved in the production of inflammatory cytokines. Their major advantage is that they are oral and, theoretically, should be cheaper than biologic agents. What is known about their efficacy and safety profile will be the focus of this presentation.

China-Japan Rheumatology Symposium

CJS-1

Gene regulatory network of musculoskeletal system development and homeostasis

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Conflict of interest: None

We created a whole-mount in situ hybridization (WISH) database, termed EMBRYS (http://embrys.jp), containing expression data of 1520 transcription factors and cofactors expressed in E9.5, E10.5, and E11.5 mouse embryos--a highly dynamic stage of skeletal myogenesis. This approach implicated 43 genes in regulation of embryonic myogenesis, including a transcriptional repressor, the zinc-finger protein RP58 (also known as Zfp238). Knockout and knockdown approaches confirmed an essential role for RP58 in skeletal myogenesis. Cell-based high-throughput transfection screening revealed that RP58 is a direct MyoD target. Microarray analysis identified two inhibitors of skeletal myogenesis, Id2 and Id3, as targets for RP58-mediated repression. Consistently, MyoD-dependent activation of the myogenic program is impaired in RP58 null fibroblasts and downregulation of Id2 and Id3 rescues MyoD's ability to promote myogenesis in these cells. Our combined, multi-system approach reveals a MyoD-activated regulatory loop relying on RP58-mediated repression of muscle regulatory factor (MRF) inhibitors. We applied our systems approaches to other locomotive tissues research including cartilage and tendon, and revealed novel molecular network regulating joint cartilage development and homeostasis via miRNA-140 (Genes and Development, 2010; Arthritis and Rheum, 2009) and tendon development by Mkx (PNAS, 2010).

CJS-2

Pathophysiology of autoimmune arthritis - From clinic to bench and vice versa-

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Conflict of interest: Yes

The cause of rheumatoid arthritis (RA) is still mystery, although recent advances in understanding the pathogenesis of the disease have developed new therapeutics including biologics targeting TNFa and IL-6, and T cells with CTLA-4 Ig. In Japan, six biologics have been approved and confirmed clear therapeutic efficacy to RA. From the clinical evidences unraveled by these therapeutics, there are three fundamental axes they leads arthritis are, inflammatory cytokines, autoreactive T cells and autoantibodies. We and others have developed glucose-6-phosphate isomerase (GPI) and its peptide induced arthritis model that can provoke arthritis via GPI immunization to genetically unaltered mice. In this model, these three axes are crucial in the generation of arthritis confirmed by the similar therapeutic effectiveness with biologics to RA. In this symposium, I will discuss and summarize recent finding of pathogenesis of arthritis that is highlighted by the study from clinic to bench and vice versa in Japan.

CJS-3

Small-molecule drugs targeting tyrosine kinases; novel DMARDs as effective as biologics on rheumatoid arthritis

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Conflict of interest: Yes

Treatment for rheumatoid arthritis (RA) has developed dramatically by the use of biologics targeting TNF and IL-6. The old treatment goal was to control the symptoms with NSAIDs and classical DMARDs. However, the latest suggest goal for RA treatment is to achieve clinical remission and moreover, radiographic remission which has been described as "Treat to target (T2T)". Major issue with this treatment concept is the outrageous medical cost and parenteral administration of biologics. Tyrosine kinases are a group of proteins that are activated in the cytoplasm after the inflammatory cytokines binds to their unique receptor expressed on the cell surface. Depending on the dramatic effect of biologics, small-molecule drugs have been expected to show pronounced anti-rheumatic effect. Recent clinical trails with JAK-inhibitor, tofacitinib (previous CP-690,550) and Syk-inhibitor fostamatinib (R788) has proven this idea and is expected to become a novel DMARD in the near future. Herein, the result of clinical trials of the small-molecule drugs will be overviewed and the mode of action of tofacitinib will be discussed.

CJS-4

Premature atherosclerosis of systemic lupus erythematosus: risk factors and pathogenesis

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Conflict of interest: None

Systemic lupus erythematosus (SLE) is a complex multisystem autoimmune disease that involves multiple organs as a result of autoimmune-mediated tissue damage. With the improved treatment, the long-term survival of SLE patients has also improved. However, an increased risk of accelerated atherosclerotic diseases has been associated with SLE, leading to increased cardiovascular morbidity and mortality. Much effort has been made to analyze the mechanism of premature atherosclerosis. In a study, we evaluated the prevalence of subclinical atherosclerosis in Chinese premenopausal systemic lupus erythematosus patients. Patients with longer disease duration, higher cumulative prednisone dose and more cumulative organ damage, were more likely to have carotid plaque. The increasing prevalence of atherosclerosis in SLE is likely attributable to a complex interaction involving traditional risk factors and disease-related factors. The interplay of multiple inflammatory mediators, including leukocytes, cytokines, chemokines, adhesion molecules, complement, as well as antibodies, promotes damage of endothelium and formation and rupture of the plaques. Among them, autoantibodies and type I interferon are attracting more attention for their multiple roles in SLE and atherosclerosis, and there is accumulating evidence indicating how these factors play a role in the initiation and progression of atherosclerotic plaque. The expression of proinflammatory cytokines and chemokines have been recognized to play a pathogenic role in atherosclerosis. IL-12, TNF-a, MCP-1 and IL-1 may give rise to atherosclerosis by promoting formation of atherosclerotic plaque. Recent studies from multiple research groups including ours indicated that type I interferon, a key pathogenic factor in SLE, is involved in atherosclerosis through several different mechanisms including promoting abnormal vasculogenesis, plaque formation and disruption.

CJS-5

Chinese SLE Treatment And Research group (CSTAR) registry with Chinese Rheumatology Information System (CRIS): a model of translational study in Chinese rheumatology

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Background: Limited epidemiological data exist to date from China on systemic lupus erythematosus (SLE). CSTAR developed the first on-line registry of Chinese patients with SLE, which is supported by Chinese National Key Technology R&D Program. **Objectives:** The goals of CSTAR include: 1) designing and implementing a nationwide SLE registry for collecting and storing clinical data and biospecimens; 2) providing these resources for future studies of SLE; 3) establishing a platform to facilitate both practice and research. **Methods:** CSTAR started with a multicentre, consecutive and prospective design. The clinical data was collected by e-CRF of CRIS from 142 rheumatologic centers, which covered 30 provinces in China. All centers use the same protocol-directed methods to provide uniform evaluations. The biospecimen were collected and stored in different centers, but were also registered in CRIS for future management. **Results:** Preliminary data from 2104 baseline evaluations was available for this analysis. Of 1914 female and 190 male patients (F:M = 12.2), the mean age at onset was 29.2 y. 34 (1.6%) of the patients had a family history of SLE. The characteristics of the CSTAR cohort were compared to similarly sized cohorts from other studies. We found that 56.1% of patients presented with concurrent hematological disorders compared to only 18.2% of European patients. Moreover, 47.4% of patients presented with nephropathy compared to 27.9% of European patients. Conversely, neurological manifestations were only seen in 4.8% of Chinese SLE patients compared to 19.4% of European patients and 12.1% of U.S. patients. Pulmonary arterial hypertension and interstitial lung diseases were complications identified in 3.8% and 4.2% of Chinese lupus patients, respectively. **Conclusion:** The CSTAR registry has provided epidemiological data and unique phenotypes of Chinese patients with SLE. Clinical data and biospecimens would be valuable resources for future translational studies.

CJS-6

Safety of anti-TNF agents in inflammatory arthropathy patients with chronic or resolved hepatitis B virus infection: Results from registry data in China

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Objectives: To investigate the prevalence of HBV reactivation in inflammatory arthropathy patients with HBV infection and anti-TNF agents, and evaluate the efficacy of antiviral therapy in reducing the risk of viral reactivation in chronic HBV infection. **Methods:** Data from a registry of patients with anti-TNF agents in Chinese population were reviewed. Eighty-Seven patients were identified, including 60 patients with RA, 24 with AS, and 3 with PsA. Patients entered the registry from January 2008 to January 2011. **Results:** There were 37 patients with chronic HBV infection (including 6 chronic hepatitis B patients and 31 inactive HBV carriers) and 50 patients with resolved HBV infection. During the treatment with anti-TNF agents, ALT and HBV-DNA levels were monitored periodically. The median time of exposure to anti-TNF agents in patients with chronic HBV infection was 6 months (range 1-32 months). Among the 6 chronic hepatitis B patients treated with anti-TNF drugs, HBV reactivation was found in 2 patients without antivirus therapy, and no viral replication was detected in the other 4 patients with antivirus therapy. In the 31 inactive carriers, the increase of viral load was detected in 6 of 22 (27.3%) patients without antiviral drugs, and there was no viral reactivation in the other 9 patients with antiviral prophylaxis. Antiviral drugs can significantly decrease the risk of HBV replication in patients with chronic HBV infection (p=0.034). HBV reactivation was not found in the 50 patients with resolved HBV infection, when they were treated with anti-TNF drugs for 4 to12 months. In all these 87 patients, there was no fulminant hepatitis. **Conclusion:** It is suggested that anti-TNF therapy might increase the risk of HBV reactivation in patients with chronic HBV infection, especially in patients with chronic hepatitis B. Antiviral therapy during anti-TNF drugs treatment can decrease the risk. Anti-TNF agents seem to be safe in patients with resolved HBV infection.

Educational Lecture

EL1

Management for pulmonary hypertension in patients with connective tissue disease: best practice provided by rheumatologists

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Conflict of interest: None

Pulmonary hypertension (PH) is a condition with increased pressure in the pulmonary arteries, which leads to right heart failure, right ventricle hypertrophy, and low cardiac output. PH is classified into 5 categories, including pulmonary arterial hypertension (PAH), PH owing to left heart disease, PH owing to lung disease and/or hypoxia, chronic thromboembolic PH, and PH with unclear multifactorial mechanisms. All 5 forms of PH can occur in patients with connective tissue disease (CTD), but PAH is the most common form. Prognosis of PAH is very poor if remain untreated, with a survival of 50% at one year and <20% at 3 years after diagnosis. Recent introduction of molecular-targeting PAH drugs, such as prostanoids, endothelin receptor antagonists, and phosphodiesterase-5 inhibitors, has prolonged time to clinical worsening and survival, but PH still remains a intractable condition. Since more than half of the patients with PH have underlying CTD, rheumatologists must be involved in the joint forces with cardiologists and/or pulmonologists. This multidisciplinary approach is necessary to further improve the survival in CTD patients with PH. One of the major roles of rheumatologists in the PH management is to identify patients with early or mild PH by active screening, since patients with systemic sclerosis or mixed connective tissue disease are at an extremely high risk of developing PH. To further improve prognosis of PAH, it is imperative to reach an early diagnosis and to initiate adequate treatment at a time when it is most likely to be reversible. In addition, rheumatologists have to play an important role in optimizing treatment regimens for PH, by taking account of PH classification, disease subset and activity of underlying CTD, concomitant interstitial lung disease and myocardial dysfunction, and safety profiles of PAH drugs.

EL2

Knowledge of psoriasis required for rheumatologists to manage psoriatic arthritis with biologic agents

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Conflict of interest: Yes

Recent development of therapeutic monoclonal antibodies has introduced a new biologic era for the treatment of not only malignancies, but also a variety of immune disorders such as rheumatoid arthritis, inflammatory bowel disease, and psoriasis. Clinical use of TNFa inhibitors, infliximab and adalimumab, in dermatology began in January 2010 when additional indications for psoriasis and psoriatic arthritis were approved. In January 2011, an IL-12/23p40 inhibitor, ustekinumab, was newly approved as the third biologic agent with the same indications in dermatology. Ustekinumab is very unique in that it is only approved for psoriasis worldwide. In June 2011, the Guideline/Safety Manual for the Use of Biologic Agents in Psoriasis was revised into a unified version for all three biologic agents including ustekinumab by the Biologics Review Committee of Japanese Dermatological Association. To date, there are approximately 500 core hospitals which have been approved to initiate biologic therapies for psoriasis patients by the Committee. Several hot questions arise, such as when, how, and for what kind of patients (with or without arthritis ?), to choose among these three agents properly. As a matter of fact, mandatory post-marketing surveillance investigations are open not only for dermatologists (board-certified only) but also for rheumatologists and orthopedists. Therefore, in this lecture, I would like to provide non-dermatological clinicians with useful knowledge on psoriasis to best manage psoriatic arthritis as well as psoriatic skin lesions with biologic agents, taking together an overview on the transition of therapies and pathophysiological viewpoints of psoriasis through decades.

EL3

Establishment of the novel therapy for treatment of heart failure and analysis of the pathophysiology of the heart disease using iPS cells

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Department of Cardiology, Keio University School of Medicine

Conflict of interest: Yes

Although heart transplantation can drastically improve the survival, shortage of the donor heart is a serious problem. The regenerative medicine including cardiomyocytes regeneration and their transplantation had been long awaited. To address this question, we initially screened critical growth factors that were expressed in the developing mice heart. Firstly, we found noggin, a BMP antagonist, was transiently and strongly expressed at the cardiac crescent at E7.5. Using noggin, we found that they can efficiently induce cardiomyocytes from mouse ES cells. Moreover, we found that X factors and G-CSF were strongly expressed at the different time point of developing heart. We applied these factors for ES cells, and found that X factor could induce cardiomyocyte differentiation and G-CSF could induce cardiomyocyte proliferation. These factors were also effective for common marmoset monkey and human ES cells. ES cell-derived regenerated cardiomyocytes could be purified by application of mitochondria sensitive dye TMRM. Purity of the cardiomyocytes was more than 99.5%, and they did not make teratoma formation after transplantation. The transplanted cardiomyocytes using our technique can survive in the heart with more than 90%, and can show physiological growth after transplantation. Moreover, we also have succeeded in the induction of cardiomyocytes from human inducible pluripotent stem (iPS) cells, which were generated from fibroblasts with transfection of the four critical genes. We expect the combination of these techniques can achieve future heart regeneration.

EL4

Differential diagnosis in patients with early arthritis

Atsushi Kawakami
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Conflict of interest: Yes

Newly-onset arthritis with short disease duration is so-called as early arthritis which includes varying disease conditions. 2010 rheumatoid arthritis (RA) classification criteria is developed to purify the patients who will progress later erosive and persistent arthritis at high risk from early arthritis patients. This criteria is found to be clinically useful in Japanese early arthritis patients. However, we have to notice that the apparent non-RA patients with arthritis such as osteoarthritis, Sjögren's syndrome, polymyalgia rheumatica and psoriatic arthritis are excluded before 2010 RA classification criteria is applied. Thus, 2010 RA classification criteria scoring system is applied in the patients who are not best explained by another diseases. Therefore, the knowledge of differential diagnosis of RA is essential to use this criteria. 2010 RA classification criteria consist of 4 domains including distribution of

arthritis, serology, acute phase reactant and disease duration. If the patients are scored as greater than 6, they are classified as RA. Small polyarthritis and autoantibodies are emphasized in 2010 RA classification criteria. Immediate introduction of disease-modifying anti-rheumatic drugs (DMARDs) is recommended to the patients classified as RA. Recently, the role of methotrexate (MTX) is increasing as first-line DMARDs. However, in some cases such as acute phase reactant-negative or seronegative patients, it is difficult to classify the patients by 2010 RA classification criteria only. MRI and/or US are quite useful to qualify the joint injury in such cases and help to classify the patients. MRI detects articular synovitis, tenosynovitis, ostitis and bone erosion whereas US finds articular synovitis, tenosynovitis and bone erosion. These two methods are highly sensitive to detect joint injury as compared with physical examination. Essential points of differential diagnosis of early arthritis patients will be shown in this lecture.

EL5

Indication and selection of biological agents in RA treatment

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Conflict of interest: Yes

Biological agents targeting against the single molecule involved in the pathogenesis of Rheumatoid Arthritis (RA) have been used in the treatment of patients with RA for some 20 years, since the first human study had reported in 1993. In Japan, we have used the biologics for 10years. Given the recent progress in the medical management of Rheumatoid Arthritis, in part through the biologics, clinical practice surrounding RA has become dramatically changed, not only in the treatment, but also diagnosis and evaluation of the disease. In Japan, six biological agents including anti-TNF (infliximab, etanercept, adalimumab and golimumab), anti-IL-6R (tocilizumab) and CTLA-4-Ig (abatacept) are available for RA. One anti-TNF (certolizumab-pegol) is now on file. JCR guideline for these biologics has been announced. Indication for these biologics in the guidelines, is the RA with high disease activity such as SJC≧6, TJC≧6 and CRP≧2mg/dl or ESR≧28, despite DMARD treatment such as MTX, in principle. In addition, it is also indicated for progressive erosive disease even with moderate disease activity. For the safety, several laboratory testing such as WBC count and b-d-glucan as well as screening and monitoring of infection, particularly tuberculosis, are mandatory before staring biologics. Post marketing surveillance for all cases treated with biologics has been taken, showing us the incidence and profiles of the side effects of biologics. By analyzing risk factors from the studies, the background of the patients with risk for the side effects has revealed, reflecting those in the guideline. However, it is still difficult to select the appropriate biologics in the individual RA patient. Unfortunately, guidelines for supporting the selection of the biologics have not yet established in Japan. There still remain several issues around the biological treatments in RA, not only for efficacy, but in the safety, too. Cost issues and efficient treatment algorithm with biologics have also came up. For these respects, we definitely need much more knowledge toward the personalized strategy for biologics treatment. Recent progress in such field will be introduced. Finally, I will discuss the future perspective of the biologics in RA.

EL6

New experimental and clinical findings in systemic sclerosis

Yasushi Kawaguchi
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Conflict of interest: Yes

Systemic sclerosis (SSc) is a connective tissue disease of unknown etiology, characterized by tissue fibrosis and vascular damage. The first symptoms are usually Raynaud's phenomenon and skin thickness. As the classification criteria of ACR in 1980, individuals who have skin fibrosis expanding to hand are classified into SSc. However, individuals who have skin fibrosis of only fingers, Raynaud's phenomenon, and anti-centromere antibody are not able to be classified into SSc. If those patients have either interstitial lung disease or pitting scar or loss of substance from finger pad, the patients are classified into SSc. In 2011, the new classification criteria were published from EUSTAR group. Those are preliminary criteria for the very early diagnosis of SSc. Those criteria The most serious manifestations are interstitial lung disease (ILD), pulmonary arterial hypertension (PAH), and pseudo-obstruction of small intestine. Concerning ILD, since the efficacy of cyclophosphamide has been controversial, I would like to discuss the cyclophosphamide therapy for ILD on the basis of various publications and our data. On the other hand, the new therapies for PAH have been developed and the efficacy of them has been established recently. However, the treatment of pseudo-obstruction of small intestine was not developed. In the previous report, the frequencies of anti-U3 RNP antibody and anti-muscarinic 3 receptor antibody were fairly high, suggesting that smooth muscle injury and the abnormality of acetylcholine-related response may be involved in the pathogenesis of pseudo-obstruction. Finally, polymorphisms of various genes were associated with susceptibility to SSc. In particular, the polymorphisms of CTGF and HGF were related to ILD, and NOS2 polymorphism was related to PAH. In patients with SSc, gene polymorphisms could be the useful and predicative biomarkers for ILD and PAH.

EL7

Current concepts in best timing of the surgical joint arthroplasty for rheumatoid arthritis.

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Conflict of interest: Yes

The destruction of the large joints in rheumatoid arthritis patients is common and has been a challenge for the orthopedic surgeon for many years. Total hip arthroplasty and total knee arthroplasty with a high survival rate may now be considered as gold standard procedures for RA patients. Also at other joints, the new prosthesis has improved the clinical outcome in RA patients. For getting the best clinical outcome, most important things are the preoperative joint conditions and general disease activities. In addition, evidence has been provided that the preoperative status of the joint, extremity determines the extent of postoperative functional recovery. According to our experience, the number of arthroplasty due to RA remained stable, whereas the number of large joint arthroplasty due to advanced RA joints. However, RA patients still need a more specific and intensive care than other patients. This particularly applies to the postoperative controls after joint arthroplasty, as RA patients tend to have a higher risk of revision than osteoarthritis patients.

EL8

Molecular mechanisms of Mucsule and Tendon development and its appliaction for arthritis therapy

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Conflict of interest: None

We created a whole-mount in situ hybridization (WISH) database, termed EMBRYS, containing expression data of 1520 transcription factors and cofactors expressed in E9.5, E10.5, and E11.5 mouse embryos--a highly dynamic stage of skeletal myogenesis. This approach implicated 43 genes in regulation of embryonic myogenesis, including a transcriptional repressor, the zinc-finger protein RP58 (also known as Zfp238). Knockout and knockdown approaches confirmed an essential role for RP58 in skeletal myogenesis. Cell-based high-throughput transfection screening revealed that RP58 is a direct MyoD target. Microarray analysis identified two inhibitors of skeletal myogenesis, Id2 and Id3, as targets for RP58-mediated repression. Consistently, MyoD-dependent activation of the myogenic program is impaired in RP58 null fibroblasts and downregulation of Id2 and Id3 rescues MyoD's ability to promote myogenesis in these cells. Our combined, multisystem approach reveals a MyoD-activated regulatory loop relying on RP58-mediated repression of muscle regulatory factor (MRF) inhibitors. This system approach was also applied for other locomotive tissues including cartilage and tendon, and revealed novel molecular network regulating joint cartilage development and homeostasis.

EL9

Plan and analysis in a clinical research

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Conflict of interest: None

A randomized controlled trial (RCT) is the best research approach to prove a hypothesis. Although a RCT can provide quality evidence, it is impossible to conduct a RCT at any time. Consequently, some pilot studies have been conducted to collect evidence. A pilot study might be easily implemented compared to RCT. However, it might possibly reach erroneous conclusions if we made mistakes, such as data collection, sample size calculation, statistical analysis, and description in a conclusion. To understand how to design a clinical study and the choice of data analysis method is essential even for pilot studies. In this lecture, statistics for the design of a clinical study and the interpretation of the metrics in medical papers will be covered. Since a p value is the metric which commonly used in reports of clinical research, explanation of p values will be given along with the hypothesis testing. Recently, some database studies have been conducted by collecting daily medical practice information in a systematic way. The research plan is considered to have lower priority in this framework because data have already been collected. The importance of the research plan remains equal significance in the database study, by which we will be able to come to a suitable conclusion. Additionally, some notes on this research framework will be given.

EL10

Lung complications of rheumatoid arthritis with special attention to airway disease and non-tuberculous mycobacterial disease

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Conflict of interest: None

Pneumonia has emerged as a major cause of death in patients of RA in Japan, according to the IORRA study. As a predisposing factor of pneumonia, comorbidity, especially bronchiectasis and lung fibrosis are attracting attention. It has been reported that the greater part of pneumonia patients of RA are complicated with bronchiectasis as an underlying disease, and also that more than 40% of RA patients are affected with bronchiectasis through radiological survey. The reason why RA patients are complicated with these lung diseases in such a high rate is to be inquired. Another major problem emerged recently is non-tuberculous mycobacterial(NTM) disease. This disease often develops in pathological airway or lung, that is, bronchiectasis or fibrosis. In fact sputum examination in RA patients with respiratory symptoms often reveals colonization of non-tuberculous mycobacteria. These colonization may have a potential to the development of NTM disease in the course of RA patients. Once developed as a disease, biological agents such as TNF inhibitors are prohibited in the reason that no effective therapy are available for NTM disease. Recently we conducted a multi-center study to clarify the clinical features and therapeutic response of NTM disease in the setting of biological therapy for RA. AS a result, all 13 patients showed good response to anti-NTM therapy and no death nor severe clinical course were observed. Through a review or literature we find only a few deceased cases among 34 patients involved with this disease during anti-TNF therapy. The deceased few were affected with rapidly growing mycobacteria such as *Mycobacterium abscessus* and no death are reported in case of *Mycobacterium avium*, the most frequent species in Japan and also in developed countries. Thus we should make a review on this problem, how to treat NTM disease with RA patients in urgent need of treatment with biologic agents.

EL11

Progress in Diagnosis and Treatment of Vasculitis Syndrome

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Conflict of interest: None

Primary vasculitis is classified based on the size of vessels involved: large-vessel, medium-sized vessel, and small-vessel vasculitis. Among these, six diseases are investigated by the Specific Disease Study Group of the Ministry of Health, Labor, and Welfare (WHML), Japan, and patients with these diseases receive Medical Care Certificates for Specific Disease. According to the numbers of the Certificates in 2010, the most prevalent type of vasculitis is microscopic polyangiitis (MPA) and granulomatosis with polyangiitis (GPA, Wegener's). Diagnostic tools for large- and medium-sized vessel vasculitis are MRA, 3D-CT, and angiography. ^{18}F-FDG-PET, combined with CT, is useful to visualize active legions. For small-vessel vasculitis, sera are tested for anti-nuclear antibody, anti-neutrophil cytoplasmic antibody (ANCA), cryoglobulin, and so on. Tissue biopsy is important not only for diagnosis but also to determine the best therapy. Therapeutic protocols have been proposed based on randomized controlled trials. Guidelines and recommendations available are those of JCS (2008), EULAR (2009), and MHLW (2011). The first line therapy for large-vessel vasculitis is glucocorticoid (GC). Immunosuppressant is the choice for difficult diseases. Methotrexate (MTX) at 10-15 mg/week is effective in giant cell arteritis. Category-based treatment for ANCA-associated vasculitis is recommended by EULAR. Remission induction protocol is cyclophosphamide (CY) + GC for generalized type, MTX + GC for early non-renal type, and CY + GC + plasma exchange for severe renal type. A prospective study for Japanese patients with MPA (JMAAV) indicated the usefulness of severity-based treatment. A standard protocol for remission maintenance is low-dose GC + azathioprine. New therapeutic strategy has been invented for refractory vasculitis. These include biological agents such as infliximab and rituximab.

EL12

Surgical treatment for the patients with rheumatoid arthritis

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Conflict of interest: None

In recent years a concept of "Treat to target (T2T)" is introduced into medical treatment of rheumatoid arthritis (RA), and tight control toward the goal of remission (REM) or low disease activity (LDA) is recommended from the early stage of the disease. However, it is difficult to relieve all of the patients in a true REM, even if biological agents (Bio) are fully used. Surgical reconstruction is indicated to the joints with persistent synovitis and progressed joint deterioration. The patients with an ambulatory disturbance due to lower extremity involvement and those with a difficulty in activities in the daily living due to upper extremity involvement are candidates for the surgical treatment. The best timing of surgery is in the stage in which joint deterioration advanced to Larsen grade (LG) III or IV in the patient without infectious diseases and with well-controlled comorbidities. In the upper extremities in particular, if a surgery is performed in the state of LDA or REM and such state continues after surgery, the most favorable outcome is provided **(Surgical windows of opportunity)**. Without consideration to disease activity, shoulder reconstruction needed to be performed prior to a complete tear of the rotator cuff. Entrapment neuropathy and tendon rupture should be surgically treated before an irreversible change in the nerve and the muscle occurs. Decline of disease activity is expected by surgical intervention to a disorder at a small number of the joints. Recently, disease activity is controlled well and surgery is performed at a few joints in a state of good remaining of bone stock and soft tissue structures. The patients are highly motivated, and a newly developed disorder at the other joints is uncommon after the surgery. Therefore, an aggressive rehabilitation is possible, and a favorable surgical outcome is expected. Combined with medical treatment of RA, surgical intervention enables to acquire a higher level of ADL and QOL**(Japanese T2T)**.

EL13

The management of gout in clinical practice

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Conflict of interest: None

Gout is one of the most popular rheumatic diseases and is classified into crystal-related arthropathies. Gout is caused by the deposition of monosodium urate crystals mainly in joints. Uric acid is the final product of purine metabolism in humans. Usually, urate production is balanced by uric acid excretion. However, several genetic and environmental factors predispose to hyperuricemia. Prolonged hyperuricemia together with other local and environmental factors facilitate urate crystal formation in joints. The acute gouty arthritis occurs when monosodium urate crystals are shed from synovial microtophi. Monosodium crystal deposition is reversible phenomenon. Gout can be considered to be cured as monosodium urate crystals are completely removed. Therefore, the primary aim of urate lowering therapy is the removal of monosodium urate crystals. Probenecid is the oldest urate-lowering drug that as developed in 1951. Other urate lowering drugs such as allopurinol and benzbromarone were developed within twenty years. These therapeutic advances occurred before modern randomized clinical trials, leading to the scarce evidence of urate lowering therapy. Recently, it has been pointed that the management of gout remains sub-optimal in clinical practice. There may be several reasons for this such as diagnostic inaccuracy, paucity of management guidelines, insufficient patient education, poor adherence and limited numbers of urate-lowering drugs. Comorbidities of gout have been reported to be one of the obstacles for the better management of gout. However, guidelines or recommendations for gout have been published in Japan, Europe, England and Taiwan. One of the newly developed urate lowering drugs has been approved in Japan in 2011. These advances will contribute to the better management of gout.

EL14

New horizon in osteoporosis management

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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.

EL15

Osteoclastogenesis 1990-2011

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Conflict of interest: None

Introduction Many papers have reported that osteoclasts (Oc) play an important role in the pathogenesis of rheumatoid arthritis (RA); however, in around 1990, the roles of Oc in bone resorption had not been elucidated. There was a belief that humoral factors are important in bone resorption. Under such a paradigm that Oc are not important cells in bone resorption, we started to investigate the role of Oc in the pathogenesis of RA. In the current review, we present our studies on human Oc from 1990 to 2011, showing new methods such as a time-lapse method. **1. Our findings on roles of Oc in bone destruction of RA** 1) IL-6 and soluble IL-6 receptors (sIL-6R) in synovial fluids from RA patients are responsible for Oc formation. Authentic Oc are present in the synovial tissue of RA patients (1996). 2) A sufficient amount of IL-17 is detected in synovial fluids from patients with RA. IL-17 induces osteoclastogenesis (1999). 3) Human T cells induce osteoclastogenesis from human monocytes through their RANKL expression (2001). 4) CD4+ T cells in synovial tissues from RA patients express RANKL. The ratio of RANKL to OPG in synovial fluids is elevated. 5) Human IFN-γ-producing T cells (Th1 cells) induce human osteoclastogenesis from monocytes via the production of RANKL. T cells expressing both IFN-γ and RANKL are elevated in the peripheral blood of RA patients (2005). **2. Our novel findings on human Oc** 1) A novel peptide from T-cell leukemia translocation-associated gene (TCTA) protein inhibits human osteoclastogenesis and the function of mature Oc (2009). 2) We detected a novel ionchannel on the plasma membrane of human Oc. Antibodies against the ionchannel inhibit human osteoclastogenesis (2011). 3) Differences

have been reported in humans and mice in the differentiation and function of Oc. In 2008, we suggested the term, 'Human osteoclastology'. **Conclusion** We are now trying to make further findings of human Oc to develop novel therapies.

EL16

Search for disease-associated genes using genome-wide association study (GWAS)

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Conflict of interest: None

After human whole-genome sequence has been determined, biomedical researches targeting at the whole genome (genome-wide approach) have become possible in addition to those based on candidate molecules (candidate gene approach). Genome-wide association study (GWAS) that searches for the association between genomic variations and a multifactorial disease using more than 100,000 SNP genotypes has become widespread in the world. This technology was developed in Center for Genomic Medicine (CGM), RIKEN in 2002, and is now used by about 55% of all the papers in Nature Genetics published in 2010. CGM, RIKEN has successfully reported various GWAS results. GWAS is essentially the method to analyze the association between genomic variations and a phenotype; however, target phenotypes had been limited to qualitative phenotypes (disease or drug response). However, the categories of the phenotypes have been extended to quantitative phenotypes (such as height), cellular level (cell number, cell size), small molecule level (clinical chemistry data), protein level, and mRNA level. GWAS has begun to contribute to a new drug application and new drug development. The information about trait-associated genes found by GWAS is used for the search for the targets of new drugs, and the prediction of phenotypes, especially for drug responses (pharmacogenomics). In addition, since next-generation sequencers produce huge sequence data, they are used to analyze the Mendelian traits by the genome-wide basis. CGM, RIKEN has reported a whole genome sequence of a Japanese individual. In addition, CGM is collaborating with National Cancer Research Center for analyzing the somatic mutations in the genomes of liver cancers by comparing the while-genome sequences between germline and cancer genomes. The difference between the germline and cancer genome sequences is very large, and the subsequent studies should elucidate which mutations are directly associated with carcinogenesis.

EL17

Clinical application of methotrexate (MTX) for the treatment of rheumatoid arthritis (RA)

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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 active RA patients. The new ACR/EULAR RA classification criteria is to discriminate from a population with undifferentiated synovitis, the subgroup with the highest probability of persistent or erosive RA, in whom physicians need to initiate MTX therapy. In Japan, more than 10 years have past since Rheumatrex was introduced into the market in 1999. However, an upper limit of MTX dose for RA is set to 8mg/week. There was a significant progress in the application for increasing the upper limit of MTX dose in 2010, an increase in MTX dose up to 16mg/week was approved in February 23, 2011, as well as the use for initial choice of RA therapy. If MTX is used in adequate doses up to 16mg/week, higher efficacy and remission rate will be obtained. On the other hand, fatal side effects such as cytopenia and pneumonitis have been accumulated since MTX was approved for RA. During the recent 3 years, infection and lymphoproliferative disorders are showing a tendency to increase. The JCR released the recommendations for the use of MTX in September 2010, and the revised edition was published in March 2011. The recommendations consisted of 9 parts and were as follows; 1. Indication, 2. Contraindications and precautions, 3. How to use; dosing, administration, and as an anchor for combination therapy, 4. Folate supplementation, 5. Workup for patients starting MTX, 6. Monitoring of safety and efficacy during the therapy, 7. Management in the perioperative period, 8. Pregnancy and nursing mothers, 9. Minimization of side effects; risk factors, monitoring and treatment for serious side effects. In this lecture, practical points of MTX use for the treatment of RA in daily clinical practice would be discussed on the basis of the JCR recommendations.

EL18

Recent advances in diagnosis and treatment for spondyloarthritis

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Conflict of interest: None

Spondyloarthritis (SpA) is a large group of inflammatory arthritides that include ankylosing spondylitis (AS), reactive arthritis (ReA), psoriatic arthritis (PsA), inflammatory bowel disease-associated SpA (IBD/SpA), juvenile SpA, and undifferentiated SpA (uSpA), as well as others, such as those associated with anterior uveitis and Behçet disease. They are characterized by certain common genetic and clinical features, association with HLA-B27, and presence of axial skeletal arthritis (sacroiliitis and spondylitis). The prevalence of HLA-B27 in the general population shows considerable geographic variation, occurring in 14% of subjects in Scandinavia, 8% in Europe and the USA, and 5% of in China and Korea, but only 0.4% in Japan. Therefore, SpA is not frequently seen in Japan. The male to female prevalence of AS is approximately 3-5:1. Inflammatory back pain (IBP) is a typical symptom of AS/SpA. Patients complain about morning back stiffness, which improves with exercise but not with rest. In addition, they report awaking up at night, usually in the second half, because of back pain that improves upon getting up and moving around. Furthermore, back pain is chronic (>3 months) and not acute, and it occurs for the first time before the age of 45 years; this also helps to differentiate AS from degenerative spine disease. Peripheral arthritis occurs frequently, but often transiently in AS patients, and presents typically as an asymmetrical oligoarthritis predominantly of the lower limbs. The hip, shoulder, knee and feet are the predominant joints associated with arthritis in Japanese patients with AS (Inoue H. Jpn Spondyl Soc. 2011;III:29-34). The new criteria for classification of axial SpA developed by ASAS provides further insights into SpA. It is of great interest that TNF blockers are effective against psoriasis, IBD, and uveitis of Behçet disease, and further study of the pathology of these disorders and the immunological mechanism of TNF blockers is required.

EL19

Epidemiology of osteoarthritis in Japan: The ROAD study

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Conflict of interest: None

Osteoarthritis (OA) is a major public health problem in the elderly that affect their activities of daily life (ADL) and quality of life (QOL), leading to increased morbidity and mortality. The number of patients with OA increases with the age of the population. According to the recent National Livelihood Survey of the Ministry of Health, Labour and Welfare in Japan OA is ranked fourth, among the diseases that cause disabilities, which subsequently, require support with regard to activities related to daily living. As the proportion of the aging population is expanding in Japan, there is an urgent need for a comprehensive and evidence-based prevention strategy for OA, including knee OA (KOA) and lumbar spondylosis (LS). However, few prospective, longitudinal studies have been undertaken, and little information is available regarding the prevalence and incidence of OA as well as pain and disability in the Japanese population. It is difficult to design rational clinical and public health approaches for the diagnosis, evaluation, and prevention of OA without such epidemiological data, such as incidence and prevalence. The Research on Osteoarthritis/osteoporosis Against Disability (ROAD) study is a prospective cohort study that aims at the elucidation of an environmental and genetic background for bone and joint diseases, represented by OA and osteoporosis; it is designed to examine the extent to which risk factors for these diseases are related to the clinical features, laboratory and radiographic findings, bone mass and bone geometry, lifestyle, nutritional factors, anthropometric and neuromuscular measures as well as to determine how these diseases affect activity of daily living and quality of life in Japanese men and women. In the present lecture, we clarified the prevalence and incidence of KOA and LS, and risk factors of these disorders in Japan by analysing the baseline and the 3-yr follow-up data of the ROAD study.

EL20

Pathogenic mechanisms of rheumatoid arthritis; lessons from animal models

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Conflict of interest: None

We have generated two rheumatoid arthritis (RA) models, HTLV-I transgenic mice and IL-1 receptor antagonist-deficient (KO) mice, that spontaneously develop T cell-dependent autoimmune arthritis closely resembling RA in humans. Because the expression of inflammatory cytokines such as IL-1, TNF, IL-6 and IL-17 was augmented in the affected joints, we have generated cytokine KO mice and shown that HTLV-I transgenic mice develop arthritis in an IL-6-dependent manner, while IL-1receptor antagonist KO mice depend on TNF. Moreover, the development of arthritis in both models as well as in other models including CIA and SKG was IL-17 dependent, suggesting that IL-17 plays a central role in the development of arthritis, by inducing inflammatory cytokines from synovial tissues, activating auto-antibody production, and enhancing osteoclastogenesis. As suggested by these models, inhibitors to these cytokines have recently been shown to be effective for the treatment of RA. We found that the expression of C-type lectins such as *Dectin-1*, *Dectin-2*, and *Dcir* and *C1qtnf6* was similarly augmented as cytokines in inflammatory joints. By generating KO mice, we have shown that Dectin-1 and Dectin-2 are the receptors for b-glucans and a-mannans, respectively, and preferentially induce differentiation of Th17 cells that play important roles in the host defense against fungal infection and the development of arthritis. *Dcir* KO mice spontaneously developed enthesitis and sialadenitis with elevated serum autoantibodies, suggesting the development of autoimmunity. Excess expansion of DCs was suggested to be responsible for the autoimmunity. Furthermore, we found that collagen-induced arthritis is enhanced in *C1qtnf6* KO mice and is suppressed in transgenic mice, suggesting that *C1qtnf6* can suppress the development of arthritis. These results suggest that, other than cytokines, these C-type lectins and C1QTNF6 are also good targets for the development of new therapeutics.

Meet the Expert

MTE1

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.

MTE2

The significance of the operative treatment for rheumatoid arthritis in the biological preparation era

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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 RA treatment 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.

MTE3

Practical use of musculoskeletal ultrasound for evaluating synovitis in rheumatic diseases

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Conflict of interest: Yes

Among various 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 rheumatic diseases. Although synovitis is depicted as either synovial hypertrophy or synovial fluid, synovial hypertrophy is more specific to inflammatory process, and when accompanied by Doppler signals, it represents ongoing synovial inflammation. Therefore, Doppler ultrasound finding plays a central role in evaluating activity of synovitis, however, its accurate interpretation depends on morphological illustration of synovium with gray-scale ultrasound. Ultrasonographic assessment of synovitis is more accurate than that by clinical examination and improves the accuracy of diagnosis and disease activity assessment of rheumatoid arthritis. Especially in atypical or equivocal cases, ultrasound can directly affect 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 demand, and clinical research, sonographers needs to be aware of the purpose(s) during the procedure. In this program, a number of case scenarios and images will be presented and various issues from indication for ultrasound to optimal machine setting will be interactively discussed. At the end of this program, participants will be able to: 1. Understand various purposes of performing ultrasound. 2. Assess severity of representative ultrasound images in different joint regions. 3. Understand image conditions required for accurate assessment of synovitis. 4. Understand machine settings required for accurate assessment of synovitis. 5. Know pitfalls in evaluating synovitis in different joint regions.

MTE4

How to use glucocorticoids

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Conflict of interest: None

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.

MTE5

MRI of rheumatoid arthritis

Hideharu Sugimoto
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Conflict of interest: Yes

General Instruction Objectives To realize MR findings of erosion, bone edema, and synovitis. To understand the role of MRI in the differential diagnosis of RA To recognize the MR findings of pathological changes of bone and soft tissue in RA The core set of MRI findings in RA includes MRI bone erosion, bone edema, and synovitis: they are depicted by T1-weighted images, fat-saturated T2-weighted or STIR images, and gadolinium-enhanced T1-weighted images, respectively. The same set of images is stick to the atlas of the OMERACT-RAMRIS (*1*). Although no imaging findings are included in the 2010 RA Classification criteria by ACR/EULAR, bone erosion is still considered to be a prima facie evidence of RA (*2*). Since MRI is superior to radiography in the depiction of erosion, it plays an important role in the diagnosis or exclusion of RA. Only MRI can demonstrate bone edema, which can predict bone destruction in the future. Bone edema 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 MRI can be a surrogate marker of joint swelling. The differential diagnosis of RA includes many disorders. MR findings may be helpful to diagnose some of these conditions. In the late RA, a variety of pathological findings are seen. MRI can be used to understand the pathophysiology of these conditions. In this program, plain radiographs are shown to participants at first to make a diagnosis, and then MR images will be presented. By this approach, the participants will experience how the MRI raises the confidence level of the diagnosis by the plain radiography. 1. M. Ostergaard *et al. J Rheumatol* **30**, 1385 (Jun, 2003). 2. D. Aletaha *et al. Ann Rheum Dis* **69**, 1580 (Sep, 2010).

MTE6

Physical examination of the joints.

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Conflict of interest: None

The primary aim of joint examination is to clearly differentiate and understand the location of pathological changes responsible for the pain reported by the patient, by determining whether the pain arises from the synovial membrane, tendon sheath, synovial bursa, tendon attachment site or muscle. Since **swelling** of the synovial membrane is the most common (and most objective sign as compared with **pain**) phenomenon, the examiner should not only inspect but really touch and palpate the involved joint(s) to feel and estimate the degree of the swelling **with one's own finger tips.** Upon finishing the examination of the joints from the head to the toes, if one does not feel confident enough about the result of physical examination of a particular joint, further study of this joint by using ultrasonography and/or MRI radiology will be considered. The knacks to improve one's examination skill of the joints are 1. Always make it a rule to palpate the joints everyday 2. If you are not sure about the finding, compare it with an area that you think is normal. 3. Always keep textbooks on the musculoskeletal and nervous system so that one can brush up one's knowledge about clinical anatomy. Following are the some tidbits about the way of examining the major joints; **SHOULDER**: Stand behind the examinee to palpate the subacromial/subdeltoid bursa. **ELBOW**: Watch out the olecranon fossa. Enthesogpathy should not be confused with synovitis. **WRIST**: Extensor tenosynovitis, particalrly the one with M.ext.carpi ulnarlis should be searched. **FINGERS**: Inspection would suffice. Bouchard's nodes should be differentiated. **HIP**: Swelling cannot be discernible. Always check the degree of internal rotation of the joint. **KNEE**: Try to elicit the phenomenon "Ballottement". Stability of the joint and the wasting of quadriceps should be looked for. **ANKLE**:Lisfranc and Bouchard joints should be palpated. **TOES**: Gentle squeezing would be enough to elicit the pain. Most difficult joints to discern the swelling!

MTE7

Respiratory infection in patients under immunosuppressive therapy

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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. 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 drug-induced pneumonitis due to methotrexate and other therapeutics for rheumatic diseases, which makes 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 rheumatic patients 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 screen for active and latent tuberculosis with computed tomography and an interferon-γ release assay and isoniazid prophylaxis 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

Treatment of refractory rheumatoid arthritis

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Conflict of interest: Yes

The aim of this meeting is to discuss the treatment of refractory rheumatoid arthritis (RA) in daily clinical practice. 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 IL-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 not able 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.

MTE9

Surgical Treatment of Rheumatoid Hands

Takaya Mizuseki
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Conflict of interest: None

With introduction of biologicals, surgical treatments of rheumatoid arthritis(RA) are drastically changed. Fewer cases of active synovitis in the small joints are encountered, while more cases want reconstruction of the deformed fingers and wrists, and ruptured tendons. The role of surgeons is moving from conventional synovectomy to reconstruction of the already destroyed joints, deformed fingers, and ruptured tendons. [Volar and/or ulnar dislocation of the wrist joint] In RA, the wrist joint is usually destroyed or absorbed, dislocating volar-ulnarly. When left untreated, it causes unstable wrist and sometimes extensor ruptures. [Button-hole deformity of the finger] Synovitis of the PIP joint will cause attenuation of the extensor mechanism, moving lateral band volarly. It will impair active extension of the PIP joint and hyperextend the DIP joint. [Swan neck deformity of the finger] This will be accompanied by synovitis of the MP joint and intrinsic muscle contracture. The lateral band move dorsally when the MP joint is volarly subluxated and intrinsic tendons are tight, causing hyperextension of the PIP joint. Secondary drooping of the DIP joint will take place. [Button- hole deformity of the thumb] Synovitis is predominant in the MP joint, attenuating extensor mechanism. It will impair active extension of the MP joint and secondarily hyperextend the IP joint. [Swan neck deformity of the thumb] Synovitis is predominant in the CM joint of the thumb. It will dislocate dorsally. The pull of the EPL will hyperextend the MP impairing IP extension. [Ulnar drift of fingers] To result in ulnar drift, such factors play a role, as ulnar extensor dislocation, intrinsic contracture, radial deviation of the carpus, ulnar translation of the flexor tendons. Their correction is not always easy. [Extensor tendon ruptures] Subcutaneous extensor ruptures are most frequently encountered in the ring and little fingers. EPL rupture follows these.

MTE10

The most appropriate surgical intervention for patients with rheumatoid arthritis in the Era of biologics

Jun Hashimoto
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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 in the each surgical procedure, improvement in treatment other than surgery, change in the goal of treatment due to transition in view of life in patients with disease, and variation of socioeconomic program. In the last decades, much progress has been made in the development of total elbow, shoulder and ankle joint replacements. Much improvement has also been made in the procedures, materials, and designs in hip and knee joint replacement and in instrument for arthroscopic surgery. These improvements in surgical treatment have the potential for the further improved functional status of patients with RA. During this current decade, the advent of new drug-therapies for rheumatoid arthritis (RA) put new treatment strategies for remission into practice. It also bestows several benefits on the patients with advanced or progressive joint disability despite the well control of disease activity with biological DMARDs. The reduced disease activity could decrease the fragility in bone and soft tissue resulted in easy procedure and handling in delicate surgery, improve the preoperative anemia, and work as motivation to better functional capacity and better quality of life. However, possible complications during the aggressive drug-therapies, such as respiratory tract infections and skin and soft-tissue infections, should be prevented and strictly monitored. Although it remains clarified whether the use of biological DMARDs constitutes an independent risk factor for postoperative SSIs, they should be also strictly monitored. So, surgical treatment of patients with RA in Era of biologics requires 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.

MTE11

Systemic sclerosis: diagnosis and treatment

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Conflict of interest: None

MTE12

Rehabilitation for the patients with rheumatoid arthritis

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Conflict of interest: None

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 such as contractures, deformities and muscle weaknesses. 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, utilization of long-term care insurance and so on. 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. Also, 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. Therefore, it must be emphasized in conclusion that the execution of more prudent rehabilitation are very important even in the time of biologics mainly used for RA patients. To understand the importance of rehabilitation for RA patients, follows are prepared in this session. 1. To understand the impairments, disabilities and handicaps due to RA. 2. To understand the rehabilitation techniques utilized for RA.

MTE13

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 possible infection, cytopenia, lung injury, 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.

MTE14

Combination strategy of biologics and surgery

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Conflict of interest: Yes

It is important to get QOL improvement by restoration of joint quality in treatment of rheumatoid arthritis (RA). However, medication by using biologics has its limitation to treat severe dysfunction of joints instead of joint destruction. It is useful that assessment of joint quality including range of motion (ROM) in even well controlled cases systemically by biologic treatment, because the limitation of severe ROM is difficult to treat by biologics. Pathological spot is thought to be intra joint cavity in RA. However it is difficult to get it normal joint. Surgical treatment also has limitation regarding to maintain its efficacy. Therefore combination therapy of biologics and surgery is possible to be useful methods to support its limitation. Synovectomy and arthroplasty were reported as one of effective method to get well in tolerated cases of biologics. Especially the surgical points of synovectomy in each joint will be lectured. In knee joint synovectomy with biologics, sufficient synovectomy of lateral recess and patella femoral joint are important to get efficacy of ROM improvement. In shoulder joint of well controlled by biologics without ROM limitation, synovectomy in rotator interval and around the long head of biceps with capsular release. In elbow joints synovectomy, it is important to remove synovium around radial neck around annular ligament besides anterior portion and posterior portion of elbow joints. In order to draw out good efficacy of surgery, its timing or indication is important. For example, how do we treat in case of 20-30 years old, female, stage IV in shoulder joints. Other methods of surgery including the points of switching biologics are discussed. Then practical preparation of synovectomy and technical procedure will be lectured by using case study. In this expert meeting, new strategy of treatment with biologics and synovectomy are blush-upped.

MTE15

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.

Workshop

W1-1

Disease activity, activity of daily living and joint destruction in patients with rheumatoid arthritis treated with anti-TNF agents followed by tocilizumab

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Conflict of interest: None

[Objectives] Although tocilizumab (TCZ) is an effective option after anti-TNF treatment have failed, the course of joint destruction in such cases are not well understood. This study investigated the effectiveness of TCZ, especially on joint destruction, in patients with rheumatoid arthritis (RA) treated with anti-TNF agents followed by TCZ. [Methods] 10 RA patients whose clinical data is available and in whom TCZ were continued over one year were used. DAS28-CRP, CDAI, mHAQ and yearly progression (YP) of mTSS were investigated at initiation of anti-TNF treatment, initiation of TCZ and last obseavation. [Results] Mean age was 54.8 yo (8 female, 2 male). Mean RA duration was 8.4 year. Mean DAS-CRP at 3 time points were 5.88, 5.53 and 2.87. Mean CDAI at 3 time points were 33.4, 30.4 and 14.2. Mean mHAQ at 3 time points were 1.225, 1.188 and 0.713. Although mean YP of mTSS in before-anti-TNF period was 10.3, mean YP in anti-TNF period and in TCZ period were 2.9 and 2.9, respectively. These results showed that TCZ not anly reduced disease activity in RA patients refractory to anti-TNF agents but also improved ADL. Joint destruction in anti-TNF period were decreased in spite of high disease activity (dissociation) and this joint protection effect was continued in TCZ period.

W1-2

Maintenance of Radiographic Remission in Rheumatoid Arthritis Following 52 Weeks Treatment with an IL-6 Inhibitor

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Conflict of interest: None

[Objectives] To investigate the maintenance of radiographic remission using ultrasound in patients with rheumatoid arthritis (RA) treated with tocilizumab. [Methods] Fifty-nine patients with RA started on tocilizumab between May 2008 and October 2010 were studied. A scan was taken using an EUB-5500 digital ultrasound scanner each time tocilizumab was administered, and the data were evaluated semiquantitatively against a 4-Grade scale based on the EULAR criteria (Grade 0: radiographic remission). [Results] Disease activity before and after treatment was significantly lower after one year by each of the scores used, viz. DAS28 (ESR) 5.27→2.64, CDAI 25.4→9.3, MHAQ 0.84→0.57 ($P<0.05$). The ultrasound assessments at baseline and after 52 weeks for the 272 joints scanned showed improvement as follows: Grade 0: 20%→72%, Grade I: 40%→25%, Grade II: 22%→2.4%, with complete disappearance of Grade III joints at 18%→0% ($P<0.05$). Percentage achievement of radiographic remission at 52 weeks compared by grade was 90% for Grade 0, 77% for Grade 1, 70% for Grade II and 58% for Grade III. Remission thus tended to be more readily achieved the lower the baseline grade. Moreover, 85% of the 166 sites exhibiting radiographic remission after 6 months treatment had maintained that remission at one year.

W1-3

Radiographic effectiveness of tocilizumab for RA patients in routine clinical practice: one-year outcome of joint destruction

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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 61 patients in our hospital treated with TCZ until October 2011 in whom X-ray evaluations could be performed after 1 year of TCZ treatment. The Total Sharp Score (TSS) was used in the evaluation. [Results] The patient characteristics included a mean age of 61.4 years, mean disease duration of 12.8 years, MTX concomitant rate of 59.0%, history of use of TNF inhibitors of 55.7% and initial TSS of 142.6. The yearly progression of joint destruction (ΔTSS/year) was 19.7 at baseline and 0.3 after treatment, showing inhibition of 98.5%. The achievement rate of ΔTSS ≤ 0.5 for structural remission was 68.9%, showing marked inhibition of joint destruction. In patients with insufficient response to TNF inhibitors, ΔTSS was 0.2 at baseline and -0.1 after TCZ treatment in an investigation of 14 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.

W1-4

Efficacy and inhibition of radiographic progression with abatacept treatment in patients with rheumatoid arthritis (RA).

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Conflict of interest: None

Objective We assessed the efficacy and inhibition of radiographic progression with abatacept treatment. **Methods**In 6-month trial, RA patients started abatacept in our department were eligible. The primary end point was the change of total Sharp score (⊿TSS). The secondary end point was the clinical activity. **Results** 40 patients were enrolled, mean age; 63.0, disease duration; 9.7 years, methotrexate was administered in 65.0%. At baseline, patients had a high degree of disease activity: SDAI 32.0, DAS28(ESR) 5.9, mTSS 50.5, CRP 2.0mg/dl, ESR 52.3mm/h, MMP-3 240.4ng/ml, RF 166.4U/ml (1)⊿TSS (0.2) was improved from that at base line (7.0). 86.5% achieved non radiographic progression (⊿TSS < 0.5). (2) SDAI 15.5, DAS28(ESR) 4.2, CRP 1.0mg/dl, ESR 45.3mm/h, MMP-3 176.9ng/ml, RF 108.1U/ml, which were lower than that at base line. (3) SDAI-remission (23%) was higher than DAS28(ESR)-remission (18%), and there were correlation between the improvement of SDAI and both swelling joint counts (SJC) and MMP-3 at 6 months. **Conclusion** Abatacept inhibit the progression of structural damage. The correlation between improvement of SDAI and both SJC and MMP-3, suggest that abatacept inhibit bone destruction via prevention of the cartilage damage (MMP-3↓) and synovitis (SJC↓).

W1-5

Study of Rapid Radiographic Progression during Biological Therapy (1st Report)

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Conflict of interest: None

[Objective] To identify risk factors of rapid radiographic progression (RRP) with joint destruction observed during any biologics (BIO). [Methods] Thirty RA patients treated with tocilizumab (TCZ) were evaluated for clinical response and twenty three patients for inhibition of joint destruction at 52 weeks. Patient demographic data (mean) were as follows: age, 60.4 years; disease duration, 8.4 years; MTX dose, 6.7 mg (63.3%); and prior use of BIO, 60.0%. [Results] Changes in parameters from baseline to 52 weeks were as follows: DAS28-ESR, 6.27 to 4.18; mHAQ, 1.60 to 0.52; and ΔmTSS/y(ΔT/y), 10.8 to 3.9. At 52 weeks, ΔT/y improved in 21 patients (91%) and worsened in two patients as compared with baseline. As shown by a change in ΔT/y in the RRP (ΔT/y>5, n=6) group (15.4 to 12.9) compared with the inhibited joint destruction (ΔT/y <0.5, n=10) group (7.2 to -0.29), the RRP group had higher ΔT/y and mTSS at baseline (P<0.05). The RRP group also had higher DAS28, MMP-3 and mHAQ at baseline. Moreover, three patients previously treated with TNF inhibitors before TCZ therapy had a decrease in ΔT/y from 16.5 to 13.4, which showed poorly inhibited joint destruction. [Conclusion] The risk factors of RRP in BIO were suggested to be high ΔT/y and increased CRP and MMP3 at baseline.

W1-6

Differences in X-ray findings after starting 4 biologicals-Possibility of repairing joint destruction–

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Conflict of interest: None

[Objectives] We examined X-ray findings after starting 4 biologicals(Bios) and the possibility of repairing joint destruction. [Methods] We examined patients who started Bio, obtained good response, and continued at least 2 years for shoulder, elbow, hand, hip, knee, ankle, sub-talus, talonavicular joint and cervical spine. X-rays findings were evaluated before and after 2 years of Bio treatment by Larsen Grade classified as improved, unchanged or deteriorated (JCR,2009). There were 327 joints in 22 infliximab(IFX) patients, 305 joints in etanercept(ETN) patients, 338 joints in 20 tocilizumab(TCZ) patients and 117 joints in adalimumab(ADA) patients. [Results and discussion] Differences between 4 Bios were seen in X-rays after 2 years with improved joints numerous in order of IFX, ETN, TCZ, ADA, unchanged in order of TCZ, ADA, IFX, ETN, and deteriorated in order of ETN, ADA, TCZ, IFX. Similar trends were seen in joints damaged to Grade 3 or higher, in which the number of improved joints was in order IFX, TCZ, ADA and ETN (50.7, 35.7, 26.2, 22.7%, respectively), suggesting that evan severely damaged joints can be repaired with Bios.

W2-1

Epidemiology and therapeutic option of bacterial pneumonia in RA patients treated with biologics. –From TBC multicenter cohort-

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Conflict of interest: None

[Background] Bacterial pneumonia(BP) is most common respiratory complication in rheumatoid arthritis (RA) patients treated with biologics, but there are few reports about detail of pathogenic bacteria or guideline to make a decision which antibiotics should be chosen. [Aim] To investigate the outline of BP in RA patients treated with biologics focusing on pathogen and therapeutic intervention. [Method] 1575RA patients were registered in TBC till 2011. 57cases were interrupted or discontinued the biologics administration due to respiratory infectious complication. We reviewed the pathogens and clinical course retrospectively. [Result] Excluded the cases of tuberculosis, NTM and PCP, 31 cases (2%) of BP were investigated. Pathogens were detected in 11 cases, and most common pathogen was *α-streptococci*(58.3%) followd by *S. aureus*, *Neisseria species*, *P. aeruginosa* and *H. influenzae*. Resistant pathogens such as *BLNAR* or MRSA were isolated. [Conclusion] The profile of pathogenic bacteria corresponded with that of nursing and healthcare-associated pneumonia(NHCAP) or hospital-acquired pneumonia(HAP) rather than that of community-acquired pneumonia(CAP). Therapeutic decision should be made under consideration about resistant or atypical pathogens as recommended in NHCAP or HAP guideline.

W2-2

Prospective cohort study of infectious disease risk management in RA patients receiving tocilizumab at 24 weeks (ACT4U-study24): 1st report

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Conflict of interest: None

[Objectives] To validate the deterrence effect of infectious disease risk management (IDRM) in RA patients receiving tocilizumab (TOC) and to examine sensitivity and specificity of CD64 on polymorphonuclear neutrophils (CD64) and procalcitonin (PCT) levels as parameters for serious infection (SI). [Methods] Forty-nine RA patients (59.7±2.8 yo, female 87.9%) receiving TOC were enrolled in this cohort stud from 4 universities and referring clinics. They received the documents about the risk of SIs before TOC treatment and were required to comply with IDRM policy. Primary endpoint was occurrence frequency of SI (OFSI) and rate of increase in CD64 and PCT. Secondary endpoint was admission due to infection, the dose of concomitant medicines, DAS28, CDAI and persistence rate of TOC. [Results] Concomitant use of MTX and corticosteroid (CS) was 60.6% and 57.6% at the entry. Average dose of MTX and CS was 8.2 and 5.6mg. Though the incidence of infection was 25.8%, occurrence frequency of SI was 0%. CD64 before and after TOC was 1477.3±199 and 1456.1±96.7, respectively. The dose of CS was reduced by 41.8% in 75.7% of patients. The results suggest that IDRM contributes to reduction of OFSI.

W2-3

Biological agent-induced neutropenia in patients with rheumatoid arthritis

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Conflict of interest: None

[Objective] To clarify the effects of abatacept (ABT) and other biological agents on neutrophil count (NC) and incidence of infection in patients with rheumatoid arthritis (RA). We examined NC and incidence of infection in RA patients under ABT, tocilizumab(TCZ) and TNF inhibitors. [Method] Twelve patients with RA (5M/7F, mean age±SD 57±14 y.o.) under ABT therapy were included in this retrospective study. They were compared with patients (n=138) under TNF inhibitors (infliximab n=41, etanercept n=83) and TCZ (n=14). Clinical characteristic and laboratory data were obtained from medical records in our department. According to these data, we assessed correlation between NCs and incidence of infection in RA patients treated with biologics. [Results] Mean NCs after ABT, TCZ and TNF inhibitors were decreased 2.7%, 34.8 % and 25.1 %. Patients under ABT, TCZ and TNF inhibitors therapy with NCs < 2000 /uL were 8.3% (n=1), 50.0% (n=7) and 10.5% (n=13). Adverse effects of infection in RA patients treated with TCZ and TNF inhibitors were 14.3% (n=2) and 11.3% (n=14), respectively. On the other hand, infection was not observed in patients under ABT therapy. [Conclusion] NCs were not decreased and incidence of infection was not increased in RA patients with ABT.

W2-4

Clinical Use of Biologics in Elderly Patients with Rheumatoid Arthritis

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Conflict of interest: Yes

[Background] Prednisolone use, lung lesions, and age 65 years and older have been identified as risk factors associated with biologics. In selecting a biologic for elderly patients with RA, safety is a more important variable than efficacy. [Subjects] The efficacy and safety of biologics were evaluated in RA patients aged 70 years and older at the start of treatment with marketed biologics at Higashihiroshima Memorial Hospital. [Results] IFX, ETN, TCZ, and ABT were respectively given to 4, 19, 9, and 7 patients who

were 70 years or older at the start of treatment. Adverse reactions leading to discontinuation occurred within a year of treatment in 4 patients treated with IFX (100%; 2 due to pneumocystis pneumonia and 1 each due to worsening of interstitial pneumonia and pancreatic cancer), 3 treated with ETN (15.8%; 1 each due to intestinal perforation, sepsis, and cellulitis), 1 treated with TCZ (11.1%; due to intestinal perforation), and 0 treated with ABT (0%). The number of patients who achieved the target of remission or low disease activity after 6 months of treatment was 0 with IFX (0%), 8 with ETN (42.1%), 6 with TCZ (66.7%), and 3 with ABT (42.9%). [Discussion] The findings indicate that ABT is safe and suitable as first-line treatment in elderly patients with RA.

W2-5

Clinical effects and significance of anti-chimeric antibody detected in Infliximab -treated rheumatoid arthritis patients

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Conflict of interest: None

[Objectives] To investigate the relationship and the meanigs of human anti-chimeric antibody(HACA) in the Infliximab(IFx)-treated rheumatoid arthritis(RA) patients. [Methods] We collected serum samples from the Japanese RA patients treated with IFx and other biologics including good IFx reponder and insufficient reponder at our hospital. Those samples were transported and detected anti-Infliximab antibody(ATI) using sandwich-designed enzyme-linked immunosorbent assay(ELISA) after checking the concentration of remained IFx. [Results] Selected total cases of RA patients are 23 and they included three samples collected with longitudinal months intervals. 13(56%) samples was evaluated HACA clearly positive, and 5(22%) cases can't be asessed becase the remained infliximab were significant and disturbed the assay. This result suggested the clearance speed of infused IFx in RA patietns were influenced by the clinical condition and background of each japanese patietns. In the result of longitudinal samples, the production of HACA have continued more the one year after IFx medication ceased. [Conclusion] Frequency of HACA/ATI is almost same as former reported and the induciton of HACA was significant and important in efficacy and side effect, however, HACA showed no effect in several cases.

W2-6

Effectiveness and safety of biological treatment in elderly patients with rheumatoid arthritis

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Conflict of interest: None

[Objectives] To discuss the effectiveness and safety of biological agents in elderly patients(pts) with rheumatoid arthritis (RA) [Methods] RA pts ≧75 years old who had been treated by infliximab (IFX), etanercept (ETN), adalimumab (ADA), tocilizumab (TCZ) or abatacept (ABT) as a first biological treatment from October 2004 to October 2011 were selected, and their background, trend of disease activity and persistence rate were examined. [Results] 43 pts were analyzed. The average of their age at the beginning of the treatment was 78.7 yrs old, disease duration was 10.7 yrs and following-up duration was 1.0 yr. The breakdown of the treatment were 9 pts in IFX, 15 pts in ETN, 9 pts in ADA, 4 pts in TCZ and 6 pts in ABT. The averages of DAS28 CRP were 3.9 at the beginning and 2.1 at 24 weeks after starting treatment. The persistence rate was 83.0 % and the average of duration was 0.87 yrs at the last time to follow up. The reasons of stopping the agents were insufficiency of therapeutic effect in 5 pts (4 by primary failure and 1 by secondary failure), adverse events in 5 pts (2 by exanthema, 1 by vasculitis, 1 by shortness of breath, 1 by pancreatic tumor, 1 by organizing pneumonia). [Conclusion] Biological treatment in elderly pts with RA showed high effectiveness and safety.

W3-1

Therapeutic efficacies of tocilizumab in patients with rheumatoid arthritis refractory to anti-tumour necrosis factor biological: one year follow up by low-field extremity MRI

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Conflict of interest: None

[Objective] It is reported that tocilizumab (TCZ) is effective for RA patient who is refractory to anti-TNF biologics. However, almost all studies, the evaluation method for therapeutic efficacies of TCZ is DAS28-ESR. TCZ is normalized inflammation makers in early phase of its infusion. Because of this, there is a possibility that the evaluation method using DAS28-ESR is inappropriate. Because of this reason, we follow up RA patient who is treated TCZ because of refectory to TNF biologics for 1 year and compare the therapeutic efficacies of TCZ by DAS28-ESR and by MRI. [Methods] Eight patients were included in this study. MRI images of both hands were obtained at baseline, weeks 20 and 44. MRI images were evaluated by compact MRI score [Results] All patients had good or moderate response by DAS28 and DAS28 was decreased significantly at 20w. However, MRI findings were not improved. At 44 week, Not only DAS28-ESR but also synovits and bone edema scores were decreased significantly. The evaluation method for TCZ using DAS28-ESR TCZ may be appropriate. However, especially in early phase, dissociation was admitted in two evaluation method. We conclude that MRI evaluation is useful for the estimation of total disease activity of RA treated by TCZ

W3-2

Sequential evaluation by low field compact MRI in patients with rheumatoid arthritis.

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Conflict of interest: None

[Objectives] The aim of this study was to evaluate progression in bone destruction and inflammation by using low field compact MRI (cMRI) in patients with rheumatoid arthritis (RA). [Methods] Sixty-six hands of 33 RA patients with the biologic treatment (bio+ group; infliximab 14, etanercept 5, adalimumab 2, tocilizumab 9, abatacept 3) and 40 hands of 20 RA patients without biologics (bio- group) were included. Hand images were taken by 0.3T cMRI in 2 sequences; coronal T1 weighted image and coronal short tau inversion recovery image, without gadolinium enhancement. Two ex-

aminations were performed in 6-12 months interval and bone erosion, bone marrow edema and synovitis were scored by cMRI scoring system. [Results] Erosion score were significantly increased at the second examination in both groups (bio+; 16.34±11.24 to 18.02±12.08, $p<0.001$, bio-; 7.26±9.26 to 9.00±11.19, $p<0.05$ respectively). There was no significant change in bone marrow edema score and synovitis score. There was significant correlation between synovitis score at the first evaluation and progression of erosion score between two examinations ($r^2=0.29$, $p=0.0031$). [Conclusion] cMRI could detect small progression in erosion of RA patients. Synovitis observed by cMRI would predict future bone destruction.

W3-3

The frequency of synovitis detected by ultrasonography and magnetic resonance imaging in the non-swollen joints of patients with rheumatoid arthritis

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Conflict of interest: None

[Objectives] To clarify the frequency of synovitis detected by ultrasonography (US) and magnetic resonance imaging (MRI) in the non-swollen joints of patients with rheumatoid arthritis (RA). [Methods] Forty-nine patients with RA (61 tests, 1342 joints) were examined by physicians, US and MRI. PD detected by US and high intensity detected by STIR MRI in the joints were defined as synovitis. The frequencies of synovitis detected by US, MRI, and US or MRI in non-swollen joints were calculated. [Results] The mean age of the patients was 50.9±14.0 years old. Eight male and 41 female were examined. The number of the times of the examination for the patients treated with biologics were 40. The mean CRP value was 0.79±1.32mg/dl. One thousand and one hundred joints out of 1342 joints were not swollen. Ninety-one joints (8.3%) out of 1100 non-swollen joints accompanied synovitis detected by US. One hundred fifty non-swollen joints (13.6%) accompanied synovitis detected by STIR sequence of MRI. One hundred ninety non-swollen joints (17.3%) accompanied syonovitis detected by US or MRI. The kappa value between US and MRI was 0.42. [Conclusion] There were US or MRI driven synovitis in 17% of non-swollen joins of RA patients.

W3-4

Development of multi-sequence analyzing system for semi-automatic cartilage segmentation in T2 mapping

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Conflict of interest: None

[Introduction] T2 mapping is a quantitative magnetic resonance (MR) imaging technique that is sensitive to the anisotropic structure of the collagen matrix, thereby useful for detecting the cartilage deterioration in arthritis. Segmentation is a necessary step for T2 quantification of cartilage, however, it should be done manually in most T2 mapping system. [Methods] In addition to T2 mapping, T2star-weighted images and proton-weighted images were obtained from 3.0T MRI scanner using an extremity coil. In multi sequence histogram space, cartilage signal was selected and segmentations were superimposed to T2 mapping. Using this system, the area of cartilage and muscle was automatically determined, and then cartilage signals were separated from muscles manually. [Results and Discussion] Automatic segmentation in only one sequence has been difficult because of the overlapped signal distribution of cartilage, water, bone, and other tissues. We developed novel mutli-sequence analyzing system to separate overlapped signals of different tissues and materials. This system semi-automatically separated cartilage signals from other signals, and was useful for calculation of T2 value of cartilage.

W3-5

The verification of a new radiographic scoring method for large joint damage of rheumatoid arthritis (ARASHI status score)

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Conflict of interest: None

[Objectives] To investigate the relationship between the major joint destruction of rheumatoid arthritis and other clinical and radiographic scores using ARASHI status score (ASS). [Methods] ASS can grade each factors of joint destruction, join space narrowing (0-3), erosion (0-3), joint surface (0-6), instability (0-4). Ten large joints (shoulder, elbow, hip, knee, and ankle) were graded to 0-16 points individually. Totaled score (0-160) was calculated as the patient's ASS. 63RA patieints, 9 males and 54 females, were evaluated in this study. The correlation between ARASHI status score and other radiographic and clinical scores, disease duration, Larsen score (ten large joints), mTSS, ESR, CRP, DAS28-ESR, SDAI, CDAI, and modified health assessment score (mHAQ). Spearman rank correlation coefficient was used for statistical analysis. [Results] The mean of patient's ASS was 11.5 (0-50) within 160pts. The correlation of ARASHI status score and Larsen score ($r=0.92$, $P<0.0001$), and mTSS ($r=0.5392$, $P=0.0002$) was observed. ARASHI status score also showed a correlation with clinical outcome scores, DAS28-ESR, SDAI, CDAI, and mHAQ. To evaluate the large joint damage exactly, this new evaluation system can be powerful tool for its detailed 16 grades in each joint.

W3-6

The relationship between foot deformity and disease stage

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Conflict of interest: None

【Objectives】 Deformities of feet are common in patients with rheumatoid arthritis (RA). But progression paterns of foot deformity are unclearly. The aim of this study is to investigate the foot deformities in patients with RA.【Methods】 We conducted the prospective cohort study (TOMORROW study) from 2010. We examined 426 feet of 208 patients with RA from this cohort. We

analyzed 393 feet excluding postoperative feet. We classified articular destruction with hand radiographs using Steinbrocker's classification. The hallux valgus angle (HVA), the intermetatarsal angle between the 1st and 5th metatarsals (M1M5) on anteroposterior radiographs, and calcaneal pitch (CP) on lateral radiographs were measured. 【Results】 The number of patient in Steinbrocker stage 1/2/3/4 were 39/53/45/70, respectively. In the patients of each Steinbrocker stage, the average disease duration was 6.9/8.1/14.8/22.3 years, the average HVA was 15.6/18.9/17.4/24.9 degrees, the average M1M5 was 29.5/29.4/30.3/29.2 degrees, and the average CP was 19.3/18.2/16.9/15.5 degrees, respectively. In this study, there was correlation between foot deformity and disease stage, disease duration in RA patients. But it was appeared that spread foot was started from early stage.

W4-1

Value of positron emission tomography/computed tomography in clinical practice in patients with fever of unknown origin

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Conflict of interest: None

[Objectives] It is important to identify the disease underlying unspecific symptoms such as fever or polyarthritis. In primary diagnoses, FDG-PET can be a useful addition to the classical diagnostic approach to fevers of unknown origin. **[Methods]** Between January 2009 and June 2011, we summarized a total of 178 cases and 185 FDG-PET studies in a search for focuses of undiagnosed inflammation or malignancy that went beyond what is already known. **[Results]** FDG-PET could identify focuses in 135 cases and 140 studies (75.7%). These included 14 cases of polymyalgia rheumatica (PMR), 10 of large-vessel vasculitis, and 10 of spondyloarthritis. In particular, FDG-PET contributed to diagnosis and therapy in 2 cases of PMR that lacked obvious musculoskeletal symptoms, 2 of para-neoplastic syndrome mimicking PMR, and 2 of bloodstream infection that had been identified as pacemaker-lead and artificial vessel infection, respectively. On the other hand, out of 43 cases and 45 FDG-PET studies without any focus, only 2 cases (chronic cholecystitis and chronic Epstein-Barr virus infection) needed additional therapy. In conclusion, FDG-PET can effectively detect focuses and distributions of diseases, and is thus useful in the consolidation of diagnosis and exclusion of diseases in need of therapy.

W4-2

FDG-PET is helpful for the diagnosis and assessment of therapeutic response in vasculitis

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Conflict of interest: None

[Objectives] FDG-PET sensitively detects inflammatory lesions as well as malignancies. This study investigated contribution of FDG-PET to diagnosis and assessment of therapeutic response in vasculitis. [Methods] We studied 24 vasculitis patients who had total 55 sets of FDG-PET examinations. According to Chapel Hill Consensus Conference, they were classified into 3 groups; large vessel vasculitis 15(aortitis 13, temporal arteritis 2), medium sized ones 2(polyarteritis nodosa 2), small ones 7(Wegener granulomatosis 1, microscopic polyarteritis 5, allergic garanulomatous angitis 1). We assessed association of FDG-PET findings with clinical diagnosis and disease activity in them. [Results] 1) FDG-PET detected abnormal FDG signals which directly contributed to diagnosis in 10 of 24 patients, including 7 of 13 large vessel vasculitis, 1 of 2 medium sized ones, and 2 of 10 small ones. 2) Of 11 patients having the follow-up study, reduced FDG signals were associated with clinical amelioration in 6 patients, while residual FDG signals or de novo lesions were found in 5 who had persistent disease activity. [Conclusion] FDG-PET is useful for the diagnosis of vasculitis, especially large vessel ones. In addition, the imaging modality is helpful for assessment of therapeutic response in them.

W4-3

Deep inspiratory breath hold PET/CT is useful for monitoring of activity in collagen disease asscociated lung interstitial pneumonitis.

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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 collagen diseases. [Methods] We assessed ILD in 41 patients with collagen diseases including 5 RA, 9 SSc, and 15 DM/PM by using DIBH-PET/CT. [Results] Abnormal accumulation of FDG was found in the active ILD lesions which were concordant with nodular, reticular, consolidative shadows and ground glass opacity illustrated by plain CT scan. SUVmax in the lesions was well correlated with serum levels of LDH and CRP. The value was significantly higher in 28 patients who were judged as being clinically active than the other 13 patients. Of 20 patients who had follow-up examinations, abnormal FDG accumulation was reduced in response to the therapies in 11 patients, whereas the findings were unchanged or deteriorated in the remaining 9 patients who had stable or progressive ILD. In spite of no interval change in plain CT scan, PET/CT detected significant changes of FDG intensity in the follow-up studies in 5 patients. FDG signal was reduced in 4 of them, whereas it was increased in one patient. In summary, DIBH PET/CT is useful for monitoring of activity in collagen disease associated ILD.

W4-4

Similarity and difference of fluorodeoxyglucose positron emission tomography/computed tomography findings in Spondyloarthropathy, Polymyalgia rheumatica and Rheumatoid arthritis

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Conflict of interest: None

[Objectives] We assessed about the similarity and difference in FDG-PET/CT findings of seronegative spondyloarthropathy (SpA), polymyalgia rheumatica (PMR) and rheumatoid arthritis (RA) patients. **[Methods]** Fifty-one patients with SpA(19), PMR(16), or RA(16) underwent evaluated FDG accumulation by SUV_{max} for each disease activity in ischial tuberosities(IT), greater trochanters(GT), spinous processes(SP), vertebral body (VB), and

sarcroiliac joint (SIJ). **[Results]** SUV_{max} for IT were significantly higher in PMR than in SpA and RA patients. SUV_{max} for GT and SP were significantly higher in PMR than in RA ($P<0.001$). SpA patients had significantly higher SUV_{max} for SIJ than those with PMR and RA ($P=0.01$). There were no significant spine differences among the groups ($P=0.488$). X-ray findings were consistent with PET/CT only in sacroiliitis 3/15 patients and by MRI in 4/7. In conclusion, Inflammation in IT, GT and SP on PET/CT is useful for discriminating between PMR and RA, but not between SpA and PMR. Especially, in elderly patients, it is necessary to determine whether FDG accumulation in them is attributed to enthesitis in SpA or bursitis in PMR. Meanwhile, PET/CT findings for SIJ in SpA are useful for differentiating between RA and PMR and for early diagnosis of sacroiliitis.

W4-5

The assessment of therapeutic effect in patients with rheumatoid arthritis using FDG-PET/CT -The relationship between SDAI/CDAI and FDG uptakes-

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Conflict of interest: None

[Objectives] F-18 fluorodeoxyglucose (FDG) positron emission tomography (PET) can be used to image synovial inflammation in patients with RA. In this study, we evaluated if there was a correlation between the difference of FDG uptakes and improvement of clinical findings in RA patients who underwent anti-TNF therapies. [Methods] Forty six patients (10 men, 36 women; average age: 55.8 years) who underwent anti-TNFα therapies were assessed. Imaging and clinical assessments were performed prior to, and 6 months after the treatment. The sums of SUVmax of all calculated joints were provided for the evaluation of therapeutic effects. Simplified Disease Activity Index (SDAI) and Clinical Disease Activity Index (CDAI) were used for the evaluation of disease activity of RA patients. [Results] The changes of sum of SUVmax before and after treatments (ΔSUV) were significantly correlated with ΔSDAI ($r=0.550$, $p<0.001$), ΔCDAI ($r=0.519$, $p<0.001$), ΔTJC ($r=0.421$, $p=0.004$), ΔSJC ($r=0.507$, $p<0.001$). FDG-PET might play an important role in the evaluation of treatment for RA.

W4-6

Relation between cumulative synovial vascularity and bone damage progression in finger joint of rheumatoid arthritis

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Conflict of interest: None

[Background] We had reported the potential for change of synovial vascularity detected by power Doppler sonography to reflect therapeutic response in anti-rheumatoid therapies (DMARDs, biological agents). Synovial vascularity could predict bone damage progression at short-term (20th week). In this study, we report relation between synovial vascularity and bone damage progression at middle-term (50th week). [Method] Thirty-two patients with active RA were analyzed (13 patients treated with ADA, 19 patients treated with TCZ). Power Doppler sonography was performed at baseline, 8th, 20th and 40th week. Hand and foot X-ray were perfomed at baseline and 50th week. [Result] Although clinical composite score value decreased all cases and persisted low level in the observational period, there were some joints with vascularity positive. We focused on these joints and analyzed relation between cumulative synovial vascularity and bone damage progression. [Discussion] We confirmed that vascularity positive joint persisted in clinical remission phase that might indicate remaining local inflammation. We would analyze a relation between cumulative synovial vascularity and bone damage progression.

W5-1

Predictive factors in the clinical practice for presence and extent of power Doppler signal in ultrasound examination for rheumatoid arthritis patients

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Conflict of interest: None

[Objectives] Ultrasound (US) is useful for precise regional diagnosis and assessment of disease activity in the clinical practice for rheumatoid arthritis (RA). Power Doppler signal (PD) is significant to monitor treatment effect and estimate bone destruction. Here, we evaluated the predictive factors in the clinical practice for presence and extent of PD. [Methods] Bilateral 1-5MCP and wrist were assessed for PD and swelling joint count (SJC), tender joint count, patient's VAS, physician's VAS, CRP, ESR, MMP-3, RF and anti-CCP were assessed. Those were compared between two patients' groups with and without PD, then, analyzed in multiple logistic analysis to derive significant predictive factors. Moreover, predictive factors associate with extent of PD were evaluated with multiple correlation and regression analysis. [Results] Only SJC was derived as predictive factor for PD and sensitivity and specificity of joint swelling for PD were 65% and 85%. Other evaluated factors as CRP, ESR and MMP-3 were considered to be difficult to predict PD. Although only clinical joint swelling promise to be roughly predictive for PD, US aid is increasingly critical for RA management in the days to come.

W5-2

Presence of anti-CCP antibody, but not its titer, contributes to radiographic progression and disease activity in rheumatoid arthritis.

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Conflict of interest: None

[Objectives] Whether or not the titer of anti-CCP antibody(Ab) contributes to radiographic progression and disease activity in rheumatoid arthritis(RA) was studied in a prospective study. [Methods] Rheumatoid patients(n=396) were divided refering to the median value of anti-CCP2 titer into negative(0-4.4U/mL) and positive(>4.4U/mL) groups. Positive groups were further subdivided into lowest(4.5-32), lower(33-121), higher(122-277) and highest(>278) quartiles. Disease activity were evaluated using DAS28

and modified Sharp score for 2 years. [Results] After treatment with DMARDs, disease activity was significantly decreased in all patients groups. Radiographic progression as revealed by the change in modified Sharp score remained significantly higher in the anti-CCP2 Ab-positive patients. The titer of anti-CCP2 Ab appeared irrelevant to radiographic progression. Radiographic prores-sion is minimal in the anti-CCP2 Ab-negative patients. [Concluion] The titer of anti-CCP2 Ab at baseline does not contribute to radiographic progression or disease activity in RA. Radiographic progression is minimal in the anti-CCP2 Ab-negative patients.

W5-3

Analysis of the association between injection reaction to adalimumab and Fcγ receptor IIIB polymorphisms

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Conflict of interest: None

[Background] Infusion/injection reaction is a major adverse event in patients with rheumatoid arthritis (RA) treated with biological agents. We previously reported that a high affinity Fcγ receptor (FcγR) IIIB polymorphism is an independent risk factor for the development of infusion reaction to infliximab in RA patients (odds ratio = 6.1). [Objectives] The aim of this study is to prospectively examine whether a certain FcγR IIIB polymorphism is associated with injection reaction to adalimumab (ADA) in RA patients. [Methods] 22 RA patients treated with ADA were enrolled in this study. Genetic polymorphisms for FcγR IIIB were genotyped in FCGR3B NA1/2 alleles using real time-PCR assay, and were subjected to logistic regression analysis to evaluate the association with clinical parameters. [Results] Injection reaction was observed in 6 patients (27.3%). The FCGR3B NA1/NA1 genotype was found in 66.7% of the patients with injection reaction and in only 25.0% of those without injection reaction. Logistic regression analysis revealed that injection reaction tended to develop in RA patients with the FCGR3B NA1/NA1 genotype (p=0.0733). [Conclusion] The FCGR3B NA1/NA1 genotype is possibly the independent predictive factor for the development of injection reaction to ADA in RA patients.

W5-4

MMP-3 improvement ratio reflects response sensitivity of biologic agents in rheumatoid arthritis treatment

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Conflict of interest: None

(Objectives) To verify MMP-3 improvement ratio as an index of response sensibility of biologic agents (BIO) for RA treatment (Materials and Methods) Ninety-one patients treated with BIO in our institute, of 27 with infliximab, 24 with etanercept, 14 with adalimumab, 3 with golimumab, 16 with tocilizumab, and 7 with abatacept, are counted. All of them have been monitored with DAS28-CRP, SDAI, and MMP-3 from just before starting BIO with every twelve weeks interval. The relationship between DAS28-CRP and SDAI, and between DAS28-CRP improvement and MMP-3 improvement ratio are plotted each other and their relationship were evaluated statistically. (Results) DAS28-CR and SDAI are closely correlated each other with correlation coefficients of 0.75, and also DAS28-CRP improvement and MMP-3 improvement ratio demonstrated close correlation with 0.89 of correlation coefficients. (Discussion) These results suggest that MMP-3 improvement ratio is closely correlated with downgrade of disease activity of RA treated with BIO. Namely, this index reflects response sensibility of the disease after treated with BIO. These facts suggest that MMP-3 improvement ratio could be valuable for judgment of BIO effectiveness, or judgment for discontinuation of BIO after attaining clinical remission.

W5-5

Rheumatoid factor as a biomarker of response to treatment of TNF inhibitor for rheumatoid arthritis

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Conflict of interest: None

Objectives: To clarify whether serum rheumatoid factor (RF) is a biomarker of response to treatment of TNF-inhibitor in patients with rheumatoid arthritis (RA). Methods: Biologics-naïve RA patients were enrolled in this study, in whom serum RF was periodically examined before and after treatment of TNF-inhibitor. Serum RF was categorized into low- (RF; 20-59 IU/ml) and high-titred (RF; <60 IU/ml), and DAS28 and EULAR response criteria were used for evaluation of disease activity and treatment effectiveness. Results: Serum level of RF was decreased after treatment of TNF-inhibitor in 87% of RF-positive RA patients, but elevated RF was normalized in only 8.7% of high-titred RF-positive patients. Among most of high-titred RF-positive patients, serum level of RF was decreased by treatment with TNF-inhibitor, and the decrease of serum RF was correlated with reduction of disease activity of RA. But some cases showed increase of serum RF despite decreased disease activity after treatment of TNF inhibitor, and 10% of high-titred RF-positive RA patients had no correspondence between serum level of RF and desease activity of RA. Conclusion: Serum RF is a possible biomarker of disease activity in high-titred RF-positive RA patients.

W5-6

No excess mortality in patients with rheumatoid arthritis treated with biologics: results from a multicenter cohort in Japan

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Conflict of interest: None

[Objectives] To evaluate the association between treatment with biologics and mortality in patients with rheumatoid arthritis (RA). [Methods] All patients with RA who received at least one dose of biologics at 6 large rheumatology centers (Biologics cohort) were included and monitored until May 15, 2010 or death, whichever came first. Standardized mortality ratio (SMR) was cal-

culated and factors associated with mortality were assessed by Cox model. [Results] Overall, 2,697 patients with RA were registered. Thirty-eight deaths were recorded among 6,940.9 patient-years and 540 patients (20.0%) were lost to follow-up. The SMR in this Biologics cohort was 1.02 (95% confidence interval [95%CI], 0.72-1.40) compared to the Japanese general population, 0.93 (95%CI, 0.66-1.28) to the IORRA cohort and 1.08 (95%CI 0.77-1.47) to Japanese general population with weighting for patients lost to follow-up. The pneumonia and malignancy specific SMR was 3.14 (95%CI 1.15-6.83) and 0.29 (95%CI 0.10-0.69), respectively. Risk factors for mortality included male gender (hazard ratio [HR], 3.01 [95%CI, 1.24-6.25]), older age (HR, 1.07 [95%CI, 1.03-1.11]), and corticosteroid dose (HR, 1.08 [95%CI, 1.01-1.17]). [Conclusion] Biologics treatment in RA patients was not associated with excess mortality.

W6-1

Safety of treatment with biologics in elderly patients with rheumatoid arthritis

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Conflict of interest: None

[Purpose:] To explore mid-term safety of treatment with biologics in patients with rheumatoid arthritis in Japan. [Patients and Methods:] We investigated the incidence rate of adverse events caused discontinuation of the treatment with bio in patients who were registered in Tsurumai Biologics Communication Registry (TBCR) until 2008. Adverse events were classified based on ICD-10 categories. The rates were compared by age and starting year using Kaplan-Meier method. [Results:] 894 registered patients (mean age, 56.3 years old, disease duration 11.4 years, and observation period 28.5 months) were explored. Total 124 adverse events were observed in this cohort. Median period to the events was 8.4 months. Respiratory system-related (R-AE) event was highest incidence rate and occurred in 53 cases. Highest tertile of age group($\geq$ 64 years) had significantly higher incident rate of R-AE, compared to lowest tertile of age group($\leq$ 53 years) ($p=0.02$). The rate of R-AE in the eldest group was clearly improving with starting year from $\leq$ 2005 to 2008($p=0.04$) while we could not find any changes in other age group. [Conclusion:] It is very important that the safety in elder patients, relatively high risk group as reported other studies, was improving with our 8 years and more of experience.

W6-2

Analysis of prognostic factors of rapid radiographic progression and Health Assessment Questionnaire remission in early elderly-onset rheumatoid arthritis by Chouju registry of Rheumatoid Arthritis on Non-biological and biological DMARDs for Elderly patients (CRANE)

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Conflict of interest: Yes

[objective] An optimal strategy in MTX-naïve early EORA is unclear. We undertook this study to evaluate poor prognostic factors of early EORA. [Methods] CRANE is a prospective monocentric observational study. Treatment target was to achieve DAS28<3.2. [Results] All of 83 EORA patients (mean age 75, mean disease duration 1.3 years, mean DAS28 6.38 and mean HAQ 1.375) started non-biological DMARDs monotherapy (MTX 74%, FK506 7%) and the proportion of biological DMARDs at 52 weeks was 35%. 44% of patients achieved DAS28<3.2. 24 of 74 patients showed Δtotal sharp score (TSS)>3, rapid radiographic progression (RRP). ΔTSS in RRP was significantly higher during the first six months than the second six months. Multivariate proportional odds analysis showed prognostic factors of RRP was anti-CCP antibody, DAS28 at 0 weeks, DAS28>5.1 at 12 and 24 weeks. Prognostic factors of abnormal HAQ (HAQ>0.5) at 52 weeks was DAS28 at 0 and 12 weeks, HAQ at 0 week and RRP. [Conclusion] CCP positive, low functional status at base line and continuous high disease activity were poor prognostic factors of early EORA. TNF inhibitors should be immediately started at 12 weeks in patients with these prognostic factors.

W6-3

An epidemiological study of patients with rheumatoid arthritis for recent 2 years in our clinic

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Conflict of interest: None

[Objectives] Recently rheumatoid arthritis (RA) treatment has changed dramatically by using biologics. We examined changes of disease activity, vital and functional prognosis of RA in recent 2 years in our clinic. [Methods] We conducted an observational study on 179 RA patients (50 men and 128 women) in 2008. Changes of disease activity, vital and functional prognosis were evaluated in 2010. [Results] Out of 179 patients, six patients died, 26 patients were referred to other clinics and 9 patients dropped out. The causes of death were bacterial pneumonia in 2, interstitial pneumonia, aspiration pneumonia malignant lymphoma and AA amyloidosis. Ninety-three patients could be assessed for changes of disease activity among the rest of 139 patients. The mean values at 2010 and the changes from the data of 2009 were as follows: the proportion of patients using biologics 38.7% (+12.9%), the average doses of MTX 7.1±2.1 mg/week (+0.3 mg/week), PSL 4.5±2.4 mg/day (-0.6 mg/day), SDAI 9.6±8.5 (-1.7), DAS28(CRP3) 2.5±1.1 (-0.4), Class 1.7±0.8 (+0.0), Stage 2.3±1.1 (+0.2). [Conclusion] In the last 2 years, increased utilization of biologics and increased dose of MTX may be related with the decreases of PSL dose and disease activity, prevention of joint damage and preservation of

function status.

W6-4

Nutrition and immune status evaluation using CONUT in patients with rheumatoid arthritis

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Conflict of interest: None

[Objectives] Some results have shown that patients with poor nutritional status experience worse outcome than patients with better nutrition. Controlling nutritional status(CONUT) is one of the method to evaluate comprehensively the nutrition and immune status. Our objective was to assess the nutrition and immune status of the patients with rheumatoid arthritis (RA) and to analyze the relationship between CONUT and Disease Activity Score 28 (DAS28). [Methods] We chose seven nutritional and immunological parameters in seventy five patients: serum protein, serum albumin (ALB), total cholesterol, hemoglobin, white blood cell count, lymphocyte count and MMP-3. DAS28 was applied for the clinical indicator. The DAS 28 cut-off point which required achieving normal CONUT point was analyzed by ROC analysis. [Results] In multiple regression analysis, DAS28 have positively correlated with TP ($t=2.94$, $P=0.0054$) and negatively with ALB($t=-3.73$, $P=0.0006$). MMP-3 had negative correlation with ALB($t = -3.09$, $P<0.001$). MMP-3 had positively correlated with CONUT($t=4.75$, $P<0.001$). DAS 28 have positively correlated with CONUT($t=3.24$, $P=0.0018$) in regression analysis. ROC analysis showed that the cut-of point required predicting achievement of normal CONUT point was DAS28<3.78.

W6-5

Delay in referral and diagnosis of rheumatoid arthritis in a community medical center in Japan.

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Conflict of interest: None

[Objectives] To examine the delay of RA diagnosis in a rural community hospitalin Japan. [Methods] A total of 340 patients with at least one swelling joint who visited our hospitalfrom January 2009 to December 2010 were included. In the patients diagnosed as RA, the time intervals from the onset of symptom to primary care physician (PCP) (patient delay), from PCP referral to a rheumatologist (PCP delay), from the onset of symptoms to rheumatology visit (total delay) were determined. [Results] Ninety-two patients were diagnosed as RA, while 82 (89%) patients fulfilled 2010 ACR/EULAR RA criteria and 68 (74%) patients fulfilled 1987 ACR RA criteria. The median patient, PCP, total delays [interquartile range [IQR]] were 8.9 weeks [3.4-30.1], 5 weeks [2-20.1], 26.9 weeks [11.4-59.6] respectively. The patient delay was longer than PCP delay ($p=0.06$), which was statistically significant in a subgroup of upper 25 quartile (130.1 weeks vs. 4.4 weeks, $p=0.005$), while it was not statistically significant in lower 25 quartile (3.6 weeks vs. 2.1 weeks, $p=0.41$). It suggests that in a rural community in Japan, the patient education is very important for early intervention.

W6-6

Satisfaction and attidudes toward therapy in patients with rheumatoid arthritis

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Conflict of interest: None

Objective: We examined associations between patient satisfaction and factors obtained in routine clinical practice, and associations with therapeutic attitude. **Methods:** A total of 220 patients with RA were enrolled in this cross-sectional evaluation. Demographic data, current disease state of RA, history of adverse events and self-reported questionnaire of patient satisfaction, attitudes toward therapy and reasons for being unwilling to change therapy were collected and analyzed. Multiple linear regression was used to identify characteristics. **Results:** Age, Stanford Health Assessment Questionnaire (HAQ) score, and visual analogue scale score of general health were the dominant correlates of satisfaction. Among the participants, 70% reported that they would not want to change therapy. The main reasons given were satisfaction with the current disease state (58%) and concern about the risk of side effects (34%). Patients who were unwilling to change therapy due to concerns about side effects did not have a significantly higher frequency of a past history of side effects, but showed a significantly higher disease activity and lower level of satisfaction. **Conclusion:** Patients who worry about the risk of side effects show poor physical function and higher disease activity.

W7-1

Expression of IgG receptors on human synovial mast cells and their function.

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Conflict of interest: None

[Objectives] The aims of this study are (1) to identify what Fc receptor(s) are expressed on MCs obtained from synovial tissue of RA patients, (2) to examine the function of the receptor(s) [Methods] Synovial tissues were obtained from RA and OA patients during joint replacement surgery and the synovial MCs were enzymatically dispersed. In some experiments, synovial cells were cultured in the presence of SCF. Receptor(s) and protease(s) expression was analyzed by FACS. The function of MCs through FceRI and FcgRI was monitored by measurement of mediators by ELISA. [Results] Primary synovial MCs obtained from both RA and OA were morphologically similar and expressed Kit, FceRI, FcgRI and FcgRII, but not FcgRIII. Aggregation of FceRI or FcgRI on primary synovial MCs induced degranulation. Cultured synovial MCs showed similar histopathological profiles to primary synovial MCs and expressed functional FceRI, FcgRI, and FcgRII on their surfaces. Both primary synovial MCs and cultured synovial MCs consist of 80% MC_{TC} and 20% MC_{T}. Synovial MCs induced degranulation, PGD_2 and TNF-a production through FcgRI. Aggregated IgG induced degranulation and TNF-a production from the MCs through FcgRI, suggesting that synovial MCs may be activated by immunocomplex in the inflammatory sites of RA.

W7-2

Nkx3.2 promotes primary chondrogenic differentiation by up-regulating Col2a1 transcription

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Conflict of interest: None

[Objectives] The transcription factor Nkx3.2 promotes chondrogenesis by forming a positive regulatory loop with a crucial chondrogenic transcription factor, Sox9. Previous studies have indicated that factors other than Sox9 may promote chondrogenesis, but these factors have not been identified. Here, we test the hypothesis that Nkx3.2 promotes chondrogenesis directly by Sox9-independent mechanisms and indirectly by previously characterized Sox9-dependent mechanisms. [Methods and Results] C3H10T1/2 cells were cultured with bone morphogenetic protein 2 (BMP2) to induce endochondral ossification. Overexpression of wild-type Nkx3.2 (WT-Nkx3.2) upregulated glycosaminoglycan (GAG) production and expression of type II collagen alpha1 (*Col2a1*) mRNA, and these effects were evident before WT-Nkx 3.2-mediated upregulation of *Sox9*. RNAi-mediated inhibition of *Nkx3.2* abolished GAG production and expression of *Col2a1* mRNA. Dual luciferase reporter assays revealed that WT-Nkx3.2 upregulated *Col2a1* enhancer activity in C3H10T1/2 cells and also in N1511 chondrocytes. ChIP assays revealed that Nkx3.2 bound to the *Col2a1* enhancer element. Thus, Nkx3.2 promoted primary chondrogenesis by two mechanisms: Sox9-independent upregulation of *Col2a1* transcription and upregulation of *Sox9* transcription.

W7-3

The function and regulation of Layilin, a novel hyaluronan receptor, in human articular chondrocytes

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Conflict of interest: None

[Objectives] Layilin is a 55-kDa transmembrane protein which has been found to be a receptor for hyaluronan (HA). Here we examined the regulation and potential function of Layilin in human articular chondrocytes (HAC), in particular, its potential interaction with HA. [Methods] Cartilage samples were obtained from patients with osteoarthritis and rheumatoid arthritis who were undergoing joint arthroplasty. Isolated HAC from cartilage were cultured in vitro by monolayer, and stimulated with IL-1β or dexamethasone (DEX). Layilin expressions were analyzed using real-time PCR and Western blot. In addition, HAC were transfected with siRNA to suppress Layilin expression, preincubated with high-molecular-weight HA and then stimulated with IL-1β to induce matrix metalloproteinase (MMPs) expressions. Then the productions of MMPs were measured with real-time PCR or ELISA. [Results] Whereas Layilin expression was significantly suppressed by IL-1β, DEX enhanced the expression. Suppressive effect of HA on IL-1-induced MMP-13 in HAC was abrogated in Layilin-downregulated HAC. [Discussion] The expression of Layilin may contribute to HA functions in arthritic condition. Also, corticosteroids may have a role in regulating Layilin expression in HAC.

W7-4

IL-26, a novel Th17 cytokine, inhibits human osteoclastogenesis

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Conflict of interest: None

【Objective】 IL-26 is produced by Th17 cells following stimulation with IL-23 (Wilson NJ et al. Nat Immunol 2007). However, it remains unclear the role of IL-26 in RA or human osteoclastogenesis (Oc-genesis) because no murine IL-26 homologue has been reported so far. Our objective is to investigate the role of IL-26 in RA or human osteoclastogenesis.【Method】1) Synovial tissues of RA or OA were immunohistochemical stained by anti-IL-26 antibody. 2) Human monocytes (Mo) were cultured with M-CSF for 3 days. Then, Mo were cultured with M-CSF and soluble-RANKL and rhIL-26 for 10 days. Osteoclasts (Oc) were stained for anti-CD51/61(vitronectin receptor) antibody. Pit formation assay was performed by using Osteologic®. 3) Mo were cultured with M-CSF for 24 hrs. Then, IL-26 was added for 24hrs and mRNA expression of RANK on Mo was assessed by RT-PCR.【Results】IL-26 was expressed on synovial tissues of RA but not on those of OA. IL-26 dose-dependently inhibited human Oc-genesis and IL-26 decreased resorption pits. Moreover, IL-26 decreased mRNA expression of RANK on Mo.【Conclusion】IL-26 expressed on RA synovial tissues inhibited human Oc-genesis and decreased osteoclastic bone resorption. Our findings suggest that IL-26 is involved with the regulation of bone destruction in RA.

W7-5

The relationship of serum Fibroblast growth factor 23 (FGF23) and osteoporosis in patients with rheumatoid arthritis

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Conflict of interest: None

[Objective] Fibroblast growth factor 23 (FGF23) is mainly produced by osteocyte in bone, and inhibits phosphate reabsorption in renal tubules and also suppresses renal $1,25(OH)_2D$ production. Although it has been known that FGF23 abnormality leads to hypophosphatemic disorders and secondary hyperparathyroidism, there have been few reports about the relationship between FGF23 and osteoporosis. We investigated the association between serum FGF23 and bone mineral density (BMD) in patients with rheumatoid arthritis (RA). [Methods] Sixty-two female patients with RA were included (serum creatinine 0.55±0.12 mg/dL) and serum FGF23, BMD, serum markers of bone metabolism and disease activity of RA were examined at two points. [Results] Serum FGF23 significantly related to serum crosslinked N-telopeptide of type I collagen (NTx) (r=0.385, p=0.002), urine NTx (r=0.266, p=0.037), DAS28 (r=0.409, p=0.001), BMD of femoral neck (r=-0.321, p=0.012). The change rate of femoral neck BMD did not relate to serum FGF23 levels. Multiple regression analysis revealed that BMD of femoral neck was significantly associated with age and serum FGF23 levels rather than serum albumin, hemoglobin, DAS28 and urine NTx. [Conclusion] Serum FGF23 in patients with RA related to bone absorption and BMD of femoral neck.

W7-6

Significance of serum RANKL and OPG on glucocorticoid-induced osteoporosis

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Conflict of interest: None

[Purpose] To clarify the significance of serum RANKL and OPG in patients with rheumatic disease under glucocorticoid (GC) therapy. [Methods] Sixty patients (female 40) with rheumatic diseases who received initial therapy with 30-60 mg/day prednisolone were included. Serum RANKL and OPG levels were measured by ELISA at 0, 1, 2, 3 and 4 weeks after GC therapy. BMD (bone mineral density) was measured before and after GC therapy. [Result] Serum RANKL level in all patients remained unchanged after GC therapy. However, serum RANKL level in higher RANKL group (≧ 75th percentile) was significantly decreased, while serum RANKL level in lower RANKL group (< 75th percentile) was significantly increased after GC therapy. Serum OPG level in all patients was significantly reduced after GC therapy. BMD after GC therapy in higher RANKL group was increased, whereas it was decreased in lower RANKL group. Serum RANKL level at baseline in patients with decreased-BMD after GC therapy was tended to be lower than those in patients with increased-BMD. [Conclusion] Cause of GC-induced osteoporosis might be explained, at least in part, by osteoclast differentiation-inducing activity *via* changes of serum levels of RANKL/OPG.

W8-1

Early effects and safety of teriparatide on osteoporosis in patients with rheumatoid arthritis

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Conflict of interest: None

[Objectives] To investigate early effects and safety of teriparatide on osteoporosis in patients with rheumatoid arthritis(RA). [Methods] 28 RA patients treated with teriparatide in our institute were used in this study. Patients characteristics, bone mineral density (BMD) in lumbar spine and proximal femur, bone turnover marker (BAP, P1NP, NTX, TRACP-5b) and adverse events were investigated. [Results] Mean age was 70.3yo. All were female. Mean RA duration was 19.7y. 7 cases started teriparatide treatment just after fractures were injured. Drugs used before teriparatide were bisphosphonate in 20 cases. Oral PSL was prescribed in 20 cases. BMD at initiation of teriparatide and at 6 months were 0.811 and 0.851 in lumbar spine (p=0.030), 0.536 and 0.533 in right proximal femur, 0.527 and 0.534 in left proximal femur, respectively. Bone metabolism marker at initiation of teriparatide and at 6months were 18.6 and 21.4 in BAP, 65.1 and 139.0 in P1NP (p=0.002), 18.6 and 23.9 in NTX, 492.5 and 571.2 in TRACP-5b, respectively. Although hypercalcemia occured in 2 cases, they improved due to discontinuation of VitD or dose decreasing of teriparatide. Teriparatide increased BMD, espedcially in lumbar spine, and bone metabolism marker, especially in P1NP, at early time of treatment.

W8-2

Comparison of the effect of Teriparatide (TPTD) on Rheumatoid Arthritis (RA) and on postmenopausal osteoporosis patients

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Conflict of interest: None

[Objectives] The aim of this study is to compare the effect of TPTD on RA patients and that of postmenopausal osteoporosis patients. [Methods] Twenty-one female RA patients (RA: mean age 68.8 years old, mean DAS28-CRP 2.9, 67% taking Bisphosphonate (Bis), 81% taking prednisolone (PSL) with average dose 3.9mg, 19% taking biologics) and 24 postmenopausal osteoporosis patients (porosis: mean age 72.6 years old, 79% taking Bis) were enrolled. Daily subcutaneous injection of 20μg TPTD was administered for 6 months without Bis, calcium, and vitamin D supplementation. The primary study outcome included change in lumbar spine and total hip bone bone mineral density (BMD) measured by DXA, changes in bone turnover markers, and fracture incidence. [Results] There was no significant group difference in prior mean age, rate of Bis administration, lumbar spine and total hip bone BMD. Change in BMD from baseline prior to TPTD administration and after 6months of TPTD administration were 0.99%→2.06% in RA and 0.46%→0.86% in porosis (lumbar spine), and were -1.76%→-0.56% in RA and -0.24%→-0.53% in porosis (total hip). BMD of RA tend to increase more rather than that of porosis. There was no incidence of vertebral or non-vertebral fracture in both groups during this period.

W8-3

Risk Factors Associated with Incident Hip Fractures in 9,720 Japanese Patients with Rheumatoid Arthritis: A Prospective Observational Cohort Study

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Conflict of interest: None

[Objectives] We evaluated the association between potential risk factors and incident hip fractures in Japanese patients with RA. [Methods] A total of 9,720 patients (82% female, median age 57 years) with RA were enrolled in the IORRA cohort study from 2000. Self-reported hip fractures were verified with patient medical records. Cox proportional hazards models were used. [Results] During a mean (SD) follow-up of 5.2 (3.3) years, 152 patients reported 152 hip fractures. Among these patients, 107 hip fractures in 107 patients (M 16, F 91) were verified with medical records. J-HAQ score (HR 2.4, 95% CI 1.9-3.0), age (per 10 years; HR 1.6, 95% CI 1.3-1.9), history of total knee replacement (TKR) (HR 3.3, 95% CI 1.4-7.7), and BMI (HR 0.9, 95% CI 0.9-1.0) were significantly associated with hip fractures. Among the scores on the 8 domains of the J-HAQ, HAQ (arising) (HR 1.7, 95% CI 1.3-2.1) and HAQ (hygiene) (HR 1.5, 95% CI 1.1-2.0) were significantly correlated to incident hip fractures. [Conclusions] High HAQ disability score, old age, history of TKR, and low BMI appear to be associated with incident hip fractures in Japanese patients with RA. Among the 8 domains of the J-HAQ, disabilities of arising and hygiene appear to correlate to incident hip fractures in Japanese RA patients.

W8-4

The prevalence and the analysis of the risk factors of the vertebral fracture in the rheumatoid arthritis patients (TOMORROW STUDY)

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Conflict of interest: None

[Objectives] Rheumatoid arthritis (RA) is a representative disease causing secondary osteoporosis. We investigated the prevalence and the risk factors of vertebral fractures in RA patients. [Methods] We have started 10-year prospective cohort study (TOMORROW Study, UMIN000003876) from 2010. This study include 208 RA patients and 205 volunteers who were matched age and sex. To evaluate the prevalence of vertebral fracture thoracolumbar spine X-ray were examined and we analyzed the factors associated with vertebral fracture. [Results] Prevalence of vertebral fractures was 45.5% in RA group and 30% in volunteer group. SQ grade 2 or more groups were significantly higher in RA patients (15.2% vs 5%). In the RA group bone mineral density, urine pentosidine, homocysteine and bone specific alkaline phosphatase (BAP) showed a significant correlation with the vertebral fractures. Urin pentosidin was significantly higher in the RA fracture group. In this analysis, we found that RA patients have many vertebral fractures compared to volunteers. Moreover, it was suggested that the bone quality marker and the presence of vertebral fractures is closely involved in RA patients. We will continue to investigate prospectively the incidence of new vertebral fractures and the progression of osteoporosis.

W8-5

Early diagnosis and early intervention by alendronate of glucocorticoid-induced osteoporosis in patients who are initially treated with glucocorticoid~Early DIagnosis and Treatment of OsteopoRosis in Japan (EDITOR-J) ~

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Conflict of interest: Yes

[Objectives] Early diagnosis of change of bone metabolism by bone markers just after the initiation of glucocorticoid (GC) therapy and clinical efficacy of early intervention by alendronate in patients who are treated with GC. [Methods] Subjects had just developed systemic autoimmune diseases and were randomized to be treated with more than 20 mg/day prednisolone and alfacalcidol 1 μg/day alone (n = 34), or GC and alendronate 5 mg/day (n = 38), or GC and alfacalcidol 1 μg/day with alendronate 5 mg/day (n = 38), each for 6 months. [Results] 1) GC increased serum CTx and NTx and urinary NTx at 1 week. 2) Alendronate decreased serum CTx and NTx and urinary NTx. 3) Alendronate with alfacalcidol increased lumber spine. 4) There was correlation between the percent changes in CTx from 1 to 24 weeks after the treatment with anti-osteoporotic drugs and in lumber spine of BMD from 0 to 24 weeks.5) Bone fracture occurred at 12 months in 5 patients of the alfacalcidol groups, 3 patients of the alendronate groups, but not in the combined group. Our results indicate that bone resorption marker was increased rapidly within the first 1 week after GC treatment. Alendronate with alfacalcidol treatment can improve bone metabolism and protect against high-dose GC-induced bone loss and bone fracture.

W8-6

Fall risk of patients with rheumatoid arthritis is not high -TOMORROW study-

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Conflict of interest: None

[Objectives] Patients with rheumatoid arthritis (RA) who have muscle weakness and stiff or painful joints may be at increased risk of falling. The aim of this study was to use a prospective design to determine the incidence of falls and their risk factors in RA (TOMORROW study). [Methods] The participants in the study were consisted 202 RA patients (54% using biological agents) and 202 age- and sex-matched healthy volunteer. We evaluated anthropometric parameters, muscle volume, and bone density, disease activity and general health status. The occurrence of falls were assessed for 1 year. [Results] There is no difference in occurrence of falls between RA patients and volunteer (18.3% vs 15.8%) during 1 year. After correction for risk factor of falls (age, gender, smoking and BMI), multiple logistic regression analysis identified that history of falls were the most significant parameters associated with falls (odds ratio: 2.71, $p<0.001$). The RA group also had lower muscle volume and bone density than volunteer, but there is no relation with rate of falls. [Conclusion] We concluded that fall rate in RA patients was not higher than in volunteer and that only history of falls may play a role in increasing the risk of falls.

W9-1

Comparison of 4 biologics - LUNDEX from 3 - year observation

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Conflict of interest: None

【Purpose】The clinical study of ETN, IFX, TCZ, and ADA. 【Method】Two hundred forty three patients (ETN:88, IFX:105, TCZ:35, ADA:15) were initiated for 36 months or more. The LUNDEX, a new index combining criteria with adherence was designed. The DAS, mHAQ, TSS, adverse effect, and the continuance rate were examined. 【Result】The percentages of patients who completed 3 years were 60.2%(ETN), 45.7%(IFX), 27.3%(TCZ), 53.3%(ADA). LUNDEX - DAS28 good+moderate rsponse:59.9%(ETN), 43.8%(IFX), 46.5%(TCZ), 31.5%(ADA). LUNDEX-DAS28 remission:23.7%(ETN), 15.4%(IFX), 27.3%(TCZ), 14.5%(ADA). No-radiographic progression(⊿TSS ≤

0.5 / yr) rate : 50.9%(ETN), 41.0%(IFX), 21.9%(TCZ), 22.2%(ADA). First-line biologics in ETN, TCZ, and ADA had higher overall LUNDEX values compared with second-line, mostly because of a higher rate of adherence.【Conclusion】As for ETN, an especially useful possibility was suggested ateffectiveness and the continuance rate.

W9-2

The follow up report of the comparison of survival rate and clinical results in three TNF inhibitors

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Conflict of interest: None

[Objectives] The aim of this follow up study is to compare three TNFa inhibitors regarding the drug survival rate and the clinical results. [Methods] We included 176 patients administered the TNFa inhibitor, Infliximab(IFX) or etanercept(ETN), or adalimumab(ADA). We investigated the drug survival rates, and the dose of MTX, PSL, DAS28, Esr at 0month, 6 months and 12 months after the administration by medical records. [Results] ETN group showed significantly high survival rate compared to other 2 drugs. IFX group showed higher DAS28 at 6 months than ETN group, and at 12 months than other 2 drugs. A past study reported that ETN had the longest drug survival rates, ADA had the highest, and IFX had the lowest rates of treatment response. Our study showed similar results in drug survival rates, but showed no difference regarding the clinical results.

W9-3

Three-Year Continuation Rate of Infliximab and Etanercept: A Single-Center Study in Japan

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Conflict of interest: None

[Objectives] We investigated 3-year continuation rate of Infliximab (IFX) and Etanercept (ETN) because there have been few investigations on the long-term continuation rate with biological agent at a single center. [Methods] IFX was started to 165 patients and ETN to 123. Their backgrounds at the start of TNF-α inhibitors and reasons of discontinue were examined. The three-year continuation rate was analyzed by the Kaplan-Meier method. [Results] The demographics of the patients on IFX and ETN with significant difference, respectively, were as follows: bio-naive, 98.2% and 80.5%; DAS28-CRP, 5.6 ± 1.2 and 5.0 ± 1.2. Three-year continuation rates of IFX and ETN were 47.9%, 73.2%, respectively, with significant difference. Among patients on ETN along with methotrexate (n = 70, 56.9%), the three-year continuation rates were 72.9%. There was significant difference of the reasons for discontinuation before three years between only primary unresponsiveness. This study demonstrated that the three-year continuation rate of ETN was significantly higher than that of IFX. The main reason for the difference was the tendency of starting IFX with higher disease activity patients. Cost was another factor; 28.5% of the patients on ETN used only 25mg weekly for symptom-stabilization.

W9-4

Comparison of infliximab and etanercept - LUNDEX from a 6-year observation

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Conflict of interest: None

[Objectives] The crinical study of ETN and IFX. [Methods] Eighty two patients(ETN:n=40, IFX:n=42) was initiated for 72 months or more. The LUNDEX, a new index combining criteria with adherence was designed. The DAS, mHAQ, TSS, adverse effect, and the continuance rate were examined. [Results] The percentages of patients who completed 6 years were 41.7%(first line ETN), 18.2%(second line ETN), 29.8%(IFX). LUNDEX - DAS28 good + moderate response: 33.6%(first line ETN), 14.9%(second line ETN), 28%(IFX). LUNDEX-DAS28 remission: 9.3%(first line ETN), 1.7%(second line ETN), 9.9%(IFX). LUNDEX - mHAQ remission:20.8%(first line ETN), 9.9%(second line ETN), 20.9%(IFX). In both, no radiographic progression (⊿TSS ≤ 0.5 / yr) rate decreased gradually from 40% to 20%. Although ETN group consisted of higher disease activity patients, first-line ETN had higher overall LUNDEX values compared with IFX, mostly because of a higher rate of adherence. As for first-line ETN, an especially useful possibility was suggested at effectiveness and the continuance rate.

W9-5

Result of multicenter long term efficacy of adalimumab use in rheumatoid arthritis (RA) patients

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Conflict of interest: None

[Objectives] To investigate adalimumab (ADA) efficacy in a three-year multicenter study of adalimumab efficacy in Japanese rheumatoid arthritis (RA) patients. [Methods] 59 RA patients received their first dose of ADA as of February 2009 in eight medical centers in Fukuoka city area in Japan. Long term efficacy was reviewed at week 144. Patients' background mean age was 61.6±11.9years, M:F ratio was 5:54, RA disease duration, was14.2±10.4years, and MTX combination use was 78.0 %. Average dose of MTX was 7.48 mg/week, 72.9% of the patients were naïve to prior biologic treatment and baseline DAS28-CRP and ESR mean were 4.54 and 5.13. The results were evaluated according to DAS28-CRP, DAS28-ESR, Boolean remission criteria and EULAR response. [Results] At week 144, mean DAS28-CRP was 2.88, with 35.6% (21 cases) clinical remission rate (DAS28-CRP<2.3) and mean DAS28-ESR was 3.58 with 19.0% (8 cases) clinical remission rate (DAS28-ESR<2.6). Also, according to Boolean criteria, 22.0% (13cases) remission was achieved. Based on EULAR (DAS28-CRP) criteria, 40.7% (24cases) achieved good EULAR response 33.9% (20cases) achieved moderate EULAR re-

sponse and no response was observed in 25.4% (15 cases) (LOCF method). After 144 weeks, 59.3% of the 59 patients maintained treatment.

W9-6

Drug survival rate for etanercept and discontinued cases -TBC registry for the patients with rheumatoid arthritis using biologics-

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Conflict of interest: None

[Objective] Survival rate of treatment is indicator of efficacy and safety of the treatment. To evaluate the drug survival rate and examine the discontinued cases treated with etanercept. Data was collected from multi-center study group for the treatment of RA using biologics (Tsurumai Biologics Communication; TBC). [Method] We determined the rate by Kaplan-Meier and examined the discontinued patients in detail using 883 cases in that were using etanercept as 1st biologics from TBC study group. Non responder and transfer cases were compared initial group (2005-2007) with recent group (2008-2011) each other. [Result] Survaival rate for etanercept was 62% at 60 months. Adverse events were 116 cases (average dosing period 15.4 months) and non responders were 114 cases (average dosing period 25.5 months). Transferred to another hospital were 86 cases (average dosing period 40.1 months). Dosing period of non responder recent group was shorter than that of initial group. It was the same as that of transfer cases.

W10-1

The efficacy of shortening intervals for infliximab and dose escalation of infliximab with rheumatoid arthritis.

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Conflict of interest: None

[Objectives] To evaluate the efficacy of shortening intervals of IFX with dose escalation of IFX. [Methods] 136 cases treated by shortening intervals of IFX to 7 weeks or less and 115 cases treated by dose escalation of IFX were extracted from multi-center registry for the treatment of RA using biologics (Tsurumai Biologics Communications; TBC). [Results] In shortening cases, 33 cases discontinued IFX therapy because of loss of efficacy, 15 cases stopped IFX infusion because of adverse events(AEs). In dose escalation cases, 36 cases discontinued IFX therapy because of loss of efficacy, 10 cases stopped IFX infusion because of AEs. [Conclusion] The shortening IFX therapy and dose escalation of IFX should be considered in case of loss of efficacy during IFX treatment with 3mg/kg dose. We demonstrated that shortening intervals of IFX is superior to dose escalation of IFX by Kaplan-Meier method (Log-rank test: p=0.042).

W10-2

Comparison of dose escalation of infliximab and adding tacrolimus in rheumatoid arthritis patients with an inadequate response to infliximab therapies

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Conflict of interest: None

[Objective] The aim of this study was to compare dose escalation of infliximab and adding tacrolimus in rheumatoid arthritis patients with an inadequate response to infliximab therapies. [Methods] ESR, MMP-3, DAS-28 ESR and EULAR response criteria at Month 6 were evaluated in 22 RA patients with an inadequate response to infliximab therapies. (11 on escalation IFX, 11 on adding tacrolimus) [Result] The characteristics of each group had no significant difference. In the escalation group, the INF dose was 300-500 mg (an average of 345.5 mg), The TAC dose in the adding TAC group was 1-3 mg/day (an average of 1.9 mg/day). CRP, MMP-3, ⊿DAS28-ESR had no significant difference between both groups. [Conclusion] Adding TAC had a therapeutic effect in RA patients with an inadequate response to infliximab therapies comparable to or better than escalation IFX.

W10-3

Anti-adalimumab (ADA) antibody (AAA) may decrease the effectiveness of ADA in Japanese patients (addendum report).

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Conflict of interest: None

【Background】 In Japanese patients It has not been clear whether the effect of ADA to RA were decreased by AAA or not, though The AAA production showed the tendency to decrease the ADA blood levels in pre-marketing trial. We reported about the ADA ineffective patients due to the AAA production in JCR 2011. 【Purpose】 To clarify the relation between the clinical effectiveness of ADA, AAA production and the ADA blood level. 【Patients and Methods】 47 RA patients who were administrated ADA were enrolled in this study. The blood ADA levels and AAA levels were measured. The relation between the effect of ADA to their RA and the AAA production were examined. 【Results】 No patients pro-

duced AAA before ADA treatment. Fifteen patients produced AAA after ADA administrating. In nine of the fifteenth patients the blood levels of AAA were increased four weeks after ADA treatment. The levels of blood ADA and the effect of ADA were deceased in most of these patients. 【Conclusion】 In this study the possibility of the decrease of ADA effectiveness to RA in the patients producing AAA was suggested. The measurement of AAA may be useful to detect the ineffectiveness of ADA to RA patients earlier than physicians can feel.

W10-4

Efficacy of adalimumab treatment in RA patients without anti-adalimumab antibodies: examination of adalimumab serum concentrations and body weight

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Conflict of interest: None

Objective: To examine the association with the efficacy of adalimumab (ADA) and body weight (BW) as well as the correlation between BW and serum ADA concentrations. **Methods**: We evaluated DAS28-ESR and CDAI every 4 weeks and measured trough serum ADA level and anti-adalimumab antibodies (AAAs) in 54 RA patients treated with 40 mg ADA every other week. In 40 AAA-negative patients. We compared clinical response between BW < 53.3 kg group (19 cases) and BW ≧ 53.3 kg group (20 cases). **Results**: There was strong negative correlation between BW and serum ADA concentrations especially in monotherapy arm. When compared at taking blood samples, BW < 53.3 kg group showed significantly better ΔDAS and higher serum ADA level than BW ≧ 53.3 kg group. In addition, ΔCDAI and the rate of good and moderate response in BW < 53.3 kg group showed tendency to improve more than those in BW ≧ 53.3 kg group. When compared at week 32, there were no significant differences in the rate of good and moderate response and the remission rate between both groups. **Conclusion**: Our study suggests the possibility that the administration of 40 mg / 2 weeks ADA reach effective serum concentrations in AAA-negative cases.

W10-5

Examination of adalimumab serum concentration and efficacy of adalimumab treatment in RA patients with or without anti-adalimumab antibodies

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Conflict of interest: None

Objective: To examine the association with the anti-adalimumab antibodies (AAAs) and the efficacy of adalimumab (ADA) treatment in addition to the relationship between the AAA formation and the background factor. **Methods**: We measured trough serum ADA level and AAAs in 56 patients treated with ADA. We compared their background factor and clinical response (DAS28-ESR, CDAI) between AAA-positive group (15 cases) and AAA-negative group (41 cases). **Results**: AAA-positive group were significantly younger than AAA-negative group. More AAA-positive patients had previous anti-TNF therapy, high level of γ-globulin and positive antinuclear antibody test than AAA-negative patients. In AAA-negative group, mean DAS28 and CDAI were significantly improved all over after 4 weeks. ΔDAS28, ΔCDAI, the retention rate and rates of good and moderate response (LUNDEX score) in AAA-negative group were better than in AAA-positive group. Serum ADA concentration of AAA-positive group was significantly lower than that of AAA-negative group. One of AAA-positive patients during ADA monotherapy achieved clinical remission with undetectable AAA after the addition of tacrolimus. **Conclusion**: AAA-positive group showed less clinical improvement than AAA-negative group because of lower serum ADA concentrations.

W10-6

Secondary loss of efficacy (LOE) in patients with rheumatoid arthritis (RA) treated with adalimumab (ADA)

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Conflict of interest: None

[Objectives] We investigated secondary LOE in patients with RA treated with ADA. [Methods] In 175 RA patients passed 52 weeks with ADA therapy, secondary LOE occurred in 20 patients in multicenter study TBC(Tsurumai Biologics Communication). [Results] Secondary LOE occurred in 11% of the whole patients with ADA therapy. It occurred gradually from the 10 weeks to the 62 weeks. The period until secondary LOE occurs was shortened, so that the disease activity became high. The incidence of secondary LOE in ADA therapy increased in the group of MTX non-use and PSL use, and in the group of switchers from other ant-TNF-α agents due to secondary LOE. The incidence of secondary LOE in ADA therapy in the group of switchers from infliximab due to secondary LOE increased compared to etanercept. We suggested that secondary LOE in ADA therapy decreased in the group of low disease activity, MTX use, and PSL non-use.

W11-1

Basic analyses for development of novel therapeutic strategy for PAH, targeting right ventricular remodeling by HEXIM1

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Conflict of interest: None

[Objectives] Pulmonary arterial hypertension (PAH) causes fatal right ventricular hypertrophy (RVH). We propose a new therapeutic strategy that directly blunts RVH. Because HEXIM is the only molecule to inhibit P-TEFb, which is the key molecule for de-

velopment of cardiac hypertrophy, we speculate that HEXIM1 may be a candidate for preventing RVH with PAH. [Methods and Results] We revealed that, in cultured cardiomyocytes, overexpression of HEXIM1 could inhibit ET-1-induced cellular hypertrophy, expression of several cardiac hypertrophic genes, and phosphorylation of RNAPII. However, overexpression of a mutant HEXIM1dN, which cannot suppress P-TEFb, did not prevent those effects of ET-1. Interestingly, PGI2 induced the expression of HEXIM1 in cardiac myocytes and expression of HEXIM1 was downregulated in the heart of Prostaglandin I synthetase-deficient mice. Moreover, we revealed that cardiac muscle-specific HEXIM1 transgenic mice have attenuated hypoxia-induced RVH, cardiomyocytes hypertrophy, and RV dilatation. [Conclusion] HEXIM1 may be a candidate for preventing RVH with PAH by inhibiting P-TEFb activity. PGI2 might affect not only pulmonary arterial vasoconstriction but also the hypertrophic cell growth of cardiac myocytes in PAH, at least in part, via induction of HEXIM1.

W11-2

The clinical features of pulmonary arterial hypertension associated with connective tissue diseases: analysis of 23 cases

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Conflict of interest: None

【Background】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 2011, were included in this retrospective study. 【Results】This study comprised 23 patients including 8 with systemic sclerosis (SSc), 8 with systemic lupus erythematous (SLE), 4 with mixed connective tissue disease, and 3 with other CTD, followed up for 31 (2-167) months. Three year overall and event-free survival rate were 92% and 45%, respectively. Two patients with SLE died. WHO functional class at baseline in patients with SSc was 2.6±0.5. Patients with SSc slightly showed to have lower pulmonary arterial pressure and higher pulmonary vascular resistance than the others. Nine out of 12 non-SSC patients treated with corticosteroids achieved one or more improvement of WHO functional class at 12 weeks after the initiation of the treatment. 【Conclusion】1) Early diagnosis and treatment may improve the outcome of PAH-SSc. 2) Patients with SSc had lower pulmonary arterial pressure and higher pulmonary vascular resistance than non-SSC. 3) Immunosuppression may be effective for non-SSc PAH-CTD.

W11-3

Clinical outcomes of pulmonary arterial hypertention associated with connective tissue diseases in our department.

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Conflict of interest: None

Pulmonary arterial hypertension (PAH) is a devastating complication in connective tissue diseases (CTDs). Recently, therapies targeted at the endothelin-, nitric oxide-, and prostacyclin-mediated pathways have been developed, and the management of CTD-PAH has been advancing rapidly. To investigate the efficacy of these newly develpoed therapies, a short-term retrospective study was made of 24 patients (2 male, 22 female patients) with CTD-PAH presented to our department between April 2008 and November 2011. Patients were given a diagnosis of PAH if mean pulmonary arterial pressure was more than 25mmHg by a right heart catheter or estimated tricuspid valve pressure gradient (TVPG) was more than 35mmHg by an echocardiography. Mean duration of PAH was 3.4 years. Underlying diseases were systemic sclerosis (SSc, n=12), systemic lupus erythematosus (SLE, n=5), mixed connective tissue disease (MCTD, n=3), rheumatoid arthritis, Sjogren's syndrome, Takayasu's arteritis, and antiphospholipid syndrome (n=1). After treatment, mean TVPG was improved from 70.6mmHg to 59.8mmHg (p value=0.02). Poor responsiveness factor was SSc, coexisting IP, and high level of D-dimer. These novel therapies should be benefical to CTD-PAH, hoping that the long-term outcome will improve.

W11-4

Clinical characteristics of pulmonary disease in patients with microscopic polyangitis

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Conflict of interest: None

To clarify the clinical characteristics of pulmonary disease in patients with microscopic polyangitis (MPA), we investigated clinical symptoms and laboratory data of 42 patients (22 females and 20 males) in our hospital. The patient's median ages were 66.3 years old and median disease durations were 1.5 months. On admission, their median CRP and BVAS scores were 8.9mg/dl and 17.9. Laboratory data revealed positive test for anti MPO-ANCA and PR3-ANCA in 41 and 3 patients, respectively. All patients received oral corticosteroids. Twelve patients were treated with pulsed methylprednisolone, 17 patients with immunosuppressive drugs. Thirty two patients showed interstitial pneumonia, and 2 showed alveolar hemorrhage. MPO-ANCA and BVAS score showed no significance between patients with or without interstitial pneumonia, but patients with interstitial pneumonia showed significant positive test for rheumatoid factor. Imaging findings by HRCT revealed UIP type in 19 patients and non-UIP type in 13 patients. During the follow up period, two patients with UIP type and one patient with non-UIP type were died. Our data showed significant number of patients showed non-UIP pattern on HRCT, it is important for detailed examinations of pulmonary disease in patients with MPA.

W11-5

Acute respiratory failure in rheumatoid arthritis patients.

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Conflict of interest: None

【Background】Many rheumatoid arthritis (RA) patients have pulmonary disorder (PD), as an extraarticular manifestations. We determined clinical features of RA complicated with acute respiratory failure.【Method】We investigated chest HRCT and serological tests of 130 RA patients during 2010 - 2011 in our hospital. At the first visit, 74 RA patients came to the Department of Rheumatology, and 56 patients to Department of Respiratory medicine.【Results】48 RA patients presented acute respiratory failure (Group A), whereas 82 RA patients had no respiratory failure (Group B). However, in Group B, 55 patients were found to have pulmonary disorders (PD) (Group C). Causes of exacerbation were as follows; RA-related interstitial pneumonia (IP) for 31 cases, drug-induced RA lung for 4 cases, infections for 10 cases, and pleurisy for 1 case. Two patients died for IP exacerbation. Male predominancy (50%), smoking index (average index; 553), IL-6 titers (average index; 608 U/ml) and complications with PD such as IP (71%) had tendency to be higher in Group A than in Group B, but not in Group C.【Conclusion】It is difficult to predict the exacerbation of PD. However, we should carefully treat male RA patients with smoking habit complicated with PD to avoid acute respiratory failure.

W11-6

Research of 75 RA patients admitted by airway infection disease in our hospital

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Conflict of interest: None

Rheumatoid Arthritis (RA) patients are in high risk group of infectious diseases due to their insufficient activity of daily life and various immunosuppressive drug treatments. Especially, airway infectious diseases such as pneumonia are sometimes deadly for them, so, identification of causative agents and adequate treatments are needed. 872 RA patients were admitted in our hospital for a period of 10 years (2001-2010), Among them 75 cases were admitted mainly due to airway infectious diseases. We survey RA disease duration, drug treatments, causative agents of each case. Average RA disease duration is 12.8 years. 70 cases of 75 treated with prednisolone (7.23 mg/day in average).*H.influenzae* is most frequently identified with sputum culture. *S.pneumoniae* and *P.aeruginosa* are next. We found 8 cases treated with biologics, 2 with infliximab, 5 with etanercept, and 1 with tocilizumab. It is well known that long RA disease duration and usage of prednisolone increase the risk of airway infection. In addition to this, we refer to difference of causative agents between RA patients pneumonia and community-acquired pneumonia.

W12-1

Relation of IgA subclass and BAFF/APRIL in the patients with interstitial pneumonia associated with collagen diseases

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Conflict of interest: None

【Purpose】We analyzed collagen diseases mainly in MCTD patients and divided them into the interstitial pneumonia complicated group (IP+) and the non-complicated group (IP-). We analyzed IgA subclass and BAFF/APRIL system in these patients.【Method】63 collagen disease patients mainly on MCTD were divided into 20 IP+ group and 43 IP- group. We analyzed IgA1, IgA2 value and BAFF-APRIL value in each patient group. Furthermore, we analyzed BAFF-APRIL receptors using flow cytometry.【Result】IP+ group had high levels of BAFF/APRIL as compared with IP- group and the healthy control group. There was no significant difference in IgA1 between these groups. However, IgA2 was significantly elevated in IP+ group compared with IP- group. Moreover, even the expression of BCMA, BAFF-R and TACI on B cells had no difference between each group, there was a tendency to decrease the expression of BAFF-R by the ratio and intensity in IP+ group.【Discussion】In recent years, relations of BAFF/APRIL and IgA subclass are reported. Our results suggest that the elevated level of BAFF/APRIL drive the maturation of B cells and subsequently lead to IgA2 class switching and may cause the development of interstitial pneumonia in the patients with interstitial pneumonia associated with collagen diseases.

W12-2

Lung diseases in male patients with rheumatoid arthritis (RA)

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Conflict of interest: None

[Objectives] In RA, lung diseases including usual interstitial pneumonia (UIP), nonspecific interstitial pneumonia (NSIP), organizing pneumonia (OP), emphysema and pleuritis are known to develop. This study focused on their prevalence in male RA patients in comparison with that in female patients. Features are also compared between patients with and without lung diseases in male patients. [Methods] In- and out-patients with RA who visited our hospital from Jan., 2006 to Apr., 2011 are included. Lung diseases were diagnosed mainly based on the medical records, XP/HRCTs, pulmonary function tests. Brinkman Index (BI), and RF, KL-6 and CRP levels are also compared. [Results] Lung diseases are observed in 27/72 (37.5%) in male and 5/70 (7.1 %) in female patients. In male patients, UIP/NSIP is observed in 20, OP in 3, emphysema in 18, pleuritis in 1. 12 had both IP and emphysema. In female, UIP in 2, OP in 2, emphysema in 1, and pleuritis in 1. 1 had both IP and emphysema. The male patients with lung diseases had the age of 72.2±10.3 (without lung diseases, 63.7±12.9), RF of 511±390 (140±141) U/mL, and KL-6 of 801±735 (277±179) U/mL. Higher BI was also seen. When their arthritis was stable, CRP level was low in patients with UIP/NSIP/emphysema, but it was high in those with OP/pleuritis.

W12-3

Increase of serum KL6/SP-D levels predicts prognosis of Patients with active interstitial pneumonitis in polymyositis /dermatomyositis.

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Conflict of interest: None

[Objectives] To evaluate clinical significance of serum KL-6 and SP-D in patients with active interstitial pneumonitis(IP) associated with polymyositis /dermatomyositis(PM/DM). [Methods] We retrospectively analyzed serum KL-6 and SP-D levels and clinical records in patients with active IP in PM/DM. [Results] Serum KL-6 and SP-D levels were within normal range in 26% and 34%

at the onset of active IP, respectively. Serum KL-6 levels were increased during 3months after starting of treatment and then were decreased gradually, whereas serum SP-D levels were peaked at 0-2weeks. Serum KL-6 and SP-D levels at diagnosis failed to predict prognosis of patients. Patients with less than 1000U/ml of KL-6 during 1st4weeks after the therapy had good prognosis. Patients with increase of KL-6/SP-D levels during 1st4weeks had poor prognosis. As additional risk factors, DM, alveolar opacities in HRCT, and increased $AaDo_2$ were identified. Multivariate analysis revealed increase of KL-6/SP-D levels during 1st4weeks as only poor prognostic factor. Patients with the ratio of KL-6 levels at 1st 4week to those at 0 weeks over 1.7 were poor in prognosis. [Conclusions] The ratio of KL-6 levels at 1st 4week to those at 0 weeks predicts prognosis of active IP in PM/DM.

W12-4

Mycophenolate mofetil therapy for intractable interstitial pneumonia in two cases of dermatomyositis

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Conflict of interest: None

Therapeutic efficacy of MMF was estimated in two patients with interstitial pneumonia (IP) and dermatomyositis (DM). Case 1: A 56 year-old female developed rapidly progressive IP with positive serum anti-CADM140 antibodies and amyopathic DM. A combined therapy was started immediately using high dose steroids, tacrolimus and intravenous cyclophosphamide (IVCY). Although partial improvement of IP was obtained, IVCY therapy had to be discontinued because of prolonged leukocytopenia, and slowly progressive respiratory failure, radiological worsening and increasing levels of serum KL-6 followed. Then, we started MMF therapy at dose of 2000mg/day, which led to improvement of respiratory functions and pulmonary shadows, and serum KL-6 levels were decreased from 4275 U/ml to 672 U/ml in eight months. Case 2: A 72 year-old female patient with DM developed exacerbation of IP, which had relapsed several times during nine-year-disease course despite maintenance steroid therapy combined with tacrolimus or cyclosporin. We changed 4mg/day of taclorimus to 2000mg/day of MMF. Thereafter, serum KL-6 levels were decreased and tapering dose of steroid was accomplished. In conclusion, MMF may be effective for progressive interstitial pneumonia accompanied by dermatomyositis.

W12-5

Prognostic factor in SSc and PM/DM associated interstitial lung disease

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Conflict of interest: None

【Objective】We investigated whether or not clinical data analyzed by the non-invasive examination, were prognostic factors for patients with SSc and PM/DM-associated ILD (SSc and PM/DM-ILD), retrospectively.【Methods】The HRCT findings in patients with 64 SSc and 46 PM/DM-ILD were classified to UIP and not-UIP patterns. We investigated the relationship between several clinical data and history and outcome in patients.【Results】Twenty-two (34.4%) in 64 SSc-ILD patients died for 2008.5 (718.5-3401.5) days as median follow-up period. Causes of death were 31.8% by infection, 22.7% by malignancy and acute exacerbation of ILD, 9.1% by deterioration of ILD and 13.6% by another causes in 22 patients. Fourteen (30.4%) in 46 PM/DM-ILD patients died for 2253.5 days as median follow-up period. Causes of death were 50% by acute exacerbation, 14.3% by deteriotation of ILD, infection, malignancy, 7.1% by another causes in 14 patients. Murtivariate analysis showed that independent poor prognostic factor were treatment without immunosuppressive angents (P=0.0179) and UIP pattern in HRCT (P=0.0149) in patients with SSc-ILD, high age (≧58 years old, P=0.0063), low %vital capacity (<70%, P=0.0461).

W12-6

The clinical efficacy and safety of bolus infusion of ulinastatin, a human urinary trypsin inhibitor to refractory interstitial pneumonia in patients with systemic connective tissue diseases

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Conflict of interest: None

[Objectives] Interstitial pneumonia (IP) complicated with systemic connective tissue diseases (SCTD) often have poor prognosis due to rapid progression of IP and treatment-associated adverse effects (AE) such as infection. Ulinastatin, a human urinary trypsin inhibitor, has anti-inflammatory and organ-protective effects. We investigated efficacy and safety of bolus infusion of ulinastatin (UT pulse). [Methods] 19 patients with IP with SCTD refractory to conventional treatments were included. The primary endpoint was CT score at 1 month after 3rd UT pulse. The secondary endpoints were KL-6, dose of corticosteroid (CS) and AE. [Results] Primary endopoint was assessed in 9 patients (MCTD 1, MPA 2, DMy 2, SSc 4) and CT scores were significantly decreased from 1.8 to 1.6 ($p<0.05$) and KL-6 titer decreased from 2153 to 1083 U/ml ($p<0.05$) within 1 month by UT-pulse therapy. Accordingly, the dose of daily CS was tapered from 29.9 to 15.5 mg ($p<0.01$). Although 2 patients treated by UT pulse with immunosuppressant had mild infections, severe adverse effects by UT pulse were not observed. Long-term repeated use of the thearapy was also effective and safe. [Conclusion] We thereby propose that UT pulse is efficacious and safe for refractory IP in the patients with SCTD.

W13-1

The efficacy and safety of treating with non-biological and biological DMARDs for elderly RA to target in Chouju registry of Rheumatoid Arthritis on Non-biological and biological DMARDs for Elderly patients (CRANE)

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Conflict of interest: Yes

[Objectives] It is unclear whether treating to target is strategies

to reach optimal outcomes of elderly RA (ERA). This study evaluated the efficacy and safety of the treatment to target in ERA. [Methods] CRANE is a prospective monocentric observational study. Treatment target was to achieve low disease activity (LDA) with sequential monotherapy. [Results] 40% of ERA patients (mean age 74, mean DAS28 6.34) achieved LDA at 52 weeks. 64% in the group achieving LDA and 70.5% in the non-achievement group started MTX monotherapy and the proportion of biological DMARDs at 52 weeks was 26.8% and 43.5%, respectively. The mean change of total sharp score was significantly lower and improvement of HAQ was significantly greater in the group achieving LDA than in non-achievement group. Incidence of severe infection was significantly lower in the group achieving LDA (hazard ratio: 0.34, 95% CI: 0.13-0.91) and HAQ remission (hazard ratio: 0.41, 95%CI: 0.18-0.95). Rates of infection were not increasing in patients receiving etanercept (hazard ratio: 0.18, 95% CI: 0.02-1.32) and anti-TNF antibodies (hazard ratio: 1.62, 95%CI: 0.75-3.51). [Conclusion] Achieving LDA in ERA with non-biological and biological DMARDs reduced the risk of joint destruction, functional disability and serious infection.

W13-2

Epidemiological study of Methotrexate-associated lymphoproliferative disorder (MTX-LPD) with rheumatoid arthritis

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Conflict of interest: None

Methotrexate (MTX) is the most common DMARDs for RA treatment. Recently, the opportunity and dosage of MTX tend to increase with RA patients. On the other hand, adverse event (AE) of MTX becomes issue in RA treatment. Especially, MTX-LPD is one of the serious AE. However, the review of MTX-LPD is not enough because of rare AE. In addition, there are some debates over whether MTX act on LPD. Our object is to characterize MTX-LPD in RA patient with MTX therapy. Additionally, we investigate the participation in LPD of MTX. We enrolled 28 MTX-LPD and 125 MTX non-LPD patients for 5753 RA patients from June 2003 to May 2011. We compared MTX-LPD to MTX non-LPD patients who were matched age and gender. We weighed the age of RA onset, Steinbrocker stage (Stage), Steinbrocker functional class (Class), duration of RA, total and average dosage of MTX, duration of MTX therapy, biologics and complication with Sjögren syndrome between two groups. By the single variable analysis between two groups, we showed significant difference with Stage, duration of RA and average dosage of MTX. Furthermore, average dosage of MTX differed significantly for the multivariate analysis. We suggested that Stage, duration of RA and average dosage of MTX could become the risk factor of the LPD onset.

W13-3

Hospitalization and risk of hospitalized infection in patients with rheumatoid arthritis based on IORRA cohort

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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 the IORRA survey, hospitalized patients from October 2009 to September 2010 were extracted based on self-report and confirmed by 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 6,168 patients, 5,182.5 person-years observation, 427 hospitalization (8.24/100 p-y) in 363 patients were confirmed. The causes of hospitalization were infection in 81 (1.56/100 p-y) in 78 patients, orthopedic diseases except planned joint surgery in 45 (0.87/100 p-y), digestive diseases in 43 (0.83/100 p-y), malignancy in 42 (0.81/100 p-y) and circulating diseases in 35 (0.68/100 p-y). Patients with hospitalized infection were older and had higher disease activity, worse physical dysfunction, lower serum albumin and frequent use of corticosteroids ($p<0.05$). The risks for hospitalized infection were low serum albumin (OR 2.6, 95%CI 1.2-6.1) and corticosteroid use (OR 2.4, 95%CI 1.4-4.3).

W13-4

Pulmonary comorbidities predispose patients with rheumatoid arthritis to serious adverse events; analyses from the REAL database

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Conflict of interest: None

[Objectives] To investigate association between pulmonary comorbidities (PC) and serious adverse events (SAEs) in rheumatoid arthritis (RA) patients. [Methods] We analyzed types and incidence rates of SAEs in Japanese RA patients with and without PC. Analysis included 359 patients with PC [PC group, 589 patients-years (PY)] and 1385 patients without PC (non-PC group, 2325 PY). [Results] In the PC group, patients were significantly older, percentage of male was higher, and patients had higher disease activity and poorer physical function. The crude incidence rate ratios comparing the PC group with the non-PC group for SAEs and serious infections (SIs) were 2.3 (95% CI 1.9-2.9) and 2.8 (2.0-3.9), respectively. In the PC group, Cox proportional hazards analysis revealed that age by decade (HR:1.5 [95% CI, 1.1-2.1]), Steinbrocker's stage (III or IV) (HR:2.0 [1.1-3.7]), and DAS28 (3)/CRP (HR:1.3 [1.0-1.7]) were significant risk factors for SIs. In the non-PC group, age by decade (HR:1.8 [1.4-2.3]), presence of diabetes (HR:2.0 [1.1-3.6]) and use of oral corticosteroids $\geq$7.5mg/day (HR:2.0 [1.1-3.5]) were identified as risk factors for SIs. [Conclusion] RA patients with PC are more vulnerable to SAE and SI than those without PC. Risk factors for SIs were different between the two groups.

W13-5

Rheumatoid arthritis is a risk factor for atherosclerosis -TOMORROW study

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Conflict of interest: None

[Objectives] Recently, cardiovascular diseases (CVD) have been recognized as important causes of mortality in patients with rheumatoid arthritis (RA). We conducted a prospective study named the TOMORROW study from 2010. In this study, we evaluated the possible association between atherosclerosis and RA by using carotid ultrasound. [Methods] As part of the TOMORROW study, 402 subjects were studied (mean age 59.0), including 200 patients with RA and 202 volunteers. We performed carotid ultrasound to assess atherosclerosis. The presence of carotid atherosclerotic plaques and plaque score defined as sum of the thickness of carotid plaques were evaluated by carotid ultrasound. [Results] The prevalence of carotid plaques (47% vs. 37%; $p<0.05$) and plaque score (1.74 vs. 1.02; $p<0.01$) were significantly greater in patients with RA than in controls. Multivariate logistic regression analyses showed that high plaque score (>3.0) was associated with RA after adjustment for atherosclerotic risk factors (OR 1.74, $p<0.05$). Furthermore, plaque score correlated with Steinbrocker stage and class in RA patients. [Conclusion] Atherosclerosis is independently associated with RA. These observations may explain at least in part the high risk of atherosclerosis and CVD observed in RA patients.

W13-6

The influence of cigarette smoking on rheumatoid factors and anti-cyclic-citrullinated antibody

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Conflict of interest: None

[Objectives] There are some reports that the cigarette smoking influences the onset of RA. The aim of this research is to examine the influence that smoking gives to RF and anti-CCP antibody. [Methods] We practiced the inventory survey to the RA patients who consulted our hospital from February to November in 2011. 875 cases were targeted for the comparison examination of the smoking habits, anti-CCP antibody, and the RF. [Results] 619 ware woman and 256 ware men. Their average was 62.5 years old (SD 12.2). The smoking rates were 53.1% of men, and 12.9% of women. And the average of smoking number and smoking period are 20 cigarettes per day and 35 years respectively. Anti-CCP antibody ($p<0.01$) and RF ($p<0.01$) of the group with the smoking habits at the onset of RA were significantly higher than that of the group with not. And RF ($p<0.05$) of the men and anti-CCP antibody ($p<0.05$) of the women who were smoking at the onset of RA were more significantly high. About the odds ratio of anti-CCP antibody and RF positive to the smoking habits, the men and women together, the positive rate of the group with smoking habits is higher. [Conclusions] More detailed examination about smoking number, smoking period and the smoking situation is necessary.

W14-1

Chromatin protein HMGB2 regulates articular cartilage surface maintenance via β-catenin pathway

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Conflict of interest: None

[Objectives] The superficial zone (SZ) of articular cartilage is critical in maintaining tissue function and homeostasis and represents the site of the earliest changes in osteoarthritis. This study addresses potential interactions between HMGB2 and the Wnt/β-catenin pathway in regulating SZ cells. [Methods] Activation Wnt/β-catenin signaling in articular cartilage was assessed by immunostaining in TOPGAL reporter mice. Functional interactions of β-catenin and HMGB2 was examined by Luciferase assay, and molecular interactions were examined by GST-pull down assays. We conditionally inactivated β-catenin in chondrocytes isolated from β-catenin floxed mice (Ctnnb1flox/flox) with adenovirus-GFP-Cre and performed apoptosis assays. [Results] We found that the Wnt/β-catenin pathway is active specifically in the SZ in mouse knee joints and co-localizes with HMGB2. HMGB2, Lef1 and β-catenin form a trimolecular complex on a promoter containing a Lef1 motif. This complex enhances the binding of Lef-1 to its target sequence and potentiates transcriptional activation. Furthermore, conditional deletion of β-catenin in cultured chondrocytes induced apoptosis. These findings define a pathway where protein interactions of HMGB2 and Lef1 enhance Wnt signaling and promote SZ chondrocyte survival.

W14-2

18F-fluoride PET uptake correlates with stress distribution in the hip joint

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Conflict of interest: None

Background/Purpose 18F-fluoride Positron Emission Tomography (fluoride-PET) is a functional imaging technique that mainly detects the acceleration of bone metabolism. The purpose of this study was to calculate stress distribution of patients with coxalgia by using the finite element analysis (FEA), and to examine its correlation with fluoride-PET uptake. **Method** Fifteen patients who had hip pain were enrolled in this study. Twenty hips with osteoarthritic or dysplastic changes have pain, and 10 hips without radiologic change have no pain. In fluoride-PET, the maximum standardized uptake value (SUVmax) was measured as an index of accumulation. FE models were obtained from CT data, and equivalent stress in the hip joint was analyzed, and compared to SUVmax. **Results** Painful hips exhibited a significantly higher SUVmax and greater equivalent stress than hips without pain($p<0.05$). A significant correlation was confirmed between SUVmax and maximum equivalent stress. ($R=0.69$ $p=0.0074$). **Discussion** The results suggest that the acceleration of bone metabolism detected by fluoride-PET was caused by mechanical stress concentration. **Conclusion** Fluoride-PET uptake and mechanical stress concentration on hip joints were correlated, and the correlation was confirmed by quantitative evaluation.

W14-3

Sensory innervation and inflammatory cytokines in synovium associate with pain transmission in the hip joint

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Conflict of interest: None

[Objectives] To clarify sensory innervation and inflammatory cytokines in hypertrophic synovia associated with pain transmission in the hip joint. [Methods] A piece of the synovium was extracted during reconstruction surgery in 50 patients with osteoarthritis of the hip as inflammatory synovium and in 12 patients with femoral neck fracture as a normal. Each sample was processed for immunohistochemistry using antibodies as follows: neuron-specific class III β-tubulin (TuJ-1) as a general marker for nerve fibers, calcitonin gene-related peptide (CGRP) for sensory nerve fibers, nuclear factor-κ B (NFκB) for the protein complex controlling the transcription of DNA in cellular responses to painful stimuli, and tumor necrosis factor-α (TNF-α) for cytokines involved in acute inflammation. [Results] In the inflammatory synovium, TuJ-1 was positive in 46% (23 hips). Of those positive for TuJ-1, 78% (18 hips) were also positive for CGRP. NFκB was positive in 68% (34 hips). Of those with NFκB positive, 76% (26 hips) were also positive for TNF-α. In the normal synovia, all four substances were negative. We suggest sensory innervation and inflammatory cytokines in hypertrophic synovia are associated with nociception in osteoarthritis of the hip.

W14-4

The effect of prostanoid selective EP4 agonist on expression of ADAMTS-4 and -5 in synovium for the preventing the development of osteoarthritis

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Conflict of interest: None

[Objectives] Possibility of roles of aggrecanases (ADAMTS-4 and 5) in synovium for the development of osteoarthritis (OA) were already reported. This time, we investigated the effect of EP4 agonist for the regulation of osteoarthritis focusing on ADAMTS-4 and -5 expression in synovium. [Methods] The synovial fibroblasts were isolated from the synovial tissue after total joint replacement surgery of OA (n=10). Confluent cells were stimulated with either interleukin (IL)-1b (10 ng/ml) with or without EP4 agonist for 24 hours in a serum-free condition and the expressions of ADAMTS-4 and -5 were quantified by realtime-PCR. [Results] Expression of ADAMTS-4 and 5 was higher in cells from the OA patients who underwent surgery within a year from the original complaint, whereas that of both were inhibited with EP4 agonist. [Summary] Our data suggest that synovial cells may participate in the development of OA, and EP4 agonist has the effect in preventing the development of osteoarthritis.

W15, W16-1

Ultrasonagraphic assessment of submandibular glands in anti-centromere antibody positive primary Sjogren's syndrome

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Conflict of interest: None

Objectives: The present study we evaluated submandibular glands (SG) by using ultrasonagraphy (US) in anti-centromere antibody positive (ACA+pSS) and negative (ACA−pSS) primary Sjogren's syndrome patients. **Methods:** Twenty ACA+pSS and 30 ACA−pSS patients were studied. SG involvement was evaluated using US staging (range 1 to 4). The pulsatility index (PI) and resistance index (RI) were calculated by the pulsed wave traces by power Doppler US at the internal SG facial arteries. **Results:** There were no significant differences between ACA+pSS and ACA−pSS patients in a median age and the amount of whole saliva by gum test. The US staging score was not significantly different between two groups (ACA+pSS; 2.45±1.1 vs ACA−pSS; 1.97±1.1), although the size of SG was significantly smaller in ACA+pSS than in ACA−pSS patients (203.0±76.0 vs 261.2±94.0 mm^2, $p<0.05$). The frequency of PI and RI measurement failure due to blood flow disappearance was higher in ACA+pSS than in ACA−pSS patients (75.0 vs 46.7%, $p<0.05$). **Conclusion:** By using US, we observed a higher frequency of SG atrophy and low blood flow in ACA+pSS as compared to ACA−pSS patients. US assessment may be useful to evaluate the differences of histopathological changes of salivary glands between ACA+pSS and ACA−pSS patients.

W15, W16-2

The correlation between salivary epidermal growth factor (EGF) levels and recurrent oral manifestations in patients with Sjogren's syndrome (SS)

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Conflict of interest: None

[Objectives] Salivary EGF plays a role in healing of damaged oral mucosa. The objective of this study was to assess changes in salivary EGF and the correlation between salivary EGF and the severity of oral manifestations in SS. [Methods] Thirty-nine patients with SS and twenty-two control subjects (non-SS) were enrolled. Saliva was collected by the gum test. Salivary EGF concentration was measured with ELISA. Oral manifestations were evaluated using the OHIP-14. The association with saliva volume, salivary EGF levels and the severity of SS-induced oral damages was analyzed. [Results] The output of salivary EGF decreased significantly in SS patients compared with control subjects ($p=0.049$). A positive correlation was found between the amount of salivary EGF and saliva volume ($rs=0.63$, $p\leqq0.01$). In SS patients without the administration of muscarinic agonisit and corticosteroid, correlation was seen more strongly ($rs=0.80$, $r=0.001$). Salivary EGF levels were correlated with the OHIP-14 score ($rs=0.75$, $p=0.01$). A negative correlation was found among salivary EGF levels and disease duration ($rs=0.47$, $p=0.008$). [Conclusion] In SS, lower salivary EGF level, that is, impairments of the saliva quality associate with recurrent oral manifestations.

W15, W16-3

Pathogenesis of spontaneous sialadenitis in orphan nuclear receptor RORgt transgenic mice

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Conflict of interest: None

[Objectives] The nuclear receptors retinoic-acid-receptor-related orphan receptors gt (RORgt) is required for the generation of Th17 cells expressing the proinflammatory cytokine interleukin (IL) -17. Recent studies showed that Th17 cells were involved in the generation of Sjögren's syndrome (SS). However, the patho-

logical role of RORgt is unknown. The aim of this study is to clarify the role of RORgt in the pathogenesis of SS. [Methods] RORgt transgenic (Tg) mice were generated by transgene of RORgt cDNA under the promoter of hCD2 into fertilized eggs from C57BL/6 mice were examined. (1) Salivary glands were investigated histologically and saliva flow was measured. (2) Cytokine expression in splenocytes stimulated with anti-CD3/28 was detected by ELISA. (3) Splenocytes from RORgt Tg mice were transferred to Rag2-/- mice (Tg→Rag2-/- mice). [Results] (1) RORgt Tg mice developed the severe sialadenitis like SS and saliva flow was decreased. (2) IFNg and IL-17 were highly produced in splenocytes of RORgt Tg mice compared with C57BL/6 mice. (3) In Tg→Rag2-/- mice, cellular infiltrations were observed in the salivary glands. [Conclution] These results suggested that the overexpression of RORgt on T cells might play a crucial role in the development of sialadenitis like SS.

W15, W16-4

Analysis of M3R reactive T cell epitopes in M3R induced autoimmune sialoadenitis

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Conflict of interest: None

<Purpose>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 M3R$^{-/-}$ mice immunized with M3R peptides mixture (N-terminal, 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) M3R$^{-/-}$ mice were immunized with 1st loop peptide alone, which was the candidate for the dominant T cell epitope, and the splenocytes were transferred into Rag2$^{-/-}$ mice (M3R1st→Rag2$^{-/-}$). On day 45 after transfer, salivary glands were histologically examined. 3) Splenocytes and cervical lymph nodes isolated from M3R1st→Rag2$^{-/-}$ mice were cultured with 1st loop peptide. The cytokines production from M3R 1st loop reactive T cells were measured by ELISA. <Results> 1) M3R reactive T cells produced IL-17 and IFN-g against 1st loop more highly than other extracellular domains of M3R. 2) Mild sialoadenitis was developed in M3R1st→Rag2$^{-/-}$ mice, and the majority of infiltrating cells were Thy1^{+} T cells. 3) M3R 1st loop reactive T cells from M3R1st→Rag2$^{-/-}$ mice produced IL-17. <Conclusion> We concluded that the major T cell epitopes in MIS might be 1st extracellular loop of M3R.

W15, W16-5

Characterization of novel autoantibody against Sjögren's syndrome nuclear antigen-1 (SSNA-1)

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Conflict of interest: None

[Objectives] We conducted the present study to clarify characteristics of anti-SSNA-1 novel autoantibody. [Methods] Reactivity for SSNA-1 protein in various autoimmune sera was measured by ELISA. Serum levels of IP-10 and BAFF were measured by ELISA. [Results] High frequency of positive sera against SSNA-1 was observed in anti- SS-A, centromere, and U1-RNP positive sera. The anti-SSNA-1 antibody was recognized only in patients with pSS and MCTD. IIF analysis revealed that the antibody stained only mitotic cells. Serum levels of IP-10 and BAFF were statistically greater in anti-SSNA-1 positive sera. [Conclusion] anti-SSNA-1 antibody appeared to be classified as novel anti-mitotic apparatus autoantibody. Moreover, IP-10 and BAFF played an important role for the autoantibody production.

W15, W16-6

SS-A/Ro52 promotes apoptosis by regulating Bcl-2 expression

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Conflict of interest: None

Objective: SS-A/Ro52, an autoantigen in SLE and Sjögren's syndrome, has been revealed to have an E3 ubiquitin ligase activity. IFN-α is known to induce the translocation of Ro52 from cytoplasm to nucleus in a p53-dependent manner. We have reported that Ro52 underwent intracellular translocation from cytoplasm to nucleus or cell surface depending on the type of stress exposures. In this study, we investigated the role of endogenous Ro52 upon stress exposure. **Methods:** We knocked down Ro52 with siRNA transfection in HeLa cells. Apoptosis was detected by flow cytometry and TUNEL assay. The levels of Bcl-2 family proteins were analyzed by Western blotting and real-time PCR. **Results:** Ro52^{low} cells were significantly more resistant to apoptosis than wild-type cells upon oxidative stress induced by H_2O_2 and diamide, as well as by various types of stimuli including IFN-α, IFN-γ & anti-Fas antibody, etoposide and γ-irradiation. Ro52-mediated apoptosis was not influenced by p53. Significantly Bcl-2 but not other Bcl-2 family molecules was upregulated by Ro52 depletion. **Conclusion:** Ro52 may be a universal pro-apoptotic molecule and its effect is exerted by negative regulation of Bcl-2. These findings add a new physiological role to Ro52, which has important roles in intracellular immunity.

W15, W16-7

Induction of aquaporin in thermotherapy strategy for Sjögren's syndrome

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Conflict of interest: None

[Objectives] Salivary gland secretion is reduced in Sjögren's syndrome. Since saliva consists of water more than 99%, aquaporins (AQPs) are very important for water transportation. It is well known that AQP-1, AQP-3 and AQP-5 are expressed in salivary gland. From the results in AQPs knockout mice, AQP-5 especially plays a major role in rapid movement of water in salivary glands. In previous studies, decrease in the expression and function of AQP-5 have been suggested to contribute to the glandular dysfunction in Sjögren's syndrome. [Methods] In this study, we investigated whether heat stress increases the expression of AQP-5 in salivary glands in experimental animals. [Results] Heat exposure of rats for 5 days increased expression of AQP-5 protein in salivary

gland. Furthermore, AQP-5 was highly expressed in the apical membranes of salivary acinar cells in histochemical analysis. Our results suggest that heat stress may improve the glandular dysfunction in Sjögren's syndrome through induction of AQP5 expression in salivary gland

W15, W16-8

Verification of diagnostic criteria for Sjögren's syndrome

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Conflict of interest: None

<Objective> To verify revised Japanese criteria for Sjögren's syndrome (SS) (JPN) (1999), revised American-European classification criteria for SS (A-E) (2002), and new classification criteria for SS proposed by the Sjögren's International Collaborative Clinical Alliance (SICCA) (2010). <Methods> 1) Study population: 55 patients with SS or SS suspected who were followed up at Tsukuba University hospital in October 2011, who had been checked about all 4 items in JPN criteria (pathology, oral, ocular, anti SS-A/SS-B). 2) Analysis: We studied the final clinical diagnosis by the physician in charge, the satisfactory rate for these criteria described above retrospectively. <Results> 1) Mean age of 55 patients: 53.4±13.8, Gender: Male 4, Female 51. 2) We regarded patients with final clinical diagnosis of SS, who satisfied at least one of these criteria, as definite SS. 48 patients were regarded as definite SS, and 7 patients were regarded as non-SS (5 of SS suspected and 2 of IgG4-related disease). 3) Sensitivity and specificity for diagnosis of 48 definite SS and 7 non-SS patients were 100% and 86% in JPN criteria, 83% and 57% in A-E criteria, 85% and 71% in SICCA criteria, respectively. <Conclusion> JPN criteria might be better for diagnosis of Japanese SS patients than others.

W15, W16-9

Clinical "Guideline2011" for the management of fibomyalgia by Japan College of Fibromyalgia Investigation (JCFI)

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Conflict of interest: Yes

Although fibromyalgia (FM) is a relatively common rheumatic disorder in elderly women, in Japan FM is not well recognized disorder among primary care physicians and rheumatologists. Japan College of Fibromyalgia Investigation (JCFI) in 2009 proposed the guideline (2009gudiline) for clinical management of FM patients in Japan at the time of limited situation for small evidence from Japanese FM patients, moreover many of evidence for management of FM patients are resulted from American or European studies. After publication of guideline2009, there are many changes in FM management in Japan; presentation of "2010preliminary diagnostic criteria" for FM by ACR, the start of clinical trials of pregabalin or new antidepressant (NaSSA), or clinical use of new analgesia (toramadol or opioid products). For more precise clinical management of FM in Japan, we revised "2009gudline" in short term, and proposed "2011gudeline" for clinical management of FM in Japan. This guideline are based on EBM in essentials for not only rheumatologists but also primary care physicians.

W15, W16-10

Fibromyalgia would be frequently misdiagnosed as spondyloarhtritis in Japan

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Conflict of interest: None

Fibromyalgia(FM) is a common rheumatic disorder in elderly women. FM and spondyloarthritis(SpA) resemble in clinical features with each other, and so frequently FM would be misdiagnosed as SpA or a some specific type of SpA. To evaluate the frequency of FM patients misdiagnosed as SpA, we analyzed the clinical pictures of FM patients from nationwide epidemiological survey and our rheumatology clinics. The 3% of FM patients from nationwide epidemiological survey are concomitant with SpA. The 13.5% of FM patients from our rheumatology clinics were misdiagnosed as SpA, before final diagnosis of FM. The 14.9% of total present FM patients fulfilled the Amor criteria for SpA(1999), however, none of FM patients did not met any criteria for SpA or a specific type of SpA (ESSG criteria, ankylosing spondylitis, enteropathic arthritis, psoriatic arthritis or reactive arthritis). From these results FM would be misdiagnosed as SpA frequently in Japan.

W15, W16-11

Fibromyalgia and climacteric symptoms

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Conflict of interest: None

(objective) A part of peri-/post menopausal women between 45 and 55 visited many different clinics, complaining of various symptoms. They include polyarthralgia and/ or arthritis, myalgia and enthesitis, suggesting of early stage of rheumatoid arthritis. Moreover, fibromyalgia was also suspected in addition of general fatigue, depression and sleepless. Receiving hormone replacement therapy (HRT) for two months is useful for differentiating from rheumatoid arthritis, fibromyalgia and menopausal arthritis. (Methods) Patients include 20 cases of FM (M:F=4:16) and 20 cases of climacteric symptoms. Mean age of FM was 51(27~69) and climacteric women was 53 (48~62). Regular HRT was administered in 11 of 16 women with FM. Climacteric symptoms was judged by simplified menopausal index(SMI). (Results) Mean J-FIQ score was 73 in 20 patients with FM and mean SMI was 57 in 16 with female FM. Among 11 patients, HRT was very effective in 4, effective in 3 and not effective in 4 patients with FM. At least 7 FM patients were satisfied with receiving HRT. On the other hand, HRT was effective in 90 % of women having climacteric symptoms. Two patients were found to have depression. (Conclusion) HRT is useful for differentiating from FM and climacteric symp-

toms.

W17-1

Results of a phase 2 randomized, double-blind, placebo-controlled study of mavrilimumab (an anti-GM-CSFRα monoclonal antibody) in subjects with rheumatoid arthritis

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Conflict of interest: None

Objectives: Mavrilimumab (MAV) is being evaluated in an international phase 2 study of up to 264 Japanese and Caucasian moderate/severe RA subjects. **Methods:** A preliminary analysis included 233 adult subjects: MAV 158; placebo (PBO) 75. Subjects were randomized 2:1 to subcutaneous MAV (10mg/30mg/50mg/100mg) or PBO in this ascending dose study. The primary endpoint (EP) was % subjects achieving DAS28-CRP decrease ≥1.2 from baseline vs PBO at wk 12. **Results:** Most subjects (MAV 149 [94%]; PBO 67 [89%]) completed the study; 1 (0.4%) MAV and 2 (0.9%) PBO discontinued due to AEs. 55.7% MAV vs 34.7% PBO subjects (*P*=.003*)* achieved the primary EP of the study. Most secondary EPs followed a similar trend. Clinical responses observed within ~2 wks achieved statistical significance against PBO by 4 wks. The 100mg group showed significant improvement vs PBO in the primary EP (*P*=.001); DAS28-CRP remission (*P*=.016); ACR20/50/70 (*P*=.005; .021; and .030, respectively); and HAQ-DI response (*P*=.009). SAEs reported in 3 (1.9%) MAV and 1 (1.3%) PBO were assessed as not treatment related. No hypersensitivity reactions, serious/opportunistic infections, or changes in pulmonary parameters were reported. The findings from this study support further clinical development of MAV for the treatment of RA.

W17-2

Phase 2 Study of LY2439821, an Anti-IL-17 Monoclonal Antibody, in Rheumatoid Arthritis (RA) Patients who are Inadequate Responders to Tumor Necrosis Factor Alpha Inhibitors (TNFi)

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Conflict of interest: Yes

[Objectives] To evaluate the anti-IL-17 antibody, LY2439821 (LY), in RA patients with inadequate response to TNFis. [Methods] RA patients were randomized to placebo (PB) [n=64], LY 80 mg [n=65] or 180 mg [n=59] at Weeks 0, 1, 2, 4, 6, 8, and 10 administered subcutaneously. At week 12, the ACR20, ACR50 and ACR70 response rates were evaluated as well as the DAS-28-CRP response and safety. [Results] More patients achieved ACR20 in the LY 80 mg (40%) and 180 mg (39%) groups compared to placebo (23%, p<.05). More patients achieved an ACR50 in the 80 mg (20%) and 180 mg (17%) groups compared to placebo (8%, p<.05). Significant differences versus PB were also observed for DAS28-CRP and ACR70 responses. Significant ACR20 and CRP responses were seen starting at Week 1. The frequency of TEAEs through Week 12 was similar across treatment arms (range: 61-64%). Infections were more frequent in LY arms compared to PB (27 vs 23%). Treatment-emergent SAEs occurred in 1 (1.6%) PB pt and 10 (8.1%) LY pts (5 [4%] were considered drug related), and serious infections occurred in 4 (3.2%) patients in LY arms. LY significantly improved signs and symptoms of RA compared to PB with a rapid onset of action with no unexpected safety concerns.

W17-3

Phase 2 Study of LY2439821, an Anti-IL-17 Monoclonal Antibody, in Rheumatoid Arthritis (RA) Patients Naïve to Biologic Therapy

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Conflict of interest: Yes

[Objectives] To evaluate anti-IL-17 antibody, LY2439821 (LY), in RA patients naïve to biologic treatment. [Methods] Patients were randomized to placebo (PB) [n=54] or LY (3 mg [n=40], 10 mg [n=35], 30 mg [n=37], 80 mg [n=57], or 180 mg [n=37]) administered subcutaneously at Weeks 0,1,2,4,6,8, and 10. The primary objective was dose-response relationship of LY at Week 12 in ACR20 response rates. [Results] A significant dose-response was observed at Week 12 (p=.031). ACR20 ranged from 51-70% at the three highest doses vs. 35% in PB. Significant effects on ACR20 and CRP responses were seen starting at Week 1. More patients achieved an ACR50 in the 10 mg (29%), 30 mg (30%), 80 mg (26%) and 180 mg (27%) groups than in PB (9%, p<.05). Significant differences vs PB were also observed for ACR70 and DAS-28-CRP responses. The frequency of TEAEs was similar across treatment arms (range: 49-61%). Infections were more frequent in combined LY arms compared to PB (25 vs 19%). Treatment-emergent SAEs occurred in 1 (1.9%) PB and 6 (2.9 %) LY pts (2 [1.1%] were considered drug related) with 1 serious infection-related event in LY 80 mg group. LY significantly improved signs and symptoms of RA compared to PB in biologic-naive patients with a rapid onset of action and no unexpected safety concerns.

W17-4

Long-term safety and efficacy of Abatacept for Japanese Rheumatoid arthritis patients (Phase III): 192weeks results

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Conflict of interest: Yes

[Objectives] To assess the long-term safety and efficacy of Abatacept (ABA) in Japanese Rheumatoid arthritis (RA) patients. [Methods] This phase III study was a multi-center, open-label, long-term extension. It consisted of 3 cohort. ABA 10mg/kg + MTX was administered to patients who had participated in Phase I or Phase II. Newly recruited patients who were intolerant with MTX administered to ABA 10mg/kg. The longest treatment period was week 192. [Results] The number and average exposure period (year) were Phase I: 13 (3.36), Phase II: 178 (2.92), New: 26 (2.15) were analyzed safety. There was no specific adverse event that increased and ABA was well tolerated by week 192. The most common AE was nasopharyngitis 56.7%(123/217). ACR20 increased and maintained steadily over the study period in entire cohort, week24: 62.7%(133/212), week48: 65.7%(132/201), week96: 65.8%(125/190), week144: 70.1%(117/167). The ratio of patients who achieved DAS28-CRP<2.6, week24: 34.3%(72/210), week48: 42.2%(84/199), week96: 43.9%(83/189), week144: 46.7%(78/167), increased and maintained steadily over the study period in entire cohort. In this study, the long-term ABA safety and efficacy were confirmed.

W17-5

Comparison of Subcutaneous Tocilizumab Monotherapy Versus Intravenous Tocilizumab Monotherapy: Results from a Double-blind, Parallel-group, Comparative Phase III Non-Inferiority Study in Japanese Patients with Rheumatoid Arthritis: MUSASHI study

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Conflict of interest: Yes

[Objectives] To compare the efficacy and safety of subcutaneous (SC) and intravenous (IV) tocilizumab (TCZ) in Japanese patients with rheumatoid arthritis (RA). [Methods] Patients with RA who had responded inadequately to any synthetic DMARDs or any biologics were randomized to receive SC TCZ 162 mg Q2W (TCZ-SC) or IV TCZ 8 mg/kg Q4W (TCZ-IV) without any DMARDs. The primary endpoint was non-inferiority (non-inferiority margin: 18%) of TCZ-SC versus TCZ-IV by the ACR20 response rate at Week 24. [Results] A total of 346 patients received at least one dose of the study drug. Baseline demographics were similar across the TCZ-SC and TCZ-IV groups. At Week 24, 79.2% in the TCZ-SC group and 88.5% in the TCZ-IV group achieved ACR20, and the non-inferiority of TCZ-SC against TCZ-IV was confirmed. The incidence of adverse events (AEs) over 24 weeks was 89.0% and 90.8% in the TCZ-SC group and the TCZ-IV group, respectively. There were no deaths. Incidences of serious AEs and serious infections were 7.5% and 1.2%, respectively, in the TCZ-SC group, and 5.8% and 2.9%, respectively, in the TCZ-IV group. [Conclusion] Non-inferiority of TCZ-SC against TCZ-IV was demonstrated. Both TCZ-SC and TCZ-IV were well-tolerated. The clinical safety profile of TCZ-SC was consistent with that of TCZ-IV.

W17-6

Pharmacoeconomic analysis of a humanized anti-Interleukin-6 (IL-6) receptor monoclonal antibody, tocilizumab, in rheumatoid arthritis using IORRA cohort database

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Conflict of interest: None

[Objectives] In Japan, substantial evidence regarding the efficacy and safety of tocilizumab for RA has been accumulated. However, the cost-effectiveness of treatment with tocilizumab has not been analyzed. [Methods] We investigated the cost-effectiveness of tocilizumab (TCZ group) compared with methotrexate alone (MTX group) using a Markov model. Markov states were defined based on the levels of dysfunction according to the J-HAQ score, and transition probabilities between those states were assumed to differ among two groups. Most parameters in the model including direct and indirect medical costs were based on clinical data from the IORRA cohort. Lifetime costs and quality adjusted life years (QALYs) were estimated in both groups. [Results] The incremental cost-effectiveness ratio for the TCZ group compared with the MTX group was 5.39 million JPY per QALY gained, indicating that tocilizumab is cost-effective in Japan based on the reported threshold (5.40 million JPY per QALY). QALYs in the TCZ group were 11.70, substantially higher than those observed in the MTX group (9.24). [Conclusion] This study has demonstrated the cost-effectiveness of tocilizumab for the first time, based on data from a large observational cohort representing daily clinical practice in Japan.

W18-1

A Study of Response to Therapy by Biologics

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Conflict of interest: None

[Objectives] To consider whether or not the associations with inflammatory cytokines of rheumatoid arthritis (RA) patients who achieved remission, and RA patients who could not, can assist in the biologics selection. [Methods] Comparisons of TNFα and IL-6 values before therapy and upon achievement of remission or discontinuation were made in a total of twenty cases, five cases in each of the Infliximab(INF) therapy group and the Tocilizumab(TOC) therapy group in which SDAI<3.3 was achieved, and five cases in each group in which therapy was discontinued due to insufficient effect. [Results] In the remission group(RG) with INF therapy, there were significant diminutions of the TNF (41.26pg/ml→10.63pg/ml) and of the IL-6 (79.55pg/ml→2.32pg/ml). In the non-remission group(NRG) there were no changes in the TNF value and the IL-6 value which remained high. The TNF value was higher in the NRG, whereas no difference was found for the IL-6. In the RG with TOC therapy, there were significant diminutions of the TNF(17.42pg/ml→4.74pg/ml) and almost no changes in the IL-6 value. In the NRG there was a diminution of the TNF value although it remained high, and an increase of the IL-6 value. The serum TNFα level is useful in the selection of the INF and TOC therapies.

W18-2

Prediction of treatment with abatacept for rheumatoid arthritis patients by using multi-cytokine ELISA system

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Conflict of interest: None

OBJECTIVE: To examine the efficacy of abatacept(ABT) for rheumatoid arthritis(RA) patients and predict the efficacy of ABT treatment by using serum or plasma levels of cytokines. **METHODS:** Clinical data of 65 RA patients was collected. The levels of

cytokines, IL-6, TNFα, IL-1β, IL-2, IL-8, IL-10, IL-12p70, IFN-γ, GM-CSF were quantified using multi-cytokine ELISA(SECTOR imager, MSD). Measurements were made at Week 0, Week 2 and Week 12 of treatment with ABT in 36 RA patients. Predicive factors at Week 12 was evaluated. **RESULTS:** The mean age was 64.9 years, with the mean disease duration of 10.3 years. Percentage of previous usage of other biologics was 28%. Remission rate of DAS28-CRP/SDAI/CDAI was 14/16/12% at Week 12 and 13/26/26% at Week 24. Good/moderate/no EULAR response rate at Week12 was 33%/47%/20% respectively. Negative correlations to EULAR response at Week 12 were long disease duration, joint destruction and disability at Week 0. Among 27 patients whose EULAR response at Week 12 were moderate or good, 25 patients' ratio of the levels of IL-8 at Week 2 to Week 0 was smaller than 3.5(92.6%). **CONCLUSIONS:** ABT demonstrated sustained efficacy in Japanese RA patients. Ratio of IL-8 at Week 2 to Week 0 was a possible marker to predict the efficacy of ABT at Week 12.

W18-3

The effects of TCZ on serum TNFα levels in patients with rheumatoid arthritis

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Conflict of interest: None

[Background] Tocilizumab (TCZ) is a novel monoclonal antibody that competitively inhibits the binding of interleukin-6 to its receptor. However, it has not been clear that changes of the cytokine levels *in vivo* after TCZ infusion. [Objectives] To investigate the effects of TCZ on serum TNFα levels in patients with RA. [Methods] Twenty-three patients with refractory RA were treated with TCZ and serum TNFα levels measured by ELISA were compared at baseline, 6 and 12 month (m.) after induction of TCZ. [Results] Significant clinical responses were observed in all patients from baseline to 6 m. and 12 m. (DAS28-ESR; baseline 5.49 ± 1.31, 6 m. 2.51 ± 1.25, 12 m. 1.94 ± 1.16). We analyzed the data by patient characteristics. Interestingly, the changes of TNFα levels divided two groups by the treatments before. In 7 patients with inadequate response to one or more TNF antagonists, serum TNFα levels were elevated at baseline and decreased at 6 m. after TCZ infusion. In the other 16 bio-naïve patients, serum TNFα levels increased at 6 m. compared with baseline, and decreased gradually at 12 m. [Conclusion] Clinical responses by TCZ infusion were significantly regardless of increased TNFα levels. The effects of TCZ on serum TNFα levels depended on former therapy.

W18-4

The effect of Tocilizumab is predictable in the early stage

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Conflict of interest: None

[Objectives] Some study to predict the effects of biologics were examined but useful factors have not been identified. In addition, the efficacy of tocilizumab (TCZ) is revealed slowly, it is difficult to determine the effect in early stage. Thus, we investigated the predictor for TCZ efficacy. [Methods] Thirty-three patients who treated TCZ more than 12 weeks (four males, 47 females) were included. The mean age was 59.4 ± 14.6, disease duration was 12.6 ± 10.7 years. Serum IL-1beta, D-dimer and fibrinogen were measured before administration of TCZ and four weeks after treatment. DAS28-ESR and CDAI were used for clinical assessment. [Results] The group in which serum IL-1beta decreased after four weeks and serum IL-1beta was below detection limit at the baseline were reduced DAS28-ESR from 5.30 to 2.79 and 5.44 to 2.88 respectively. On the other hand, in the group in which serum IL-1beta increased after four weeks, the change of DAS28-ESR was less from 5.47 to 3.79. In addition, the decrease of fibrinogen and DAS28-ESR showed significant correlation ($p<0.01$ $r=0.44$). D-dimer did not affect the prediction of clinical result. The change of serum IL-1 beta and fibrinogen from baseline to 4 weeks after may predict the effect of the TCZ.

W18-5

Analysis of serum IL-6 levels in RA patients treated with Tocilizumab.

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Conflict of interest: None

[Objectives] The aim of this study is to define the diagnostic potential of serum IL-6 concentration for RA activity and adverse events under Tocilizumab therapy. [Methods] 53 RA patients receiving Tocilizumab were investigated. Mean age was 59.8 years and mean disease duration was 13.9 years. Mean follow-up period was 41.3 weeks. Patients were subdivided into two groups according to the maximum serum IL-6 concentrations exceeding 30 pg/ml or not at 12, 24, 36 and 48 weeks. Disease activity, CRP and Serum IL-6 levels were monitored every month. IL-6 levels were additionally measured in case of adverse events. The relationship between IL-6 concentration and disease activity or adverse event was analyzed. [Results] At 24 weeks, serum IL-6 levels were higher than 30 pg/ml in 15 patients and lower than 30 pg/ml in 27 patients. Lower serum concentration of IL-6 levels was significantly related to RA remission as judged by DAS-ESR and CDAI. However, no significant relationship was observed at 12, 36, or 48 weeks. A rapid increase of serum IL-6 levels above 500 pg/ml was observed in cases of adverse events, such as infection or liver injury, preceding elevation of CRP. [Conclusion] Serum IL-6 level might be a good marker to diagnose RA activity or adverse events under Tocilizumab therapy.

W18-6

Examination of Pentraxin3 (PTX3) measurement in RA patients treated with Tocilizumab.

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Conflict of interest: Yes

[Objectives] PTX3 is a secreted inflammatory molecule which is expressed in response to IL-1β and tumor necrosis factor alpha (TNFα), in various cell types (endothelial cell, neutrophil, macrophage), and recently, PTX3 attracts attention as marker of vasculi-

tis and as activity of ischemic heart disease. Tocilizumab was recognized as medication of RA in 2008, and was used as treatment of RA. It has the characteristic which is down CRP. In the present study, we measure serum PTX3 and examined the relevance of PTX3 and inflammatory marker, disease activity. [Methods] We measured 56 RA patients treated Tocilizumab in our hospital, and analyze the relation of PTX3 and CRP, ESR, MMP-3, CH50, DAS 28(ESR4), LDL-cholesterol. [Results] PTX3 was significantly correlated with CRP LDL-cholesterol, although it was not correlated with ESR, MMP-3, CH50 and DAS 28(ESR4). Three patients complicated with some infection treated with Tocilizumab. Only one patient elevated PTX3 and the other patients were not elevated PTX3. [Discussion] We suggest that PTX3 is not connected with evaluation of the disease activity of RA except for some case which complicated with infection.

W19-1

Analysis on Results of Japanese Clinical Trials with Golimumab (Simponi®) in Patients with Rheumatoid Arthritis (2): Clinical Efficacy and Blood Golimumab Concentration

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Conflict of interest: Yes

Objectives: To assess the relationship between efficacy and exposure of golimumab (GLM) in Japanese clinical trials. **Methods:** Blood GLM concentration (24w, 52w) in GO-FORTH (MTX resistant patients (pts): 261) and GO-MONO (DMARDs resistant pts: 308) were integrated and subgrouped with quartile points, and compared improvement rates on ACR20, 50, 70 and inhibition rate on progress of joint destruction (ΔTSS≤0). The influence of expressed anti GLM antibodies on efficacy and GLM in blood was examined. **Results:** ACR improvement rates were increased above 0.98μg/mL (24w) and 0.62μg/mL (52w) in blood concentration in GO-FORTH and were lower than other groups below 0.24μg/mL (24w) and 0.45μg/mL (52w) in GO-MONO. The highest inhibition rates were marked with above 1.70μg/mL (69.4% at 24w, 72.2% at 52w) and 1.53μg/mL (60.0% at 24w, 57.8% at 52w), respectively. Anti GLM antibodies were observed in 10 pts (3.6%) at 24w and 8 pts (3.1%) at 52w only in GO-MONO with ACR improvement decreased. Blood GLM concentration was lower in anti GLM antibody positive pts. **Conclusion:** Blood GLM concentration was higher in GO-FORTH than in GO-MONO, however, clinical efficacy was increased along with elevation of blood GLM concentration in both studies.

W19-2

Certolizumab pegol improved physical function and health-related quality of life in patients with active Rheumatoid Arthritis who could not be treated with methotrexate: results form HIKARI study

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Conflict of interest: Yes

[Objectives] To assess the impact of certolizumab pegol (CZP) on physical function and Health-Related Quality of Life (HRQoL) in patients with active rheumatoid arthritis (RA) in whom methotrexate (MTX) could not be administered. [Methods] In this 24-week, multicenter, double-blind, randomized, placebo-controlled study (NCT00791921), Japanese patients with active RA who could not be treated with MTX were randomized to 1 of 2 treatment groups: CZP 200 mg or placebo (PBO) subcutaneously every 2 weeks. [Results] A total of 230 pts were randomized. ACR20 response rates at week 12 in CZP and PBO groups were 67.2% and 14.9%, respectively. ACR20 and ACR50 response rates were significantly higher in the CZP group than in the PBO group at weeks 12 and 24. As early as week 1 through week 24, HAQ-DI was improved in the CZP group compared to that in the PBO group. CZP showed significantly greater improvements in both the physical and the mental components of the SF36 than PBO at weeks 12 and 24. [Conclusion] Treatment with CZP resulted in a rapid and sustained reduction in RA signs and symptoms, and improved physical function and HRQoL in Japanese RA patients who cannot be treated with MTX.

W19-3

Certolizumab pegol improved physical function and health-related quality of life in patients with active Rheumatoid Arthritis despite treatment with methotrexate: results from the JRAPID study

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Conflict of interest: Yes

[Objectives] To assess the impact of Certolizumab pegol (CZP) with methotrexate (MTX) on signs and symptoms, physical function and Health-Related Quality of Life (HRQoL) in patients with rheumatoid arthritis (RA). [Methods] In this 24-week, multicenter, double-blind, randomized, placebo-controlled, study (NCT00791999), 316 patients with active RA who had an inadequate response to MTX were randomized to CZP 100, 200, 400 mg or placebo (PBO) subcutaneously every 2 weeks + MTX. [Results] ACR20 response rates at week 12 in CZP 100, 200, 400 mg and PBO groups were 62.5%, 76.8%, 77.6%, and 28.6%, respectively. As early as week 1 through week 24, HAQ-DI was improved in the CZP group compared to that in the PBO group. Improvements of HAQ-DI at week 24 were -0.43, -0.55, and -0.57 in CZP groups, vs -0.18 in PBO group. CZP 200 and 400 mg showed significantly greater improvements in the physical and the mental components summary of the SF36 than PBO at weeks 12 and 24. [Conclusion] CZP + MTX showed rapid and sustained reduction in RA signs and symptoms, and improved physical function and HRQoL in RA patients who had an inadequate response to MTX.

W19-4

Efficacy and Safety Evaluation of Iguratimod, a Novel Anti-rheumatic Agent –Iguratimod-MTX Combination Study (52 weeks) in Rheumatoid Arthritis Patients with an Inadequate response to MTX

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Conflict of interest: Yes

[Objectives] This study evaluated the efficacy and safety of a combination of iguratimod (T-614) and MTX (52 weeks) in RA patients with an inadequate response to MTX. **[Methods]** This study was conducted in RA patients with an inadequate response to MTX. Upon completion of a comparison study (24 weeks) of T-614-MTX combination therapy, T-614 + MTX Group received T-614 until Week 52 and placebo + MTX Group received T-614in substitution of placebo until Week 52. Folic acid was orally administered in all patients at 5 mg/week. **[Results]** Of 165 patients in T-614 + MTX Group, 132 patients completed the 52-week of treatment. Response rates of ACR20, ACR50 and ACR70 at Week 52 were 71.3%, 49.4% and 23.8%, respectively. Incidence of adverse reactions was 65.2% and frequently reported adverse reactions were gastrointestinal disorders, infections including nasopharyngitis, and abnormal clinical laboratory test values. Serious adverse reactions of gastroduodenal ulcer and interstitial lung disease each were reported in a patient by Week 24. Results of the group switching from placebo to T-614 are also included in this report. **[Discussion]** A combination therapy of T-614 and MTX in RA patients with an inadequate response to MTX was well tolerated for a long period and considered to be effective.

W19-5

Inhibitory effects of the JAK inhibitor CP690,550 on cytokine induction in human CD4$^+$ T lymphocytes

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Conflict of interest: None

Objective: The present study was undertaken to assess the effects of CP690,550 on cytokine production and cellular signaling in human CD4$^+$ T cells. ***Methods:*** Human CD4$^+$ T cells isolated from peripheral blood samples from healthy subjects were activated by stimulation with anti-CD3 monoclonal antibodies. Cytokine production was measured by enzyme-linked immunosorbent assay and mRNA was measured by real-time polymerase chain reaction. STAT-activation status was analyzed by Western blot. ***Results:*** CD4$^+$ T cells produced IL-2, IL-4, IL-17, IL-22 and IFN-γ in response to anti-CD3 antibody stimulation. CP690,550 almost completely inhibited the production of IL-4, IL-17, IL-22 and IFN-γ at the optimal concentration (500nM). However, CP690,550 only marginally affected IL-2 production from these activated CD4$^+$ T cells. Moreover CP690,550 inhibited anti-CD3-induced phosphorylation of STAT1, STAT3, STAT4, STAT5, and STAT6, but not the TCR-associated phosphorylation of ZAP-70. ***Conclusions:*** These findings suggest that JAK inhibition using CP690,550 induces immunosuppression by abrogating the induction of the Th1, Th2 and Th17-related cytokines. CP690,550-mediated modification of the JAK/STAT pathway may be a new immunosuppressive strategy in the treatment of autoimmune diseases.

W19-6

Molecular mechanism of new inflammatory drug that inhibits NF-κB induced transcription

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Conflict of interest: None

[Objectives] We found a small nuclear protein (abbreviated as MTI-II), which is a new member of the glucocorticoid-receptor/co-activators complex. MTI-II plays an important role both in hormone action and in anti-inflammation. MTI-II binds to NF-κB directly and inhibits transcription activity of NF-κB. MTI-II protein is expected to show anti-inflammatory effects as strong as glucocorticoids when used as an anti-inflammatory drug. However, MTI-II is a protein, therefore it does not move into the cell by itself. [Methods] To solve this problem, we have constructed two proteins of MTI-II fused with protein transduction domain (HM11R and H11RM). We then examined whether these protein show the anti-inflammatory activity in inflammatory model animals. [Results] We demonstrated that HM11R and H11RM successfully showed anti-inflammatory effects. Here, we analyzed the biochemical characters of the HM11R and H11RM proteins. A patent of this work has been applied in JPN (PCT/JP2005/11851), US (11/631,202 allowed) and EU (05755776.1).

W20-1

Association of intrarenal B cell infiltrates with clinical outcome in lupus nephritis: a prospective study of 192 cases

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Conflict of interest: None

Lupus nephritis (LN) in systemic lupus erythematosus (SLE) remains a major cause of morbidity and end-stage renal disease. Dysfunction of B lymphocytes is thought to be important in the pathogenesis of SLE/LN. In this study, intrarenal B cells were analyzed in 192 renal biopsies from patients diagnosed with lupus nephritis. Intrarenal B cells were more likely to be associated with class IV LN and were mainly distributed in the renal interstitium, with very few in the glomerulus. The Systemic Lupus Erythematosus Disease Activity Index (SLEDAI), blood urea nitrogen and serum creatinine levels were all significantly greater in the LN-B cell groups compared with the LN-non-B cell group (all $P<0.05$). LN renal activity and chronicity indices correlated with B cells infiltrates (all $P<0.0001$). Renal biopsies were classified into four distinct categories according to the organizational grade of inflammatory cell infiltrates. Germinal center (GC)-like structures

were not identified in any LN biopsies. It is hypothesized that intrarenal B cells enhance immunological responses and exaggerate the local immune response to persisting autoimmune damage in the tubulointerstitium.

W20-2

Elevation of the numbers of glomerular fibroblast-specific protein 1(FSP1) expressing cells and urinary FSP1 levels in active lupus nephritis

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Conflict of interest: None

Fibroblast-specific protein1(FSP1) is one of S100 Ca binding proteins, which is a family of secreted and cytosolic proteins. Recently, FSP1 expressing cells ($FSP1^+$ cells) are reported to accumulate in kidneys showing renal damage. In this study, we evaluate glomerular $FSP1^+$ cells (g-$FSP1^+$ cells) and urinary FSP1(u-FSP1) levels of patients with lupus nephritis(LN)(n= 70). The g-FSP1+ cells counts were significantly elevated in LN of WHO IV, in comparison to that of WHO I, II, V. The g-$FSP1^+$ cells counts were significantly correlated with the activity of LN. In addition, u-FSP1 levels also significantly increased in patients with LN of WHO IV, in comparison to that of WHO I, II, V, and u-FSP1 levels were significantly correlated with g-$FSP1^+$ cells counts. In conclusion, the accumulation of g-$FSP1^+$ cells and the increase of u-FSP1 levels may be related with the activity of LN, therefore, u-FSP1 levels may be a useful marker for LN activity.

W20-3

Frequency and predictive factors of ISN/RPS class III and IV lupus nephritis in SLE patients without clinical renal involvement

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Conflict of interest: None

[Objectives] To determine the frequency and predictive factors of ISN/RPS class III and IV lupus nephritis in SLE patients without clinical renal involvement. [Methods] The 195 renal samples biopsied at our institute between 1994 and 2005 were histologically classified according to ISN/RPS classification. We analyzed the frequency and predictive factors of class III and IV lupus nephritis in two subsets, patients with and without clinical renal involvement. [Results] Number of enrolled patients with and without clinical renal involvement was 109 and 86, respectively. The frequency of class III and IV with and without clinical renal involvement was 70 patients (64%) and 14 patients (16%), respectively. Longer disease period, higher anti-DNA antibody titers and lower C3 were revealed in class III and IV without clinical renal involvement, as compared from other classes. The sensitivity and specificity values predicting the development of class III and IV were 77% and 73% for cut off levels of both 40 IU/mL for anti-dsDNA antibody and 55 mg/dL for C3 (odds ratio 8.8, P = 0.0011). [Conclusion] ISN/RPS class III and IV lupus nephritis could be hidden in SLE patients with both a high anti-dsDNA antibody and a low C3, even when they don't have active urinary findings or renal function.

W20-4

Calcium/calmodulin-dependent protein kinase type IV is essential for mesangial cell proliferation and lupus nephritis

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Conflict of interest: None

[Objectives] Renal involvement in systemic lupus erythematosus (SLE) remains a major cause of morbidity and mortality. Although immune parameters that instigate renal damage have been characterized, their link to local processes, which execute tissue damage, is poorly understood. Previously reported that calcium/calmodulin-dependent protein kinase type IV (CaMKIV) is upregulated in SLE T cells and contributes to altered cytokine production. Using genetic deletion and pharmalogical inhibition approaches we observed the role of CaMKIV in lupus nephritis. [Methods] Primary mesangial cells(MC) were isolated from 8 weeks old of MRL*/MPJ*, MRL*/lpr* and MRL*/lpr. Camkiv-/-* mice. We analyzed cell cycle signal by flow cytometry and westernblot. IL-6 production was measured by ELISA and PCR. IL-6 promoter activity through AP-1 binding was also analyzed by Electrophoresis Mobility Shift Assay. [Results] We provide evidence that pharmacologic inhibition or genetic depletion of CaMKIV in lupus-prone MRL/*lpr* mice results in decreased mesangial IL-6 production, reduced MC proliferation and less kidney damage trough suppression of AP-1 binding in IL-6 promoter. Our data suggest a prominent role for CaMKIV not only in expression of systemic autoimmunity, but also that of local renal damage.

W20-5

Methotrexate combined with intravenous cyclophosphamide therapy overcomes P-glycoprotein-induced multidrug-resistance inof SLE patients with intractable refractory lupus nephritis

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Conflict of interest: None

P-glycoprotein (P-gp) overexpression on activated lymphocytes is associated with active efflux of drugs from the cells, resulting in the development of drug resistance. When lupus nephritis (LN) progressed despite the use of TAC, AZ, MZ and RTX, lymphocyte significantly infiltrated in renal interstitial tissue and P-gp was expressed on active peripheral $CD69^{high}CD4^+$cells producing IL-2, IL-4 and IL-6 spontaneously. MTX with monthly IVCY markedly reduced multidrug-resistant active $CD4^+$cells ($P\text{-}gp^{high}CD69^{high}CD4^+$cells producing interleukin s) in LN patient, along with improvement of clinical symptoms, which resulted in long-term remission and tapering of corticosteroid (CS). However, multidrug-resistant active CD4 cells were remained in the patient whose disease activity was not controled despite high dose CS with biweekly IVCY which suppressed humoral immunity. The unresponsiveness to conventional therapies in patients with highly active LN might be mediated by P-gp overexpression on activated $CD4^+$cells. Therefore, inhibition of CD4-mediated disease activity and down-regulation of P-gp expression on CD4 cells by by control of humoral and cellular immunity with MTX-IVCY therapy needs to be considered to overcome unresponsiveness to conven-

tional therapies.

W20-6

Efficacy and safety of multitarget therapy by combination with tacrolimus, mycophenolate mofetil and steroid in patients with active lupus nephritis

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Conflict of interest: Yes

[Objective] In the current study, we retrospectively analyzed the efficacy and safely of multitarget therapy using TAC, mycophenolate mofetil (MMF) and steroid for induction therapy in patients with active LN. [Methods] All 8 patients with active LN (ISN/RPS 2003 class III, IV, V) who were treated with multitarget therapy for induction therapy between Oct. 2009 and Jan. 2011 in our department were included in this study. The average patient age was 34.8 ± 9.0 years. Three patients were treated for LN for the first time, whereas 5 patients were treated for LN flares. The mean serum creatinine level and urinary protein/creatinine ratio before treatment were 0.61 ± 0.15 mg/dL and 5.0 ± 2.9 g/gCr, respectively. Six patients received a renal biopsy immediately before the induction therapy: 1 with class IV-G(A), 1 with class IV-S(A/C)+V, 1 with class IV-G(A/C)+V and 3 with class V, according to the ISN/RPS classification. Two patients had received one previously: 1 with class III(A) and 1 with IV-G(A). [Results] All the patients achieved a complete remission (CR) at 5.4 ± 4.9 months after the administration. CR rate at 6 months was 75%. There was no serious adverse event. [Conclusion] The present study showed that multitarget therapy was an effective induction therapy for active LN.

W21-1

The 1st interim analysis of a prospective cohort study of ANCA-associated vasculitides in Japan, the RemIT-JAV study

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Conflict of interest: None

[Objectives] To investigate the effectiveness and safety of remission induction therapy currently performed for ANCA-associated vasculitides (AAV) in Japan. [Methods] AAV patients enrolled in the RemIT-JAV study undertaken by the MHLW intractable vasculitis research group were categorized by severity according to BSR/BHPR guidelines and information relating to remission induction therapy was collected. [Results] Data from 132 of 156 patients became available by March, 2011. All patients used corticosteroid (CS), and concomitant cyclophosphamide (CY) was used in 33.3 % (11/33) of patients with localized/early systemic disease and in 35.3% (35/99) of generalized or severe disease. Remission rates at 6 months of treatment for localized/early systemic disease in patients treated with and without CY were 90% and 95%, respectively. Similarly, remission rates for generalized or severe disease with and without CY were 86% and 91%, respectively. Two and five patients with generalized or severe disease treated with and without CY died by 6 months, respectively. These data indicate that Japanese patients with AAV may respond well to CS therapy, irrelevant to concomitant CY, at least in terms of initial remission induction. Further analysis is warranted to determine a role of CY in long term.

W21-2

Hypertrophic pachymeningitis with ANCA associated vasculitis successfully treated with Methotrexate: Report of four cases

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Conflict of interest: Yes

Hypertrophic pachymeningitis (HP) is an inflammatory fibrous process which involves the dura matter. We report four cases of HP with ANCA associated vasculitis: the two are microscopic polyangitis and the others are granuromatous with polyangitis. All patients had headache, and the other symptoms are visual loss, hearing loss, and seizure. Gd-enhanced MRI revealed thickened dura in all cases. Pathologic examination revealed small granulomas and giant cell in a case of GPA. One of MPA case was treated with corticosteroid, the other 3 cases were treated with combination of methotrexate and corticosteroid. All cases of dural thickening improved on Gd-enhanced MRI after treatment, although a case treated with only steroid deceased because of infectious disease. In three cases treated with MTX, corticosteroid can be tapered rapidly. This is a first report that MTX therapy is safe and effective in HP patients with ANCA associated vasculitis.

W21-3

Five cases of vasculitis with application of FDG-PET for the diagnosis and the evaluation of activity

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Conflict of interest: None

We applied FDG-PET to 5 patients with vasculitis. Case1. A 75 year-old man visited because of FUO. FDG-PET revealed high accumulation to bilateral femoral arteries. Angiography showed stenosis of abdominal arteries and the diagnosis of classical PN was made. Case 2. A 40 year-old woman visited because of neck, chest and back pain. Difference in BP of bilateral extremities and Bruit were noticed. FDG-PET showed accumulation at aortic arch and branching arteries which were stenotic by 3D-CT. She was diagnosed as Takayasu disease. Case3. A 73 year-old man visited because of FUO, neck pain and BW loss. Since FDG-PET showed accumulation at various muscles including neck, we thought that he had classical PN. Case 4. A 68 year-old man visited because of polyarthralgia and cough. FDG-PED showed accumulation at right lung at where OP was suspected by chest CT. Granuloma, PR3-ANCA and proteinuria were positive and the diagnosis of Wegener granulomatosis was made. Case 5. A 44 year-old woman visited because of ischemic symptoms of the brain. 3D-CT showed stenosis at bilateral subclavian arteries but FDG-PET did not show accumulation. We evaluated that the activity of vasculitis was low. Application of FDG-PET was useful in the diagnosis and the evaluation of activity.

W21-4

Prevalence and Clinical Characteristics of Large Vessel Involvement in ANCA-Associated Vasculitis: A Single Clinical Center Retrospective Study

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Conflict of interest: None

[Objectives] We examined the prevalence and clinical characteristics of large vessel involvement in ANCA-associated vasculitis (AAV). [Methods] We retrospectively investigated patients who received a diagnosis of AAV during Jan 2006 to Oct 2011 in our department. Large vessel involvement was defined as the existence of thickened vascular walls or inflammatory perivascular soft tissue masses around aorta and its branches which were depicted by contrast-enhanced CT and/or 18F-FDG-PET/CT. [Results] Forty-three patients were identified to have AAV. According to the Watts' algorithm, they were classified into Churg-Strauss syndrome (n=1), granulomatosis with polyangiitis (Wegener's) (GPA, n=20) and microscopic polyangiitis (n=22). Large vessel involvement was observed in 4 patients out of 43 AAV patients, indicating its prevalence as 9.3%. The diagnosis was GPA in these 4 patients. One patient had both thoracic and abdominal lesions and the others had only abdominal lesions. PR3-ANCA was positive in 2 and MPO-ANCA in 2. All patients presented elevated serum CRP levels. [Conclusion] Large vessel involvement is not infrequently observed in AAV patients. Careful examination for large vessel involvement by contrast-enhanced CT and/or FDG-PET/CT would be important in the management of AAV.

W21-5

The relapse and the maintenance immunosuppressive therapy in patients with ANCA associated vasculitis

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Conflict of interest: None

The strong immunosuppressive therapy has introduced the remission of ANCA associated vasculitis (AAV). However, relapse has still remained as a significant issue. We analyzed the relation between the maintenance therapy and relapse in 35 patients with AAV. The mean age of patients (32 with microscopic polyangitis, 2 with granulomatosis with polyangitis: Wegener granulomatosis, 1 with eosinophilic granulomatosis with polyangitis: Churg-Strauss syndrome) was 67.7 years. Relapse occurred in 13 cases (37.1%) and the relapse rate in patients treated with mizoribine (MZB) was 80%. In MZB group, more patients were treated with GC pulse therapy and lower dose of GC was used at the initiation. There was no difference of the remission rate between the patients without immunosuppressive agents (11 cases) and patients with azathioprine (AZ, 18) (27.3% vs. 27.8%), while the dose of GC was reduced more rapidly in AZ group. 4 patients (22.2%) switched AZ to other drugs because of the adverse events, and the relapse rate of patients who could continue AZ was 14.3%. All patients in AZ group were inducted remission by cyclophosphamide pulse therapy (IV-CY), indicating the significance of the remission induction by IV-CY, the initiation with enough doses of GC and the rapid reduction of GC with AZ.

W21-6

Renal and patient survival of microscopic polyangiitis

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Conflict of interest: None

We retrospectively investigated risk factors about end-stage renal disease (ESRD) and death in 44 patients (20 males and 24 females), who were diagnosed with MPA according to the Watts' algorithm. Their mean age was 69.2±12.8 years. Of the 44 patients, 14 (29.5%) resulted in dialysis-dependent and 13 (31.8%) died. The most cause of death was infection. We used proportional hazard model to explore predictors of the outcomes of ESRD and death. We analyzed presence of pulmonary hemorrhage and interstitial pneumonia, laboratory findings at diagnosis. Mortality was no significant difference for either factor. Renal prognosis was significantly associated with hemoglobin (HR 0.581, 95% CI; 0.405~0.832), creatinine (HR 1.236, 95% CI 1.098~1.392, blood urea nitrogen, lactate dehydrogenase, serum β2 microglobulin, proteinuria. There were no significant differences in MPO-ANCA titer and CRP level. When we set the cutoff as serum creatinine of over 4.7mg/dl in MPA patients, the sensitivity of Cr in ESRD was 78.6% and the specificity was 86.7%.

W22-1

Implication of NKT cells reactive with vascular endothelial cells in the pathogenesis of small vessel vasculitis

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Conflict of interest: None

[Objectives] Env-pX rats develop small vessel vasculitis. Cells reactive with self vasculature were involved in the development of vasculitis in these rats. To clarify the pathogenesis, we extracted the pathogenic cells from env-pX rats. [Methods] Lymph node cells were obtained from env-pX rats immunized with vascular endothelial cells (ECs). These cells were stimulated by ECs in vitro, and then a continuous cell line PC4 showing EC-dependent proliferation was obtained. By limiting dilution of PC4, a clone 1B8 was established. [Results] Intravenous injection of 1B8 induced small vessel vasculitis in wild type rats; therefore, indicating the pathogenicity of 1B8. The phenotype of 1B8 was $TCR\alpha\beta^+$ $CD3^+$ $CD4^-$ $CD8^-$, and the cytokine/chemokine profile was INF-γ^+ IL-2^- IL-4^+ IL-10^- and IL-17^-. The TCR was composed of Vα14 and Vβ8.6 chains. These findings indicated 1B8 as an NKT cell clone. When incubated with ECs, 1B8 produced IL-2, IL-17, and eotaxin; thus, suggesting that 1B8, which have recognized the EC antigen, recruited the inflammatory cells, and then injure the vessels in vivo. Furthermore, Gene X was identified as the molecule recognized by 1B8, by screening the COS7 transfectants carrying the rat cDNAs. The molecule coded by Gene X might be the target of small vessel vasculitis.

W22-2

The role of IL-25 (IL-17E)/IL-17RB in patients with ANCA-associated vasculitis

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Conflict of interest: None

[Objectives] To evaluate role of IL-25(IL-17E) and it's receptor IL-17RB in patients with ANCA associated vasculitis, [Methods] we analyzed the serum level of IL-25 and expression of IL-25/IL-25 receptor, IL-17RB in patients with allergic granulomatous angiitis(AGA), microscopic polyangiitis(MPA), and granulomatous polyangiitis(GPA). AGA4, GPA5, MPA15 samples were used. [Results] Level of IL-25 was measured by Enzyme-labeled immunoabsorbent assay(ELISA). Expression of IL-25 and IL-17RB detected by immunohistochemical analysis. Level of serum IL-25 in patients with GAG was higher than that of MPA, GPA (AGA1019±705pg/ml, MPA582±785pg/ml). These IL-25 levels decreased by steroids therapy under detectable levels correlated with clinical symptoms improved. However high level of IL-25 detected in 5 patients with MPA. These MPA patients had peripheral neural involvements. Immunopathological IL-25 and IL-17RB showed infiltrated eosinophil and dermal epithelial cells in biopsy specimens of erythma of patients with GAG. Conclusions: these data indicated IL-25(IL-17E)/IL17RB was a important role in pathogenesis in patients with ANCA-associated vasculitis such as AGA, MPA.

W22-3

Two types of cutaneous manifestations of myeloperoxidase antineutrophil cytoplasmic antibody with a high affinity, NETs formation and a low affinity in small vessel vasculitis.

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Conflict of interest: None

[Objectives] We studied cutaneous manifestations, the titer and affinity of MPO-ANCA, NETs formation in skin biopsy in relation to vasculitis activity in microscopic polyangiitis (MPA). [Methods] 50 patients with newly diagnosed MPA were observed cutaneous manifestations by cutaneous specialty doctor in relation to kidney and lung vasculitis activity. The MPO-ANCA titer and affinity of IC_{50} that was determined by a competitive inhibition method using the ELISA. Skin biopsy tissue were stained by enzyme-labelled antibody techniques with MPO, PAD4 and CH. [Results] 15 patients of 50 MAAV (30%) revealed cutaneous manifestations. 15 patients could be classified into type I: palpebral massive purpura, nail side erythema with a high affinity type MPO-ANCA (IC_{50} <0.1 μg/ml), rapidly progressive renal failure or acute respiratory distress syndrome. Type II: mutiformed erythema, spot like purpura with a low affinity type of MPO-ANCA (IC_{50} <0.25 μg/ml), chronic renal failure or chronic interstitial pneumonitis. Active MPA case with high titer of MPO-ANCA (3500EU) and high affinity of MPO-ANCA (IC_{50} <0.1μg/ml) was lower legs palpebral massive purpura skin biopsied with small vessel fibrinoid necrosis colocalized PAD4, MPO and CH (NETs formation).

W22-4

Changes of gene expression profile in a case of granulomatosis with polyangiitis patient before and after Tocilizumab treatment

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Conflict of interest: None

[Objectives] To assess the changes of gene expression profile (GEP) in a granulomatosis with polyangiitis (GPA) patient before and after Tocilizumab (TCZ, a humanized anti-IL6 receptor antibody) treatment. [Methods] GEPs of the peripheral blood cells from a GPA patient were obtained by DNA microarray and compared with those of 45 healthy volunteers. The abnormal molecular network was identified by Ingenuity Pathways Analysis. [Results] 218 up-regulated and 233 down-regulated genes were identified in the GPA patient before administration of TCZ. The up-regulated genes were relevant to cell death, cellular movement, antigen presentation, cell-to-cell signaling and interaction. IL-6 was in the center of the network constructed by these genes. After TCZ treatment, the expression levels of most up-regulated genes in this network decreased to healthy level. Among them, the expression levels of 12 up-regulated leukocyte activation related genes decreased and were positively correlated with the neutrophil numbers. On the other hand, the levels of 233 down-regulated genes remained low. [Conclusion] IL-6 was in the center of the network constructed by the up-regulated molecules in GPA and TCZ therapy improved it, suggesting that such network abnormality pathologically contributed to GPA.

W22-5

Crinical study of the association of MPO-ANCA titer and the rate of remission and relapse of MPO-ANCA associated vasculitis

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Conflict of interest: None

[Objectives] To study the association of MPO-ANCA titer and the rate of remission and relapse of MPO-ANCA associated vasculitis patients. [Methods] We retrospectively studied 18 patients with MPO-ANCA associated vasculitis who were diagnosed in our hospital since January 2007. [Results] There were 6 males and 12 females. The mean age±SD of onset was 68.5±11.0 years old. The diagnosis were ; MPA: 14, EGPA: 2, GPA: 1, Unclassifable: 1. Pulmonary involvement, renal involvement and polyneuropathy was present in 10 cases, 14 cases and 10 cases. 8 patients received m-PSL pulse therapy. The mean initial dose of PSL was 44.4mg/day. 9 patients received IVCY. 7 patients treated with immunosuppressiant (AZA: 3, MZR: 4) as maintenance therapy. The initial level of MPO-ANCA±SD was 272.4±206.8EU. The levels of MPO-ANCA±SD at one month and three months after the first therapy were 95.9±88.3EU and 15.4±12.6EU. All patients achieved a remission. 6 patients were relapsed. 3 of them treated with PSL alone. another treated with PSL alone after received IVCY. another recieved IVCY only two times. The other was not able to take medicine well. Most of patients who were not relapsed, did not recieve strong immunosuppressive therapy.

W22-6

Induction of abnormal conformation and impaired degradation of neutrophil extracellular traps (NETs) by propylthiouracil (PTU): Possible implication of disordered NETs in the pathogenesis of MPO-ANCA-associated vasculitis (MPO-AAV)

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Conflict of interest: None

[Objectives] The pathogenesis of small vessel vasculitis is criti-

cally associated with ANCAs. NETs composed of chromatin fibers and antimicrobial proteins, such as MPO, play important roles in the innate immune system. Recent studies suggest that NETs may be involved in the pathogenesis of MPO-AAV, and that impaired regulation of NETs may trigger autoimmune response to NETs. PTU, an anti-thyroid drug, is known to have a risk to induce MPO-ANCA production and MPO-AAV. Thus, we hypothesized that PTU can induce impaired regulation of NETs and consequently result in the induction of MPO-ANCA and MPO-AAV. [Methods] NETs were induced by treatment of neutrophils with PMA *in vitro*. We examined whether the addition of PTU can influence the NETs formation induced by PMA and degradation by DNase I, which is regarded as a regulator of NETs. Furthermore, we examined whether the NETs generated by PMA with PTU can induce MPO-ANCA and MPO-AAV *in vivo*. [Results] When NETs were induced by PMA with PTU *in vitro*, abnormal conformation of NETs was observed. Interestingly, the abnormal NETs were hardly digested by DNase I. Moreover, rats immunized with the abnormal NETs induced by PMA with PTU produced MPO-ANCA. We further established a rat model for induction of MPO-ANCA and MPO-AVV using PMA and PTU.

W23-1

The trimethoprim-sulfamethoxazole dose-escalation regimen may improve tolerance to the antibiotics for prophylaxis against pneumocystis pneumonia in patients with rheumatic disease

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Conflict of interest: None

[Objectives] Trimethoprim-sulfamethoxazole (TMP/SMX) administration for prophylaxis against pneumocystis pneumonia (PCP) often has adverse effects, leading to its discontinuation. Occasionally, PCP occurs in patients who discontinued TMP/SMX. We conducted a retrospective study to investigate whether the dose-escalation regimen is better than the routine regimen for continuation of TMP/SMX. [Methods] We examined 51 patients with rheumatic disease, who were treated with immunosuppressive agents and TMP/SMX for prophylaxis of PCP in our hospital. [Results] Thirty-three patients were treated with 1 tablet (1 g) of Baktar® (routine group). The remaining 18 patients were treated with 0.1 g of Baktar®, and the dose was gradually increased to 1 g (escalation group). In the routine group, 1 g Baktar® was continued for 21 patients (63.6%), the dose was reduced for 8 patients (24.2%), and administration was discontinued for 4 patients (12.1%). In the escalation group, 13 patients (72.2%) were continued on 1 g Baktar® or the doses were escalated to 1 g, and 5 patients (27.8%) were continued on stable doses of lesser than 1 g; none of the patients required discontinuation of Baktar®. The dose-escalation regimen may improve tolerance to TMP/SMX as compared to the routine regimen.

W23-2

A prospective comparative study of trimethoprime-sulfamethoxazole (TMP/SMX) prophylaxis regimen against for prevention of *Pneumocystis jiroveci* pneumonia (PCP) in patients with autoimmune connective tissue diseases (CTD)under glucocorticoid (GCP) therapy.

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Conflict of interest: None

Purpose: This study was conducted to compare the efficacy and safety of twice a week and once daily regimens of TMP/SMX prophylaxis against PCP in patients with CTD under GC therapy. Patients and methods: We conducted a prospective randomized comparative study of twice a week and once daily therapeutic regimens in 37 adult inpatients with CTD who were treated with GC, the equivalent of more than 30 mg/day of prednisolone. Patient who gave an informed consent to this study was assigned to receive a tablet of TMP/SMX either once daily (n=19) or twice a week (n=18). Results. In the group of once daily regimen, 8 of 18 patients (44%) were discontinued, while 4 of 17 patients (24%) with twice a week regimen. However, there was no statistically significant difference between these two groups. All of the reasons for discontinuation of SMX/TMP in both regimens were adverse events. We could not find any statistically significant differences in background conditions between two groups. Conclusion: In our prospective study, once daily regimen of TMP/SMX against PCP showed the equivalent efficacy to twice a week regimen. Twice a week regimen had a trend of lower incidence of adverse events.

W23-3

Clinical characteristics and risk factors for *Pneumocystis jirovecii* pneumonia in patients with rheumatoid arthritis receiving TNF inhibitors

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Conflict of interest: None

[Objectives] We previously described the risk factors for *Pneumocyttis jirovecii* pneumonia (PCP) in rheumatoid arthritis (RA) patients treated with TNF inhibitors (TNFi). The purpose of this study was to identify clinical characteristics and predictors of PCP in RA patients receiving TNFi. [Methods] We compared RA patients who did and did not develop PCP during the treatment with TNFi. [Results] Baseline characteristics of PCP patients (n=51, IFX 19, ETN 15, ADA 17) were as follows: mean age, 65.5 years;female, 70%; mean disease duration, 10.8 years; pulmonary comorbidities, 47%; diabetes mellitus, 24%. At the onset of PCP, median dosages of prednisolone (PSL) and methotrexate were 9.3 mg/day, and 8.2 mg/week, respectively. Of the 51 PCP patients, 98% received therapeutic doses of TMP/SMX and 90% were treated with high-dose corticosteroids. Based on the results of the multivariable analysis, older age, pulmonary comorbidities, diabetes mellitus and PSL ≧5mg/day were identified as predictors for PCP. Kaplan-Meier analysis indicated that the accumulated probability of PCP was significantly raised as the number of predictors increased. [Conclusion] Careful monitoring for PCP is recommended for RA patients who have multiple these predictors and receive treatment with TNFi.

W23-4

Pneumocystis jiroveci pneumonia in patients with rheumatoid arthritis- analysys from IORRA database –

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Conflict of interest: None

[Objectives] To demonstrate Pneumocystis jiroveci pneumonia (PCP) complicated to patients with rheumatoid arthritis (RA). [Methods] Fifteen patients who developed PCP from April 2010 to August 2011 (PCP group) were compared to RA patients in IORRA survey in October 2010 (IORRA cohort). [Results] Fifteen patients (0.27 %) developed PCP during the observational period. Compared to IORRA cohort, patients with PCP had older age (70.2 vs 59.9 years), longer disease duration (17.4 vs 13.7 years) and higher disease activity (DAS28:3.83 vs 2.96). There was no difference in sex and BMI. Although methotrexate (MTX) use was prevalent in PCP group (83.7 vs 71.8 %), there was no difference in dose (8.5 vs 8.4 mg/week) among these two groups. Predonisolone (PSL) use (70.0 vs 41.3 %) and its dose (6.9 vs 4.1 mg/day) and biologics use were higher (27.8 vs 13.2 %) in PCP group than those in IORRA cohort. Prevalence of PCP according to medication was 0.33 % in MTX, 0.36 % in tacrolimus, 0.44 % in PSL and 0.53 % in Biologics, respectively. Treatment for RA in PCP group was MTX in 13 (86.7 %), biologics in 4 (26.7 %) and PSL in 11 (73.3 %). [Conclusion] Patients developed PCP were older, had higher disease activity and more frequent use of corticosteroids and biologics.

W23-5

Clinical study of patients with rheumatic diseases complicated by cytomegalovirus-antigenemia

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Conflict of interest: None

We divided CMVantigen (pp65-ag)-positive patients into those requiring treatment with anti-CMV agents and those in which course observation without treatment was possible. We then investigated whether there were characteristic differences and test findings between the groups. 381 patients with rheumatic disease were admitted to our hospital and underwent immunosuppressive therapy between April 2008 and Sep. 2011. pp65-ag was tested in 183 cases, of which 49 were positive and 134 were negative. 17 patients underwent anti-CMV therapy. The other 32 pp65-ag-positive patients became pp65-ag-negative in course observation. In laboratory tests, the lymphocyte count and serum albumin level were significantly lower in the CMV treatment group. The pp65-ag level has been reported to be correlated with disease activity and this level was significantly higher in the CMV treatment group than in the course observation groups. In immunosuppressive therapy, the required dose of prednisolone was significantly higher in the CMV treatment group. Even if the pp65-ag level is low, continuous pp65-ag monitoring and investigation of preventive administration of an anti-CMV agent may also be necessary for a patient under high-dose steroid treatment or with hypoalbuminemia or lymphopenia.

W23-6

Gastric cytomegalovirus infections during immunosuppressive therapies

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Conflict of interest: None

[Objectives] To investigate clinical characteristics of gastric cytomegalovirus (CMV) infections in patients with rheumatic diseases. [Methods] Hospital records over 7 years were reviewed for gastric CMV infections defined by biopsies, and 9 cases in 8 patients (RA 3, SLE 2, DM 1, SSc 1, Overlap syndrome 1) were identified based on pathology (gastric ulcer 6, gastritis 1, perforated duodenal ulcer 1, esophageal ulcer 1). [Results] Low dose steroids and methotrexate had been administered in 2 cases, and high dose steroid monotherapies or combination therapies (methotrexate, cyclosporine, or cyclophosphamide) in 7 cases. CMV-antigenemia (Ag) tests showed negative results in 6 cases and a low titer in one case within two weeks before endoscopic examination. Of these, 2 cases had received a prior anti-CMV therapy. A high titer CMV-Ag was found in 2 cases of additional CMV complications. A follow-up endoscopy at a mean 3-week-interval revealed no improvement by anti-CMV drugs in 3 of the 6 cases. Nevertheless all the patients survived including one that suffered perforated ulcer. [Conclusions] Gastric CMV infection can occur during therapies even by low-dose immnosuppressants. The ulcers are intractable but not lethal, and the diagnostic value of CMV-Ag may be small.

W24-1

The Pattern-Recognition Receptor NOD1 Promotes Production of Inflammatory Mediators in Rheumatoid Arthritis

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Conflict of interest: None

[Objectives] We analyzed here the expression, regulation and function of pattern-recognition receptors (PRRs) NOD1 in rheumatoid arthritis synovial fibroblasts (RASFs), osteoarthritis SFs (OASFs), monocyte-derived macrophages (MDMs) and peripheral blood mononuclear cells (PBMCs). [Methods] Expression of NOD1 was analyzed by immunohistochemistry in synovial tissues. Expression of NOD1 mRNA and protein was analyzed by real-time PCR and flow cytometry. ELISA was used to quantitate protein levels. Silencing of NOD1 was performed by Amaxa Nucleofector Technology. Phosphorylation levels of MAPK and IRAK1 were analyzed by Western blotting. [Results] In RA synovium, expression of NOD1 was significantly increased compared to OA synovium. In RASFs, IL-6, CCL5, MMPs, TLR2 and NOD2 were significantly up-regulated by stimulation of NOD1 which also induced phosphorylation of p38. There was a synergistic effect of NOD1 with TLRs in the production of IL-1β and IL-6 in RASFs, MDMs and PBMCs. IL-6 production and the phosphorylation of IRAK1 induced by TLR2 stimulation was significantly decreased by silencing of NOD1. [Conclusion] NOD1 is expressed in RA synovium and induces proinflammatory signals. NOD1 might contribute to persistence of chronic inflammation and bone destruction in RA.

W24-2

Analysis on Toll-like receptor mediating signal pathway in septic and aseptic tissues around total hip prostheses

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Conflict of interest: None

【Introduction】The two major long-term complication of total hip arthroplasty are septic loosening caused by implant infection and aseptic loosening caused by foreign body inflammation. TLRs play a central role in innate immune system.【Methods】Septic (5), aseptic (15) tissues from loose total hip joints, and osteoarthritic synovium (5) was obtained. RT-PCR for TLR4, 9, MyD88, TIRAP, TRIF, TRAM, IL-1β mRNA was performed. Immunohistochemical analysis was performed for TLRs and their adaptor molecules.【Results】Expression of TLRs and their adaptor molecules was detectable in all the samples from two different status of pathology. In septic tissues, IL-1β expression was weak rather than aseptic loosening. In septic loosening, $CD15^+$ cells were observed in focal granulocyte infiltrates, which were co-localized with each TLRs and its adaptor molecules. In aseptic tissues, immuno-reactivities to each TLRs and its adaptor molecules were observed mainly in $CD68^+$ macrophages.【Discussion】Toll like receptor can recognize exogenous and endogenous ligands. TLR system must be tightly regulated both in physiologic and pathologic states via some molecules. Signal pathway via TLR and its adaptor molecules may contribute to the pathogenesis of peri-prosthetic condition in different way.

W24-3

Use of ^{18}F-fluorodeoxy glucose and ^{18}F-fluoride PET for the diagnosis of septic loosening in total hip arthroplasty

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Conflict of interest: None

[Objectives] The purpose of this study was to reveal and compare the differences between ^{18}F-fluorodeoxy glucose (FDG) and ^{18}F-fluoride (fluoride) PET findings in loosening THA cases. [Methods] Seven THA patients, who had radiological loosening, were given FDG and fluoride PET scans and underwent surgical treatment, were enrolled in this study. Abnormally increased FDG or fluoride uptake at the bone-implant interface were defined as suggestive of infection. Intraoperative tissues were evaluated by histopathology, microbiological culture and real-time PCR. One or more positive finding in these examinations were defined as the diagnosis of periprosthetic infection. Difference between FDG and fluoride PET uptakes were investigated and the diagnosis from PET scans were compared with reults from tissue examinations. [Results] Six and 7 cases were diagnosed as infections from FDG and fluoride PET respectively. In tissue examinations, all cases were revealed to be infections. [Disccusion] We compared two different tracers, FDG and fluoride, to visualize differential uptake patterns. Nevertheless their uptake indicates different molecular reactions, several cases showed a similar uptake regions. In this results indicate that the both images pointed to an inflammation focus in infection cases.

W24-4

An analysis of the expression of CD64 and CD35 on neutrophils as markers to differentiate between bacterial and viral infections in patients with rheumatoid arthritis

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Conflict of interest: None

Background: The expression level of CD64 on neutrophils can be used to differentiate between an infection and a disease flare in rheumatoid arthritis (RA) patients. However, the CD64 expression is elevated by both bacteria and viruses, so it cannot be used to distinguish the type of infection. Aim: We herein investigated the results of a simultaneous quantitative analysis of the expression of CD64 and CD35 on neutrophils to determine whether these molecules can be used to distinguish between bacterial and viral infections in RA patients. Subjects and methods: We collected blood from 22 RA patients with pathogen-proven infections (15 bacterial and 7 viral infections). Blood samples were stained with QuantiBRITE CD64PE/CD45PerCP and CD35PE, and the mean fluorescence intensities were assessed by a FACSCalibur flow cytometer (Becton-Dickinson). The mean numbers of molecules were calculated using QuantiBrite PE beads. Results: We calculated the ratio of CD64 to the CD35 level (CD35/CD64), and used a cut-off value of 2.8 for CD35/CD64. At this value, the sensitivity for the diagnosis of a bacterial infection was 87%, and the specificity was 86%. The analysis of CD64 and CD35 expression on neutrophils might be useful to distinguish between bacterial and viral infections in RA patients.

W24-5

A Meta-Analysis: Diagnostic Accuracy of Serum Procalcitonin Concentrations for Detecting Systemic Bacterial Infection in Patients with Rheumatic Diseases

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Conflict of interest: None

[Objectives] Procalcitonin (PCT) is reported as a useful serum marker for detection of systemic bacterial infection in variety of clinical settings. However, it is still controversial that clinical use of PCT in patients with rheumatic diseases. The reported diagnostic accuracy of PCT varies from study to study and their usefulness remains uncertain. We therefore systematically conducted this meta-analysis for PCT to quantitatively clarify its diagnostic accuracy of PCT. **[Methods]** Literature search were performed by MEDLINE (through March 7th, 2011), reference lists of retrieved studies and review articles. Weighted sensitivity and specificity and an AUC of sROC curve were calculated. Meta-regression was used to identify the source of heterogeneity. **[Results]** We used a meta-analytic method to construct a sROC curve. Nine studies met the inclusion criteria and they involving 551 patients were relevant for the diagnostic accuracy of PCT. The diagnostic accuracy of the PCT was high, with an AUC from sROC of 0.920 (95% CI, 0.918-0.922) for patients with systemic infection. The pooled sensitivity, specificity and diagnostic odds ratio were 0.66(95% CI, 0.58-0.74), 0.94(95% CI, 0.91-0.96), and 25.1(95% CI, 11.3-55.9), respectively. There was no heterogeneity among studies.

W24-6

Serum cytokine profile in a case of adult-onset Still's disease with repeated shock conditions

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Conflict of interest: None

[Case] A 50-year-old woman was admitted to our clinic because of disturbance of consciousness. She had been diagnosed as adult onset Still's disease (AOSD) for 6 years. On admission, she had a high fever and showed shock level of blood pressure. The laboratory evaluation revealed CRP of 29.85 mg/dl, ferritin of 5623 ng/ml and procalcitonin (PCT) of 72.46 ng/ml. By the treatment with vasopressor, antibiotics and hydrocortisone (HDC), her fever subsided and blood pressure returned to normal. Soon after the replacement of HDC to dexamethasone, she became shock again with PCT of 30.2 ng/ml and ferritin of 26,417 ng/mL. We considered the repeated shock conditions were caused by AOSD and initiated mPSL pulse therapy. Her vital signs improved again. **[Study]** We hypothesized that her shock conditions were due to a cytokine storm caused by AOSD. Although IL-1β was undetectable, the blood levels of TNF-α, IL-6 and IL-18 were correlated with the shock conditions. Especially the level of IL-18 was extremely high (max 257,800 pg/ml). **[Discussion]** IL-18 is reported to be increased in patients with AOSD. However, the level of IL-18 in this case was much higher. We speculated repeated shock conditions and high level of PCT were related to these cytokine profiles in this case.

W25-1

Clinical features of human parvovirus B19 infection in adults and the 2010 ACR-EULAR classification criteria for rheumatoid arthritis

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Conflict of interest: None

[Objectives] Clinical presentation of human parvovirus B19 infection in adult patients varies significantly and joint swelling, heat, and erythema tend to resolve over several weeks. The aim of this prospective study is to clarify the clinical features of adult patients with parvovirus B19 infection and to evaluate the 2010 American College of Rheumatology/European League Against Rheumatism (ACR/EULAR) classification criteria for rheumatoid arthritis (RA) in parvovirus B19 infection in adults. [Methods] We performed a retrospective chart review of 22 adult patients who tested positive for IgM antibody against parvovirus B19 at our hospital from April 2006 to September 2011. Median patient age was 39.8 years, between 21 and 68 years. [Results] Clinical symptoms were arthralgia in 17 (77%), rash in 13 (59%), and edema in 10 (45%), and significantly occurred in the elder group (over 40 years old) than the group under 40 years old (64% vs 91%, 37% vs 83%, 27% vs 64%). 7 of 22 patients were fullilled the 2010 American College of Rheumatology/European League Against Rheumatism (ACR/EULAR) classification criteria for rheumatoid arthritis (RA). One patient was diagnosed Rheumatoid Arthritis with positive for anti-CCP antibody 3 months after onset of parvovirus B19 infection.

W25-2

Hapatitis B virus reactivation during immunosuppressive study in patients with rheumatic disease in Tohoku area

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Conflict of interest: None

[Objective] 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 assess the usefulness of the guideline for patients with rheumatic diseases. [Methods] A total of 107 patients with rheumatic diseases were enrolled to the study. According to the guideline, titer of HBs antigen, anti-HBc antibody, and anti-HBs antibody were measured before immunosuppressive therapy. HBV-DNA were monitored every month in patients with positive anti-HBc antibody and/or anti-HBs antibody. [Results] A total of 27 patients (25.2%) 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 27 patients (11.1%) 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 hepatitis B virus (HBV) reactivation to not only malignant diseases but also rheumatic diseases. Further evaluation is needed to clarify that how often and how long HBV-DNA should be monitored and that when entecavir should be administered.

W25-3

Tuberculosis in rheumatic diseases; comparison with tuberculosis without rheumatic diseases.

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Conflict of interest: None

We report the clinical feature of TB in patients with rheumatic diseases (RD-TB) compared with TB without rheumatic diseases (non-RD-TB). Patients were 1413 patients with TB admitted to NHO Utsunomiya Hospital or Kameda Medical Center from January 1996 to March 2011. There were 31 patients with RD-TB. Underlying diseases of RD-TB were RA in 17, SLE in 4, SSc in 3, DM in 3 and one of each of PM, AODS, AAV and Behcet's disease. Mean age was 64.5 years, which was not different from that of non-RD-TB. Percentage of female patients was significantly higher in RD-TB compared with that of non-RD-TB (67.7% vs. 32.3%). RD-TB with RA consisted of 1.2% of all the TB patients, which is approximately 3 times higher than the prevalence of RA in general population. Percentage of RD-TB with SLE and SSc was approximately 10 times higher than the prevalence in general population. Percentage of extrapulmonary TB particularly miliary and bone/joint TB was extremely high (40 %) in RD-TB. Patients with extrapulmonary TB in RD-TB had PSL with the mean of 13mg/day. Only 1 patient was a biologics user. Six patients with

RD-TB died and 4 out of 6 died of exacerbation of rheumatic diseases. We conclude that the clinical feature of RD-TB is considerably different from that of non-RD-TB.

W25-4

Tuberculous Pleurisy in an Adalimumab-treated Rheumatoid Arthritis Patient even after Sufficient Preventive Treatment of Latent Tuberculosis Infection

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Conflict of interest: None

A 32-year-old woman with 17-month history of RA. She started adalimumab 11 months before the admission. She had been positive for skin tuberculin test with no pulmonary lesions, and took isoniazid for 9 months as recommended. On admission, her chest x-ray showed unilateral pleural effusion. Thoracocentesis revealed exudative effusions with elevated adenosine deaminase (83.3 IU/L). Pleural fluid PCR and culture were negative. Medical thoracoscopy showed diffuse white nodules on pleura, strongly suggestive of tuberculous pleurisy. Biopsy specimen demonstrated epithelioid cell granulomas. After treatment for active tuberculosis(ATB), her pleural effusion was ameliorated. Medical thoracoscopy permits pleural biopsies under local anesthesia and has a diagnostic accuracy of virtually 100% for tuberculous pleurisy. For the diagnosis of patients with suspected tuberculous pleurisy with negative pleural culture, medical thoracoscopy can be a potent diagnostic option. Although the incidence of ATB in RA patients receiving TNF inhibitors is substantially decreased with preventative latent tuberculosis infection treatment, some ATB cases have been reported especially in patients with poor compliance with treatment. In this case, however, ATB was not prevented despite complete compliance.

W25-5

Pulmonary nontuberculous mycobacterial disease in rheumatoid arthritis patients receiving biological agents: a retrospective multicenter study in Japan

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Conflict of interest: None

[Objectives] Aim of our study is to clearify the clinical characteristiss of NTM disease in RA patients recieving biologic DMARDs [Methods] We conducted a retrospective chart review of 13 patients from multiple centers who had developed pulmonary NTM disease during biological therapy for RA, [Results] Most cases were asymptomatic or resulted in only common-cold-like symptoms. Abnormalities in CT imaging were protean and frequently overlapped, but not peculiar to this clinical setting. NTM disease had spread from a preexisting lesion, including bronchial/bronchiolar abnormalities or nodular lesions with or without calcification. Following the discontinuation of biological agents, most patients responded to anti-NTM therapy. Two patients showed no aggravation in the absence of any anti-NTM therapy. In one case, restarting tocilizumab therapy while continuing to administer anti-NTM therapy produced a favorable outcome. In two other patients with previous history of pulmonary NTM disease, introducing biological therapy led to recurrence, but anti-NTM therapy was effective in these cases. [Conclusion] Close follow-up of preexisting CT abnormalities can lead to early detection and timely implementation of therapeutic strategies for NTM disease in RA patients receiving biologic DMARDs

W25-6

Two cases of the Reiter syndrome caused by intravesical infusion of the BCG

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Conflict of interest: None

Case1: 68 years old male. Urination ache, the right hip joint and left foot arthralgia and both sides conjunctivitis appeared one month after infusion therapy in the first intravesical infusion of the BCG. Bacteriologic culture of the synovial fluid was negative by hip joint puncture. The symptom was improved by one-week Diclofenac Na internal use. Case2: 62 yaes old male. Urination ache, swelling and the pain of the right foot joint and both sides conjunctivitis appeared right after it was enforced intravesical infusion of the fifth BCG. Bacteriologic culture of the joint was negative by ankle puncture. The symptom was improved by 2-week Diclofenac Na internal use. Intravesical infusion therapy of the BCG is the cure that it faces each other, and is provided for superficial model bladder cancer, but it is rare to cause reactivity joint to Reiter syndrome with reactive arthritis. There are fewer reports that met 3 main symptom of the Reiter syndrome like the disorder. In addition, there are few reports from the orthopedics domain and is not generally known. When a joint symptom developed, in a patient performed by infusion therapy intravesical infusion of the BCG, should think about possibility of the Reiter syndrome.

W26-1

Analysis for the gene expression induced by DcR3 in rheumatoid synovial fibroblasts

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Conflict of interest: None

[Objectives] Decoy receptor 3 (DcR3) is a secreted decoy tumor necrosis factor receptor and competitively binds and inhibits the TNF family including FasL, LIGHT, and TL1A. Recent studies have reported that DcR3 acts as a ligand. We reported that 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, we searched the genes of which expressions are regulated by the ligation of DcR3 on RA-FLS. [Methods] RA-FLS were incubated with DcR3-Fc or IgG1 for 12h. Gene expressions were detected by microarray assay and the relative expression of the genes were analysed. [Results] Microarray data analysis revealed that DcR3 regulates the expression of various genes in RA-FLS. The functions of up-regulated genes included protein complex assembly, cell motility, regulation of transcription, and cellular protein catabolic process. Meanwhile, those of down-regulated genes included transcription regulator activity, RNA biosynthetic process, cytoskeleton, zinc finger region, protein complex assembly, phosphate metabolic process, mito-

chondrion, and ion transport. It is suggested that DcR3 may affect the pathogenesis of RA by regulating gene expression of RA-FLS.

W26-2

Functional analysis of *p53*-mutants found in *AID*-expressing fibroblast-like synoviocytes from rheumatoid arthritis.

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Conflict of interest: None

[Objectives] A part of fibroblast-like synoviocytes (FLS) from RA ectopically expresses *AID* (Activation Induced cytidine Deaminase), which is an indispensable gene for somatic hypermutation of immunoglobulin variable region in B lymphocyte. Furthermore, somatic mutations in *p53* gene accumulated at a higher frequency in *AID*$^+$RA-FLS. We studied the functional characteristics of these *p53* mutants in *AID*$^+$RA-FLS. [Methods] By inverted-PCR using a cDNA of wild type *p53* as a template, we obtained the 12 mutants of *p53* with one base-pair replacement found in *AID*$^+$RA-FLS. After forced expression of each mutant in Hep3B that lacks endogenous *p53,* we examined the effects on proliferation, sensitivity to apoptotic stimuli, or induction of *p53*-target genes (*cell cycle-dependent kinase inhibitor p21*, a pro-apoptotic gene *Bax*). [Results] Under the oxidative stress, 4 mutants suppressed the induction of *p21* to the comparable levels by R175H; a gain-of-function type mutant at a cancer hot spot. Furthermore, two mutants among 4 also reduced the expression of *Bax*. These results suggest that those gain-of-function mutants of *p53* in *AID*$^+$RA-FLS could allow survival and cell-cycle progression even with DNA injury, leading to accumulation of somatic mutation and acquisition of the tumor-like properties.

W26-3

Transcriptome analysis of Rheumatoid arthritis patient's synovial cells stimulated with IL-17

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Conflict of interest: None

[Objectives/Methods] Because IL-17 has been reported to contribute to the pathogenesis of RA, objective of the study is to determine the target molecules of IL-17 expressed in RA synovial cells. We utilized synoviocytes derived from RA patients and performed transcriptome analysis. [Results/Discussion] IL-17 induced various chemokines that are involved in the chemotaxis of neutrophils, among which CXCL1 was most highly induced in RA cynoviocytes. We also performed ELISA and observed that CXCL1 protein was significantly induced more from synoviocytes of RA patients than from those of osteoarthritis patients. Though past reports suggested that CXCL1 directly induced osteoclastogenesis, we showed no such direct effects of CXCL1. In spit of the previous thought, RANKL was not induced significantly by IL-17 stimulation at the mRNA level in RA synoviocytes. From these data, it is obvious that IL-17 contribution to RA pathogenesis may be more complicated than expected.

W26-4

Analysis of core promoter context of SPACIA1/SAAL1 gene, which is related to synovitis

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Conflict of interest: None

[Objectives] Abnormal synovial proliferation is one of major characteristics of rheumatoid arthritis (RA). However, the molecular mechanisms behind this process are still unclear. Recently we identified a functionally unknown gene, named SPACIA1 which associated with the synoviocyte proliferation. SPACIA1, when overexpressed, results in increased synovitis and worsened disease in collagen-induced arthritis (CIA), a mouse model of RA (***Arthritis & Rheumatism*** (2011) e-publish, ***Nature Reviews Rheumatology*** 7, 620 (2011) "Research Highlight"). This study was undertaken to elucidate the precise mechanisms of transcriptional regulation via core element of SPACIA1 gene promoter. [Methods] We performed reporter assays by using deletions and mutations of AP-1- and κB-like binding sites on the SPACIA1 promoter with several stimulators. [Results] We identified a core element of the SPACIA1 promoter, which is located in the proximal transcription start site of the SPACIA1 gene. The deletions and point mutations of AP-1- and κB-like binding sites significantly reduced the promoter activity. However several stimulators of AP-1 and NF-κB did not upregulate the core promoter activity via these sites. We are now biochemically isolating transcriptional factors that bind the core element.

W26-5

Analysis of processing mechanisms of miRNA-146a

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Conflict of interest: None

[Objectives] MicroRNAs (miRNAs) are small non-coding RNAs that act as key post-transcriptional regulators of gene expression, involved in diverse physiological and pathological processes. However, the processes regulating miRNA biogenesis are largely unknown. We previously reported that miRNA-146a (miR-146a) is expressed more intensely in synovial tissues from rheumatoid arthritis patients. Also, the miR-146a has been implicated as a negative feedback regulator of NF-κB activation. In this study, we aimed to identify the processing regulators of miR-146a. [Methods] To identify the processing regulators of miR-146a, we performed High-throughput Screening (HTS). The HTS is luciferase assay system using cells transfected with miR-146a sensor vector containing complementary miR-146a sequence in 3'-UTR of luciferase gene, primary-miR-146a expression vector and about 6,000 genes of expression vector. [Results] This HTS identified some genes that upregulate luciferase activity of miR-146a sensor vector. Furthermore, knockdown of the genes in A549 cells showed down-regulation of mature miR-146a expression. These data suggested that these candidate genes promote the miR-146a processing.

W26-6

The comparison of genome-wide gene expression profile between rheumatoid arthritis (RA) and polymyalgia rheumatica (PMR)

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Conflict of interest: None

Background: Although classification of RA into subgroups is useful to suspect the most effective therapeutic method, it has not been elucidated. On the other hand, there are many similarities between PMR and RA, whereas joint destruction is only observed in RA. Therefore, detecting the differences in gene expression may reveal the most important pathway that plays a crucial role in the pathogenesis of RA. **Objectives**: To classify RA into subgroups, and to identify the gene expression signature that may distinguish RA from PMR. **Methods:** The study included 44 RA and 10 PMR patients. Peripheral blood was drawn for RNA preparation from the newly diagnosed patients. The mRNA levels were analyzed with using DNA micro-array technology. **Results:** The hierarchical clustering showed that the number of clusters was 5. Although the 4th and 5th cluster consisted of RA only, PMR was nested and distributed in the 1st to 3rd clusters. Application of pathway analysis reveals that B cell receptors pathways were up-regulated in the 4th and 5th clusters. **Discussion:** RA and PMR seem to be overlapped in gene expression profile. The finding that B cell receptor pathway was up-regulated in the "only-RA" clusters may suggest that it may be the important therapeutic target to prevent joint destruction.

W27-1

Blockade against connective tissue growth factor (CTGF) ameliorates progression of arthritis in murine model of rheumatoid arthritis

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Conflict of interest: None

【Background】 We have shown that CTGF was excessively produced in synovial tissue of rheumatoid arthritis (RA) and played an important role for pathogenesis of RA through inducing abnormal osteoclasts activation. In this study, we analyzed effects of blockade against CTGF on the pathogenesis of RA in CIA mouse. **【Methods】** CIA was introduced in DBA/1J mice by immunization with typeII collagen. The efficacy on prevention for progression of arthritis was evaluated in the CIA mice treated with or without neutralizing anti-CTGF mAb. **【Results】** The blockade of CTGF by anti-CTGF mAb treatment ameliorated arthritis score in the CIA mice compared to the non treated controls. Moreover, serum levels of CRP and MMP-3 in the anti-CTGF mAb treated mice. The blockade of CTGF also reduced a capability of osteoclastic differentiation and inhibited T lymphocytes proliferation against typeII collagen stimulation. **【Conclusions】** The present study demonstrated that the blockade of CTGF significantly prevented a progression of arthritis in CIA mice. CTGF was considered to be associated with abnormal osteoclastic activation and pathogenic T cell proliferation in the pathogenesis of RA.

W27-2

Immunotherapy of antigen-induced rat arthritis with an Anti-Folate receptor-beta recombinant immunotoxin.

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Conflict of interest: None

[Objectives] Clinical and experimental studies demonstarate the important roles of synovial macrophages in the pathogenesis of rheumatoid arthritis. We have previously determined that synovial sublining macrophages express folate receptor beta (FRβ). The present study evaluated the efficacy of intra-articular administration of a recombinant immunotoxin to FRβ for treating rat antigen-induced arthritis. [Methods] We produced mouse anti-rat FRβ monoclonal antibody (mAb) and recombinant immunotoxin composed of the Fv fragment of an anti-rat FRβ mAb fused to a truncated *Pseudomonas* exotoxin A. Rats with methylated bovine serum albumin induced arthritis were treated intra-articularly with the immunotoxin every other day for 7 days after arthritis onset. Joint swelling was measured and histological evaluation was performed. [Results] Immunostaining revealed that inflammatory macrophages express FRβ while tissue resident macrophages in normal tissues express no or low levels. Intra-articular administration of an immunotoxin attenuated joint swelling and improved histological findings by reducing the number of FRβ-expressing macrophages. [Conclusions] Intra-articular administration of an immunotoxin to FRβ is effective for improving rat antigen-induced arthritis.

W27-3

Dynamic *in vivo* imaging of bone-resorptive functions of mature osteoclasts in live bones by using intravital multiphoton microscopy

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Conflict of interest: None

RA is a chronic autoimmune disease characterized by joint synovial inflammation and progressive cartilage/bone destruction. Recently it has been reported that Th17, a CD4$^+$ T cell subset expressing RANKL, increases in the synovium of RA patients and enhances bone destruction. However it remains unclear how the bone-resorptive functions of osteoclasts are controlled *in vivo* and how Th17 cells influence osteoclastic bone resorption. To answer these questions, we have visualized fluorescently-labeled mature osteoclasts in live bones by using intravital multiphoton microscopy, and identified two different populations of live mature osteoclasts, 'static - bone-resorptive (R)' and 'moving - non-resorptive (N)'. We also found that rapid RANKL injection changed the osteoclast status from N to R, suggesting a novel point of action of RANKL in controlling mature osteoclast function. Furthermore, we showed that Th17 could induce rapid N to R transition of mature osteoclasts via direct cell-cell contact, revealing a mechanism by which Th17 has a potent effect on controlling bone resorption *in vivo*. These findings provide new insights into the activities of mature osteoclasts *in situ* and identify novel actions of RANKL expressed by Th17 that may be promising as a new therapeutic target in RA.

W27-4

Negative correlation between serum sclerositn levels and inflammatory marker in patients with rheumatoid arturitis

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Conflict of interest: None

[Objectives] Sclerostin inhibits bone formation by suppression of Wnt-β-catenin signaling. In patients with rheumatoid arthritis, the increase of serum levels of sclerostin is previously reported. However, the impact of sclerostin on the pathogenesis of RA remains to be elucidated. The present study aimed to clarify the relationship between serum level of sclerostin and inflammatory or bone turnover markers in patients with RA. [Methods] Ambulatory female RA patients (n=83) with normal renal function enrolled in this study. Mean age was 62.5±12.6 (SD) years old. Correlation with serum sclerostin levels and other inflammatory or bone turnover markers, such as CRP, MMP3, RF, Hb, WBC, Ca, Cre, IP, ALP, P1NP, BAP, uDPD, anthropometric factor and daily dose of predonisolone was examined. [Results] Mean level of sclerostin was 36.8±18.4 pmol/L which was higher than previously reported levels in the postmenopausal women. CRP was negatively correlated with sclerostin level (Spearman's correlation coefficient and p-value, -0.289, 0.009) and that serum Cre and Hb were positively correlated with it (0.394, 0.001, 0.221, 0.047). No correlation between sclerostin level and bone turnover markers was found. The daily dose of predonisolone was negatively correlated with the sclerostin level.

W27-5

Leptin stimulates interleukin-6 production in rheumatoid synovial fibroblasts *via* phosphorylation of signal transducer and activator of transcription-3

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Conflict of interest: None

[Objectives] To determine the effects of leptin on production of proinflammatory cytokines in rheumatoid synovial fibroblasts (RSF). [Methods] Synovial tissue was obtained from patients with rheumatoid arthritis (RA) who were undergoing joint replacement surgery. Fibroblast-like cells from the third or fourth passage were used as RSF. Expression of leptin receptor mRNA was detected by RT-PCR. Inflammatory cytokines in culture medium were measured by ELISA. Expressions of inflammatory cytokine mRNA were detected by real-time PCR. The effects of RNAi targeting to leptin receptor gene and the receptor signal inhibitors were examined. The influence of leptin on signal transducer and activator of transcription 3 (STAT3) phosphorylation was measured with Western blotting. [Results] Leptin receptor mRNA was detected in RSF. Leptin increased both IL-6 mRNA and protein expression by RSF in concentration-dependent manners. Leptin induced-IL-6 production by RSF was inhibited by RNAi for leptin receptor gene, or coincubation with the receptor signal inhibitors. Enhancement of STAT3 phosphorylation by leptin was observed in RSF. In conclusion, we suggested that leptin may play an important role in pathophysiology of rheumatoid synovitis *via* STAT3 phosphorylation.

W27-6

Functional analysis of LOX-1 in Rheumatoid arthritis

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Conflict of interest: None

[Objectives] Previously, We reported that LOX-1 (Lectin-like oxidized LDL receptor 1) is expressed in chondrocytes, and involves in RA joint destruction. LOX-1 can be cleaved and released as soluble LOX-1 (sLOX-1). Then, we investigate that LOX-1 and sLOX-1 are novel targets for the diagnosis and the treatment of RA. [Methods] The expression of oxidized LDL (ox-LDL) and LOX-1 were investigated byimmunohistochemistry. 2) Levels of sLOX-1 were determined by ELISA. 3) Mice were assigned to two groups, arthritis group: intraarticular injection of ox-LDL, treatment group: pretreatment of anti-LOX-1 antibody. And the histological change was investigated. [Results] The ox-LDL and LOX-1 were expressed in the synovia of RA.2) sLOX-1 levels were significantly higher in the plasma and synovial fluid of RA patients compared with osteoarthritis patients and healthy controls, and were positively correlated with inflammatory markers and with disease activity of RA. 3) Ox-LDL caused synovitis and proteoglycan loss compared with the controls. In contrast, pretreatment with the anti-LOX-1 antibody prevented these arthritic changes. **Discussion** sLOX-1 is a novel biomarker for the diagnosis of RA, and that LOX-1 may be a potent therapeutic target for RA.

W28-1

Lysophosphatidylcholine enhances the suppressive function of human naturally occurring regulatory T cells

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Conflict of interest: None

[Objectives] Naturally occurring $CD4^+CD25^+$ regulatory T cells (nTregs) play a pivotal role in the maintenance of self-tolerance and immune homeostasis. The identification of molecules controlling Treg function is important in understanding autoimmune diseases such as RA. [Methods] From a library of bioactive lipids, we obtained lysophosphatidylcholine (LPC) as a molecule that enhanced the Foxp3 expression and suppressive function of human nTregs. [Results] The expression levels of TGF-β in LPC-treated nTregs were significantly higher than those in control nTregs. LPC enhances Foxp3 expression and the suppressive function of nTregs through TGF-β produced by nTregs themselves. Experimental knockdown of G2A and GPR4 showed that this LPC-induced TGF-β expression in nTregs was due to G2A signaling, and did not involve GPR4. Moreover, LPC activated MAPKs via G2A. In contrast, LPC did not induce the production of TGF-β from naive T cells and memory T cells. LPC is a bioactive lysolipid highly abundant in the circulation. Therefore, LPC may contribute to the maintenance and function of human nTregs in vivo. LPC displays inflammatory activity in chronic inflammation such as RA. However, LPC may contribute to suppress inflammation when sufficient number of nTregs exists in the site.

W28-2

Clarification of pathogenic CD4+ T cell subset in RA by a novel classification approach

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Conflict of interest: None

Objective: Human CD4+ T cells can be classified as either naïve, central memory (TCM), or effector memory (TEM) cells using CCR7 and CD45RA. We recently reported that they can be phenotypically subdivided into six subsets by using additional two surface markers, CD27 and CD28. To elucidate the CD4+ T cell subsets which play central roles in the pathogenesis of rheumatoid arthritis (RA), we classified CD4+ T cells from RA patients into six subsets, and analyzed the cytokine and Foxp3/RANKL expression in each subset. **Methods**: Peripheral blood CD4+ T cells from RA patients or healthy controls were subdivided by the expression of CCR7, CD45RA, CD27 and CD28. The expression of cytokines, Foxp3 and RANKL were analyzed by using eight-color flow cytometry. **Results**: The proportion of CD27+CD28+ TCM subset was significantly decreased in RA patients, compared to healthy controls. In addition, CD27+CD28+Foxp3+ TCM subset was significantly decreased in RA. Moreover, the expression of IL-17 and TNF-α in CD27+CD28+TEM subset was significantly increased in RA. **Conclusion**: Our novel classification approach is useful to explore the pathogenic CD4+ T cell subset in RA. We found that particular subset plays an important role in the inflammatory cytokine production or the regulatory function.

W28-3

Effects of abatacept on cytokine production of peripheral blood mononuclear 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 cytokine production of peripheral blood mononuclear cells(PBMC). [Methods] PBMC were obtained from healthy adult volunteers by centrifugation of heparinized venous blood over sodium diatrizoate-Ficoll dradients. PBMC(1.25×10^6/ml) were cultured with staphylococcal enterotoxin B(100pg/ml) in the presence of abatacept or control IgG(0.1 or 1 or 10μg/ml) for 5 days. Cell growth was measured by MTT assay. The concentrations of IFNγ, TNFα, IL-6 in the culture supernatants were measured using ELISA. [Results] Abatacept significantly suppressed the cell growth and the production of IFNγ of PBMC. By contrast, abatacept appeared to upregulate the production of IL-6 and TNFα by PBMC, although it did not reach the statistical significance. [Conclusion] The results indicate that the primary action of abatacept is T cell responses. The data suggest that switch to TNFα inhibitors deserves consideration in patients who do not adequately respond to abatacept.

W28-4

Identification of novel citrullinated autoantigens by in vitro citrullination

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Conflict of interest: None

To understand pathogenic and immunogenic roles of citrullination in RA, identification of citrullinated autoantigens is essential. Thereby, we made surveillance of citrullinated autoantigens using an in vitro-citrullination system. Specifically, cell lysate of Jurkat cells, citrullinated in vitro, were separated by 2-dimensional electrophoresis, and then were reacted with serum samples from patients with RA. Comparing the resulting panel with that using non-citrullinated lysate, citrullination-dependent autoantigens were detected and then identified by mass spectrometry. One of the identified proteins was adenosine deaminase (ADA), which converts adenosine to inosine. ELISA using recombinant citrullinated ADA confirmed its citrullination-dependent antigenecity. Further, we demonstrated that citrullination decreased the activity of ADA. Considering the previous reports that ADA is increased in rheumatoid synovium and that one of the therapeutic mechanisms of methotrexate is increase of the adenosine level, the citrullination of ADA may be beneficial to the amelioration of RA by keeping the adenosine level.

W28-5

Plasma talin is a new diagnostic and monitoring marker for rheumatoid arthritis

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Conflict of interest: Yes

[Background] In this paper, we focused on plasma talin, which completes the link between integrins and the actin cytoskeleton, as a diagnostic marker for RA. [Methods] Plasma and sera were obtained simultaneously from 50 (22 (44.0 %) were early-onset (≤ 6 months)) RA patients and 70 controls (Ctrl) (30 OA, 20 SLE, and 20 normal healthy controls (NC)). Plasma talin was quantified using a sandwich ELISA. [Results] Plasma level of talin was significantly ($p<0.0001$) higher in RA patients than in OA, SLE, and NC, respectively. The area under ROC curve (AUC) of talin (0.902) was larger than AUC of ACPA (0.770) in differentiation between RA and Ctrl. Moreover, the sensitivity of talin (82.3%) for the diagnosis of RA was higher than that of ACPA (58.0%), rheumatoid factor (Rf) (76.1%), and MMP-3 (74.0%) while its specificity (85.1%) was higher than that of Rf (57.0%) and MMP-3 (55.3%). Interestingly, the plasma level of talin before treatment of infliximab (IFX) was significantly ($p<0.001$) down-regulated to the normal range after IFX treatment in Remission group at 14wks whereas it did not reduce to the normal range in Non-remission group. [Conclusions] Our findings suggest clinical usefulness of plasma talin as a new diagnostic and monitoring biomarker for RA.

W28-6

Dose endocrine therapy for breast cancer induce rheumatoid arthritis?

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Conflict of interest: None

We had two cases who was diagnosed rheumatoid arthritis(RA) after endocrine therapy for breast cancer. We want to know whether there is some relation between endocrine therapy and RA. Case1 A 57-year-old woman was diagnosed as brest cancer and mastectomy were performed. After chemotherapy and radiotherapy she started aromatase inhibitor(AI). A year later she had joint pain. It was getting worse and she came to orhthopedia two years later. Her both PIPs and wrists had pain and swelling. Biomarkers were positive and she was diagnosed RA. Case2 A 43-year-old woman was diagnosed as brest cancer and mastectomy were performed. She had radiotherapy and LHRH agonist for two years. She had symptom like menopausal disorder and knee pain. 6 month later she had pain in both wrists. Her both PIPs and MCPs also had pain and swelling. Biomarkers were positive so she was diagnosed RA. There are three ways in endocrine therapy, AI, LHRH agonist and anti estrogen drug. Joint pain is written ininterview form of AI and LHRH agonist. So we investigate the symptom who is taking those. There are 60 patients taking AI and 10 injecting LHRH agonist. 25had arthraldia, 9 had hand stiffness, 7 had rocked fnger in AI and 1 had arthraldia in LHRHagonist from case recoords. We're going to interview them and check biomarker.

W29-1

Therapeutic response of biological agents in RA patients: outcomes in clinical practice from Y-CURD biologics registry

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Conflict of interest: None

[Objective] To examine the therapeutic response of biological agents (BIO) in clinical practice in RA patients from a regional registry. [Methods] This study enrolled 698 RA patients receiving BIO of registered patients in Y-CURD Biologics from 2003 to 2009, which is a regional registry of south-east area in Kanagawa prefecture. Patients are classified into three groups based on clinical response of DAS28; primary nonresponder (PNR), secondary nonresponder (SNR), and responder (RES). Patient profile, DAS28 at the start of BIO and clinical course were assessed. [Results] One hundred twenty two patientspatients were categorized as PNR, 65 as SNR, and 286 as RES. There was no difference in age of the disease onset and poor prognostic factors among these groups. Compared with RES, PNR showed higher concomitant usage of MTX (70.5% vs.64.3%) and lower DAS28 at the satrt of BIO (4.4 vs.5.3), whereas SNR showed higher concomitant usage of steroid (64.2 vs.51.7%). Each group was subdivided into the four categories according to the initial DAS28. PNR showed persistently higher DAS28 than RES during the clinical course, irrespective of the four categories. SNR showed significantly higher DAS28 than RES after 52 and 108 weeks in low to moderate and high disease activity categories, respectively.

W29-2

Study of factors affecting drug survival and long-term remission of etanercept

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Conflict of interest: None

[Objectives] The main goal of rheumatoid arthritis treatment is to improve long-term QOL by controlling symptoms and preventing progression of joint destruction. Thus, remission should be maintained via appropriate drug survival. We studied background factors affecting the rate of drug survival and long-term remission of etanercept (ETN). [Methods] Our pts on ETN were stratified by background to compare the rate of drug survival and long-term remission. [Results] The rate of drug survival in 548 pts who were initiated ETN before Jul/2011 was calculated by Kaplan-Meier method. Rate of overall 6-year drug survival was 56.3%. By background: (1) <55 yo, 61.8%; ≥55 yo, 52.4% ($p<0.001$), (2) concomitant MTX, 61.9%; w/out MTX, 52.3% ($p<0.001$). Long-term remission rate in 102 pts achieving clinical remission (DAS28-CRP <2.32) at 1-year of ETN treatment among 220 pts eligible for ≥5-year follow-up (remission rate: 46.4%). Remission was maintained up to year 5 in 50 pts (49%). Pts w/ relapse (n=22) had significantly longer disease duration than pts w/ long-term remission. ETN could achieve high rate of drug survival and long-term remission. Data suggests that start of ETN w/ MTX in younger age enables drug survival and start of ETN in early stage enables long-term remission.

W29-3

Efficacy and adherence of etanercept for two years from the aspect of patients' background

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Conflict of interest: Yes

Objective: To analyze if patients' background affects efficacy and adherence of etanercept(ETN) on rheumatoid arthritis (RA). Method: Involved in this study were 65 RA patients (18 males) who received ETN from July 2005 to Aug 2009 in our Hospital and could be followed up for 2 years. The mean age was 58.0 years old and mean disease duration was 8.0 years. Steinbroker's stage; I:5, II:16, III:14, IV:30. Mean CRP: 2.99 mg/dl, mean DAS28-ESR4 score: 5.75. MTX was administered to 30 patients (mean dose 6.8mg/wk). PSL was administered to 48 patients (mean dose 6.49mg/day). Nineteen cases had previously been received other biologics. The patient backgrounds in each outcome (using the EULAR response criteria) were analyzed. Results: Clinical outcomes of end of 2nd year included, good response: 9, clinical remission: 8, and discontinuation: 18. Reasons for discontinuation were inefficacy (9), interstitial pneumonia (3), drug eruption (2), infection (2) and others (2). Mean duration untill discontinuation was 9.7 months. Comparing 47 cases who could continue ETN for 2 years to 18 cases who couldn't, females continue ETN statistical-

ly more than males(Odds ratio 0.1702, CI 0.03997→0.7249). Conclusion: Gender could be the important factor determining whether RA patients could continue ETN or not.

W29-4

Influence of age on the outcome of etanercept in patients with RA on TBC registry.

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Conflict of interest: None

[Objectives] To investigate the influence of age on the effectiveness and tendency of ETN in patients with rheumatoid arthritis. [Methods] On our biologics study group (Tsurumai Biologics Communication; TBC), it was 958 cases were enrolled to have given ETN as a first biologics in all registration 2,072 cases. We studied 813 effective examination cases. [Results] We categorized 813 cases into two groups according to their age at first initiation of ETN therapy (under 65 years old group and 65 years old or older group) and examined it. Elderly rate was 32.8%. Baseline data of ETN of the younger group and elderly group (the following, this order) were follows. Male ratio (%) 12.8:24.7, age 49.2:71.6, RA duration (year) 9.9:11.0, Class3or4 ratio (%) 30.5:56.7, anamnesis rate (%) 32.2:49.4, MTX combination rate (%) 51.6:31.8. Drug survival rate (%) was 63.9:56.2, adverse event rate of discontinuation (%) was 9.3:24.0 and final DAS28 was 2.90:3.75. The ETN elderly start group had high Class3or4 ratio and anamnesis rate, and MTX combination rate was low. And elderly group was inferior to younger group with the effectiveness, and the rate of discontinuation by the adverse events was high. However, there was no great difference in survival rate between the younger group and elderly group.

W29-5

Influences of treatment course of methotrexate as pre-treatment on effects of adalimumab in patients with rheumatoid arthritis

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Conflict of interest: None

[Objectives] To investigate the influences of treatment course of MTX as pre-treatment on effects of adalimumab (ADA) in RA patients. [Methods] RA patients registered in TBC, who were bio-naive, with concomitant MTX and in whom ADA was started within a year after MTX initiation, were used in this retrospective study. Disease activity at MTX initiation and at ADA initiation and treatment course of MTX were compared between patients who achieved remission (DAS28-CRP<2.3) at 24 weeks after ADA initiation (RG; n=16) and patients who did not achieve remission (NRG; n=20). [Results] DAS28-CRP was significantly lower in RG than in NRG at MTX initiation. Improvement of CRP during MTX treatment was significantly greater in RG than in NRG. ROC analysis revealed that DAS28-CRP at MTX initiation and improvement of CRP during MTX treatment were good predictors for remission in ADA treatment. Cut-off values were 4.73 and -0.06mg/dl, respectively. In conclusion, remission in ADA treatment is likely to be achieved when DAS28-CRP at MTX initiation is below 4.73 and when CRP is not elevated during MTX treatment. MTX dose escalation or temporary prednisolone treatment before ADA treatment might be necessary when DAS28-CRP is over 4.73 at MTX initiation or when CRP is elevated during MTX treatment.

W29-6

Serum MMP-3 as a predictor of the disease activity in patients with rheumatoid arthritis (RA) treated with adalimumab (ADA)

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Conflict of interest: None

[Objectives] Serum MMP-3 is recognized to be correlated with disease activity in RA patients. We should judge disease activity and a drug effect appropriately in the present when remission becomes the treatment target of RA, and practice tight control. Our aim in this retrospective study was to evaluate serum MMP-3 as a predictor of the disease activity in rheumatoid arthritis in RA patients. Our aim in this retrospective study was to evaluate serum MMP-3 as a predictor of the disease activity in RA patients. [Methods] We examined the correlation of serum MMP-3 and CRP in patients with RA in ADA therapy in multicenter study TBC(Tsurumai Biologics Communication). We used ROC analysis to determine the cut off value instead of CRP lebel≦1, because the value is one of Boolean core measure sets. [Results] In ADA therapy, serum MMP-3 can become the index of disease activity and the remission prediction in ADA therapy like CRP. We considered to be a necessary condition of 52-week Boolean remission by the 4th week of the ADA therapy that serum MMP-3 value was 231 or less.

W30-1

Remission rates based on the new ACR/EULAR remission criteria and concomitant use of steroid and methotrexate in RA patients on biologics in daily practice – analysis of IORRA cohort database

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Conflict of interest: None

[Objectives] To examine remission rate and concomitant use of MTX and steroid in RA patients with each biologic drug. [Methods] RA patients commenced on biologics from 2008 to 2010 were extracted. DAS28, remission rate based on the ACR/EULAR remission, and frequencies of use and doses of MTX and steroid be-

fore and after 2 years from initiation of each biologic drug was calculated. [Results] DAS28 before and after infliximab (IFX: n=98), etanercept (ETN: n=181), tocilizumab (TCZ: n=90) and adalimumab (ADA: n=101) were 4.54/2.96, 4.35/2.93, 4.63/2.73 and 4.23/3.30, respectively. The remission rates of Boolean(trial)/SDAI/Boolean(practice)/CDAI in INF, ETN, TCZ and ADA users were 14.3/33.7/17.4/29.6%, 26.0/33.2/27.1/31.5%, 15.6/24.4/15.6/22.2% and 20.8/33.7/23.8/30.7%, respectively. Although both the frequencies of use and doses of steroid in all biologics users decreased except for steroid dose in ADA user, approximately 50% of biologics users were still treated with steroid. The frequencies of use of MTX in ETN and TCZ users decreased and that increased in ADA users, while doses of MTX in IFX and ETN users decreased and those in TCZ and ADA users increased. [Conclusion] Changes in concomitant use of steroid and MTX in RA patients on biologics were commonly observed in daily practice.

W30-2

Boolean remission prediction after the one year treatment of adalimumab (ADA) in patients with rheumatoid arthritis (RA)

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Conflict of interest: None

[Objectives] The goal of treating RA should be remission. We should adjust the treatment every 3 months. In RA patient who treated with ADA, we investigated when Boolean remission after one year (52 weeks) can be predicted, and when adjustment of treatment should have been taken into consideration. [Methods] In 153 RA patients passed 52 weeks with ADA therapy, 14 patients resulted in Boolean remission in multicenter study TBC(Tsurumai Biologics Communication). We predicted remission rate after one year by evaluating Boolean remission, DAS28-CRP, ⊿DAS28 in the 4, 12, and 24th week in ADA therapy. [Results] The remission rates of one year after at the time of resulting in remission in the 4, 12, and 24th week in ADA therapy were 3% (2/60), 5% (2/44), and 0% (0/30), when it did not result in remission 60% (3/5), 50% (3/6), and 63% (10/16), respectively. The remission rates of one year after in the case of being moderate disease activity, high disease activity, ⊿DAS28-CRP<1, no responder, and CRP>1 were 8.9%, 2.0%, 9.8%, 5.0%, and 4.0%, respectively. We suggested that the Boolean remission rate after the one-year ADA therapy can be predicted at four weeks.

W30-3

Comparison of the clinical efficacy among the TNF inhibitors, infliximab, etanercept and adalimumab

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Conflict of interest: None

[Objectives] To examine the effectiveness of infliximab (IFX), etanercept (ETN) and adalimumab (ADA), IFX, ETN and ADA were administered to 54, 60 and 35outpatients, respectively with refractory rheumatoid arthritis. [Methods] The average age of patients administered for over one year with IFX, ETN and ADA were 57.3 years, 55.7 years and 59.4 years, and the periods until starting IFX, ETN and ADA were12.9 years, 11.1 years and 13.2 years, respectively. [Results] DAS28ESR and DAS28CRP 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 16, 13 and 11 cases, and their adverse reaction was seen in 11, 8 and 2 cases, respectively. Remission of INF and ADA was seen in 5 and 3 cases. Continuous rates show ETN>ADA>INF, adverse reaction rates show INF> ETN>ADA and remission rates show INF>ADA>ETN. [Conclusion] According to remission rates, the anti TNF blockade is highly preferable to TNF receptors. These results show that it is important to select biologics on the basis of continuity, remission and adverse reaction rates.

W30-4

Effects of early, vigorous intervention with infliximab on treatment target (remission)

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Conflict of interest: None

Objectives: To investigate the effects of early, vigorous intervention with infliximab (IFX) on the treatment target. **Methods**: The subjects were 200 IFX-treated RA patients who could be monitored for at least 150 wk. They showed RA without (Stage I) and with joint destruction (Stage II~IV) at initiation of the treatment. DAS28-CRP and disease activity time-courses were evaluated by the LOCF method. The numbers of patients at Stage I, II, III and IV were 65, 91, 38 and 6. **Results**: At 150 wk, 36.5% of patients continued on IFX, and 58% of them discontinued IFX except 5.5% with follow-up impossible. Discontinuation was due to marked efficacy (36%), insufficient efficacy (32%), adverse reactions (11%), and others (9%). In Stage I patients, the mean DAS28-CRP at 14 wk was 1.83 ± 0.71 (SD), having a rapid decrease below the remission criterion (DAS<2.3). The remission/low disease activity (LDL) achievement rates were 84.4 and 85.9% at 14 and 150 wk. In Stage II~IV patients, DAS28-CRP at 14 wk was 2.63 ± 0.98, below the LDL criterion (2.7). The remission/LDL achievement rates were 48.9 and 60.7% at 14 and 150 wk. **Discussion**: The results suggest that early IFX induction thorough assessment of the indication can obtain higher treatment targets and maintenance of efficacy for 150 wk.

W30-5

A comparative study of early clinical efficacy among three anti-TNF agents ~Drag Race Study~

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Conflict of interest: None

[Objectives] To compare early clinical efficacy among three anti-TNF agents (IFX, ETN, ADA) in RA patients. [Methods] Bio-naive RA patients treated with one of three anti-TNF agents with concomitant MTX were included. Clinical data at initiation and at 6 weeks in IFX-G (n=64) and clinical data at initiation and at 4 weeks in ETN-G (n=43) and ADA-G (n=24) were used. Improvement rate (%) and improvement value (Delta) of 6 indices(DAS28-ESR, DAS28-CRP, VAS, CRP, ESR, MMP-3, mHAQ) were compared between groups. Comparison between ETN25mg/w-G and ETN50mg/w-G was also performed. [Results] d-DAS28-ESR was1.20±0.91 in IFX-G, 1.20±0.86 in ETN-G and 1.11±0.87 in ADA-G. d-CRP was 2.1±2.3 in IFX-G, 2.1±2.0 in ETN-G and 2.3±2.2 in ADA-G. %DAS28-ESR was 22.3±15.8% in IFX-G, 22.

0±16.1% in ETN-G and 18.3±13.0% in ADA-G. %CRP was 56.4±44.4% in IFX-G, 64.7±32.6% in ETN-G and 56.9±36.7% in ADA-G. No significant difference was observed between groups. d-DAS28-ESR in ETN25mg/w-G was 1.32±0.89 and 1.01±0.82 in ETN50mg/w-G. There was no significant difference in early clinical efficacy between ETN25mg/w-G and ETN50mg/w-G. This study showed that all of three anti-TNF agents had early clinical efficacy in same extent and that early efficacy in ETN25mg/w-G was comparable to that in ETN50mg/w-G.

W30-6

The efficacy and retention rate of biologics in our hospital

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Conflict of interest: None

[Objectives] To examine the efficacy and retention rate of biologics in our hospital. [Methods] 320 patients who started to treat biologics between May, 2001 and August, 2011, were included in this study. The average age was 55.7. The average follow-up period was about 2.0-year. They were subdivided as follows; Infliximab(IFX); 54, Etanercept(ETN); 54, ETN+Methotrexate (MTX); 110, Tocilizumab(TCZ); 64, Adalimumab(ADA); 31, and Abatacept(ABA); 7, 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 4.4 in IFX, 4.2 in ETN, 4.2 in ETN+MTX, 4.8 in TCZ, 3.4 in ADA, and 3.6 in ABA group, respectively. Then 6 months after, each value was 2.8, 2.7, 2.4, 2.5, 2.5, and 2.2. The retention rate 1 year after was 86% in IFX, 82 % in ETN, 94% in ETN+MTX, and 86% in TCZ group, respectively. The retention rate 2 years was 68, 70, 69, and 68%, respectively. [Discussion] These findings suggest that each group showed almost the same efficacy in DAS28(3)-CRP. Although ETN+MTX group showed highest retention rate in 1 year after introduction, each group showed almost the same retention rate in 2 years.

W31-1

Histological changes of synovium after DMARDs or biologics treatment for RA

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Conflict of interest: None

[Objectives] We examined histological changes of synovium before and after DMARDs or biologics treatment for rheumatoid arthritis (RA). **[Methods]** The paraffin embedded synovial tissues were obtained from 18 RA patients. Each patient took biologics after DMARDs treatment. We examined histological and immunohistochemical changes of synovium before and after treatment by DMARDs or biologics, respectively. **[Results]** The inflammatory score such as the number of synovial lining cells, blood vessels and inflammatory cells decreased more massive after treatment by biologics than DMARDs. In addition, the number of positive cells of MMP-3, TNF α, CD68 and CD34 decreased more massive after treatment by biologics than DMARDs, too. Especially, the effect of the biologics was massive in non-responder of DMARDs. **[Discussion]** By using histochemical examination, the results suggest that biologics have stronger anti-inflammatory effects especially in non-responder of DMARDs. **[Summary]** Histologically, biologics suppress the synovial inflammation even in refractory RA.

W31-2

The Cytotoxic Effects of Certolizumab pegol and Golimumab Mediated by Transmembrane Tumor Necrosis Factor α

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Conflict of interest: None

Objective.The aim of this study was to investigate cytotoxic effects mediated by transmembrane TNFα of new anti-TNFα agents, certolizumab pegol and golimumab. ***Methods***. Transmembrane TNFα-expressing Jurkat T cells which did not express TNF receptors were used. The binding ability to transmembrane TNFα, antibody-dependent cell-mediated cytotoxicity (ADCC), complement-dependent cytotoxicity (CDC), and apoptotic effect mediated by each anti- TNFα agent were examined. ***Results***. Certolizumab pegol and golimumab bound to transmembrane TNFα. Golimumab mediated ADCC and CDC, in contrast certolizumab pegol did not. Certolizumab pegol directly induced cell death on transmembrane TNFα-expressing cells by the manner different from apoptosis induced by other anti-TNFα agent. The apoptotic effect of golimumab was less than those of infliximab and adalimumab. ***Conclusion***. We have shown for the first time that certolizumab pegol directly induces cell death in transmembrane TNFα-expressing cells. This direct cytotoxic effect may explain the efficacy of certolizumab pegol for crohn's disease. The apoptotic effect of golimumab was weak compared to the other full-length antibodies, infliximab and adalimumab.

W31-3

The effect on bone metabolism markers by etanercept treatments for patients with rheumatoid arthritis

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Conflict of interest: None

In order to clarify a bone destructive control mechanism by etanercept, the influence on the bone metabolism related markers by etanercept was investigated. [Objects and methods] 30 RA patients are treated with etanercept. Serum and urine are extracted

before medication of etanercept and after-medication three months, and six months, The pyridinoline (PYD) and deoxypyridinoline of urine (DPD), cross-linked N-telopeptides of type I collagen (NTX) and serum bone alkaline phosphatase (BAP), osteoprotegerin (OPG) and soluble receptor activator of NF-kappaB ligand (sRANKL) and furthermore, serum IL-23 and IL-17 were measured. DAS28-CRP, serum CRP, erythrocyte sedimentation rate (ESR), and a CA-RF value were measured as a clinical laboratory test. [Results] Compared with etanercept medication before, serum CRP, ESR 2h, CA-RF, and DAS28-CRP significantly fell after after-medication three months. The DPD and the PYD of urine and serum sRANKL fell significantly after etanercept medication in six months, and serum IL-23 significantly fell after etanercept medication in three months. The serum BAP significantly increased after etanercept medication in three months. Moreover, there was no significant change of the serum OPG, serum IL-17 and NTX of urine.

W31-4

Effects of anti-tumor necrosis factor therapy on periodontal condition in rheumatoid arthritis patients

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Conflict of interest: None

[Objectives] Anti-tumor necrosis factor (TNF) therapy has been shown as an effective approach in the treatment of rheumatoid arthritis (RA). TNF play an important role in the pathogenesis of RA and periodontitis. The aim of this study was thus to evaluate the effects of anti-TNF therapy on the clinical periodontal condition in RA patients. [Methods] Periodontal and rheumatologic examination were performed in 26 RA patients who received anti-TNF medication (anti-TNF group) and 26 age-, gender-, and smoking status-balanced RA patients without anti-TNF blockade (control group) at baseline and 6 weeks later in Niigata Rheumatic Center. Serum levels of interleukin-6, TNF-α, and anti-cyclic citrullinated peptide (CCP) antibodies were determined by ELISA. [Results] Significant improvements of periodontal conditions were observed in the anti-TNF group, although oral hygiene levels proved comparable between the time points. Decreased changes in serum levels of TNF-α were also found in the anti-TNF group. Furthermore, significant differences in the changes in serum levels of anti-CCP antibodies were shown between the groups. These results suggest that anti-TNF therapy may have a beneficial effect on the periodontal condition in patients with RA.

W31-5

Analysis of factors influencing induction of anti-DNA antibodies during TNF-alpha blocking therapy for rheumatoid arthrtis

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Conflict of interest: Yes

[Objective] An elevation of serum anti-DNA antibody level and onset of drug-induced lupus erythematosus (DILE) has been rarely observed, although it is well known that TNF-alpha blocking therapy frequently induces production of anti-nuclear antibodies. However a few cases of DILE during treatment with TNF-alpha blocking agents has been recently reported. We investigated association between induction of anti-DNA antibody and clinical factors during TNF-alpha blocking therapy for rheumatoid arthritis (RA). [Methods] Eighty-eight patients with RA treated with TNF-alpha blocking agents (infliximab 41 patients, etanercept 47 patients) were analyzed. Serum levels of anti-DNA antibodies were measured by RIA. [Result and Conclusion] Two cases were diagnosed as DILE. The prevalence and mean serum levels of anti-DNA antibody were 18.2% and 39.4 IU/ml as a whole, 24.4% and 51.3 IU/ml in the infliximab group and 13.0% and 19.5 IU/ml in the etanercept group, respectively. Forty percent of RA patients accompanied by Sjogren's syndrome showed the positivity of anti-DNA antibody. DILE might developed more frequently than had been previously recognized and it should be careful for the treatment with TNF-alpha blocking agents for RA patients accompanied with Sjogren's syndrome.

W31-6

Adalimumab overcome P-glycoprotein -mediated multidrug-resistance in a patient with intractable Felty syndrome

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Conflict of interest: None

Felty syndrome (FS) is an intractable complication of progressive RA associated with neutropenia and splenomegaly. P-glycoprotein (P-gp) on activated lymphocytes mediates drug resistance by active efflux of drugs from the cells. We observed a FS patient with highly active RA characterized with severe neutropenia, positive anti-neutrophil antibody and splenomegaly despite high dose corticosteroid (CS). P-gp was highly expressed on B cells, resulting in exclusion of intracellular CS (iCS) and in low iCS levels in lymphocytes in vitro. Because disease activity of FS and P-gp overexpression were not controlled by the treatments with MTX, TAC and mPSL pulse therapy, a TNF-inhibitor adalimumab (ADA) was used. Two weeks after starting of ADA, the P-gp expression on B cells was decreased and iCS was recovered. Subsequently, elimination of anti-neutrophil antibody and neutropenia, improvement of splenomegaly and clinical remission (CR) of RA were observed and CS was terminated. A marginal expression of P-gp and CR were maintained for 52 weeks. These results indicate that TNF-inhibitors such as ADA are effective for refractory FS complicated with RA, and that successful efficacy of ADA could be brought by the reduction of P-gp on B cells and the overcoming of multi-drug resistance.

W32-1

Immune complexome analysis for a novel serum proteomic strategy toward patients with rheumatoid arthritis

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Conflict of interest: None

Objective: Circulating immune complexes (IC) are the direct and real-time mirror to immune response, and we have tried to examine the sera of patients with RA through immune complexome analysis. Methods: We have proposed a novel proteomic strategy of immune complexome analysis, which consists of IC separation from serum, direct tryptic digestion and nano-liquid chromatogra-

phy-tandem mass spectrometry, for identification and profiling of antigens in IC and applied it to RA as a model target. Sera from patients with established RA as well as early-stage RA were examined. Results: As for the patients with established RA (N = 21, healthy controls: N = 13), circulating IC containing thrombospondin-1 (TSP-1) and platelet factor 4 (PF4) were specifically detected in sera of RA patients. Especially, the sensitivity of IC containing TSP-1 was defined as 81%. The same results were found in patients with early-stage RA (N = 26), and especially, IC containing TSP-1 was determined in sera of anti-CCP Abs/RF-negative RA patients (5 out of 9 samples). Conclusions: Immune complexome analysis may be a valuable and novel serum proteomic strategy trying to identify the biomarkers in patients with RA. Additionally, IC containing TSP-1 could be a noble biomarker in seronegative RA patients.

W32-2

Assessment of the therapeutic effect by Multi-Biomarker Disease Activity (MBDA) in patients with rheumatoid arthritis treated with TNF inhibitors

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Conflict of interest: None

[Objectives] A simple, objective blood-based disease activity (DA) index is expected to be useful for management of rheumatoid arthritis (RA). We analyzed the multi-biomarker DA (MBDA) algorithm in the BeSt study, and here evaluate it in Japanese RA patients (pts). [Methods] A total of 147 pts with TNF inhibitors (TNFi) (IFX 49, ETN 49, ADA 49) were analyzed. 12 biomarkers (VCAM-1, EGF, VEGF-A, IL-6, TNF-RI, YKL-40, MMP-1, MMP-3, leptin, resistin, SAA, CRP) were measured by Meso Scale Discovery (MSD) at 0, 24, and 52 weeks after starting TNFi and input into the Vectra DA algorithm to calculate a single MBDA score between 1-100. Spearman correlation and AUROC were performed. [Results] Baseline characteristics were: age 60 [50-68], DAS28 5.7 [5.0-6.5], and disease duration 60 [18-168] mo (Median [IQR]). MBDA score was correlated to DAS28 (rho = 0.64, 95%CI = 0.54-0.73, p < 0.001, and distinguished low disease activity (AUROC = 0.80, 95%CI 0.72-0.87, p < 0.001). At 52 weeks, 56% of the pts achieved EULAR good response (GR), and DMBDA score distinguished GR +/- (AUROC = 0.68, 95%CI 0.58-0.76, p < 0.001). No differences in the MBDA/DAS28 relationship were found between the three TNFi. [Conclusion] The MBDA score can assess the efficacy of TNFi in Japanese RA pts.

W32-3

Clinical significance of Brachial Flow Mediated Dilation in Patients with Rheumatoid Arthritis

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Conflict of interest: None

Purpose: The purpose of this study was to evaluate the clinical significance of brachial flow-mediated dilation in randomly selected patients with rheumatoid arthritis (RA). *Methods*: Thirty-four patients, who met the American College of Rheumatology 1987 revised diagnostic criteria, were randomly selected for this study. The percentage of brachial flow-mediated dilation (%FMD) and the single highest carotid intima-media thickness (MaxIMT) were examined by ultrasonography (US). *Results*: Of the 34 subjects, the mean MaxIMT and %FMD were 1.2 ± 0.1mm, and 8.9 ± 0.6%. Thirty-two percent had hyperlipemia, and 38% of the patients received anti- tumor necrosis factor alpha (TNF) therapy (6 infliximab, 5 etanercept, and 2 adalimumab). The %FMD value was significantly correlated with the anti-TNF therapy (r=0.403, p<0.05), and Disease Activity Score for 28 joints- C-reactive protein (r=–0.449, p<0.01). On the other hand, there were no significant correlations between MaxIMT and several parameters, with the exception of age (r=0533, p<0.01). *Conclutions*: We found significant associations between the FMD measures, disease activity, and anti-TNF therapy in randomly selected patients with RA. Our study indicates that the measurement of %FMD might be a valuable tool for predicting RA prognosis.

W32-4

Increase of serum matrix metalloproteinase-3 in patients with connective tissue diseases and healthy individuals receiving glucocorticoids

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Conflict of interest: None

[Objectives] To examine the influence of glucocorticoids (GC) on serum MMP-3 levels. [Methods] Patients who were GC naïve, received more than 0.5 mg/kg/day of prednisolone (PSL) equivalent, and who were measured serum MMP-3 before and after GC treatment, were retrospectively collected from the charts. To examine the influence of low-dose GC, 11 healthy individuals (9 men, 2 women) received 5 mg/day of PSL for 7 days in the morning, and serum MMP-3 were measured before and after PSL administration. [Results] There were 28 patients (16 women and 12 men) with a mean age of 48.9 (range 22-79), and the diseases were the followings: DM in 7; AOSD in 4; SLE and SSc in 3 each; PM, Churg-Strauss syndrome, MPA in 2 each; and MCTD, SS, Takayasu arteritis, Behcet's disease, and retroperitoneal fibrosis, in 1 each. The dosage of GC was 20-80 mg/day of PSL equivalent (mean 49.1 mg/day). Serum MMP-3 increased from 96.8 ± 39.1 ng/ml (mean ± SD) before treatment to 394 ± 136.1 ng/ml in men, and 72.7 ± 47.2 ng/ml to 187.6 ± 101.7 ng/ml in women, after 4-31 days (mean 9.9 days). In healthy individuals, serum MMP-3 increased from 80.5 ± 25 ng/ml to 162.0 ± 48 ng/ml in one week. Therefore, MMP-3 levels should be evaluated with caution in patients with rheumatoid arthritis who are on GC therapy.

W32-5

Abnormal KL-6 values during treatment with biologics for rheumatoid arthritis

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Conflict of interest: None

[Objectives] Interstitial pneumonia (IP) is a important complication of rheumatoid arthritis (RA), making monitoring important. KL-6 is a useful marker for IP. We analyzed cases in which abnormally high serum levels of KL-6 were observed during the treatment with biologics and investigated their significance. [Methods] The transition of KL-6 values was investigated with 323 RA patients undergoing treatment with infliximab (IFX), etanercept (ETN), adalimumab (ADA), and tocilizumab (TCZ) since 2003. [Results] KL-6 shifted from normal values to abnormally high levels during treatment in 25 cases (7.7%), wherein methotrexate was used in combination in all of these cases. By formulation, it was: IFX: 15/142; 10.6%. ETN: 6/143; 4.2%, ADA: 4/19; 21%, and TCZ: 0/19; 0%. IP aggregation was observed in 5 cases upon chest CT, with actual abnormalities observed upon imaging in 1/5 of cases in which abnormally high levels of KL-6 were indicated. There were no cases with serious respiratory dysfunction. No difference was observed in the disease activity and response to therapy among cases indicated with abnormal KL-6 values and cases without change. It is possible that the action mechanism of each biological preparation is involved in the occurrence of abnormal KL-6 values.

W32-6

Serum homocysteine levels in patients with rheumatoid arthritis

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Conflict of interest: None

Objectives: Serum levels of homocysteine (sHcy) has been reported to be associated with atherosclerosis. The aim of the study was to investigate the influence of methotrexate (MTX) on sHcy in patients with rheumatoid arthritis (RA), and to evaluate the characteristics associated with the hyperhomocysteinaemia. **Methods:** Clinical and laboratory data were obtained from 863 RA patients who participated in IORRA study performed in April, 2006. sHcy was determined by enzymatic assay (FHRK100, Axis-Shield). **Results:** The median level of sHcy (μmol/L) was higher in males than that in female (17.8 vs 15.0, $p<0.0001$). In female, sHcy in patients treated with MTX was not different from patients without MTX. However, in patients treated with MTX, folate supplementation was significantly associated with decrese in sHcy (14.5 vs 15.7, $p=0.0021$). In males, treatment with MTX with or without folate supplementation had no effect on sHcy. **Conclusions:** Minimum effect of MTX on sHcy was observed in patients with RA. However, in female patients treated with MTX, folate supplementation was associated with decrease in sHcy, suggesting that folate supplementation was useful to prevent atherosclerosis in female RA treated with MTX.

W33-1

The change in hte number of orthopadic surgery for rheumatoid arthritis patients in our hospital

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Conflict of interest: None

[Objectives] The purpose of this study is to research of the change in the number of orthopedic surgery, methotrexate(MTX) and Biologics are increasingly being used to treat rheumatoid arthritis. [Methods] We research the number of orthopedic surgery and it's operative procedure for the patients of rheumatoid arthritis in our hospital from 2001 to 2010. [Results] The number of operation was approximately 35 at every year. Not decrease during a 10-yeards period. Operation of all joints of the lower extremities was not decrease. But total hip arthroplasty was decreased. Operation of all joints of the upper extremities was not decrease too. But total elbow arthroplasty and operation of fingers were increased. Synovectomy was decreased during a 10-yeards period. Through the use of MTX and Biologics, synovitis is suppression. So decrease the number of synovitis. There is the possibility that decreased number of total hip arthroplasty is due to suppression of joint destruction. The other way, the number of operation of upper extremities, ankle and foot increased. There is the possibility that the needs of these operations is increased by increasing the activity of patients through the use of MTX and Biologics

W33-2

Analysis of rheumatoid arthritis operation receiving Tacrolimus treatment

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Conflict of interest: None

[Objectives] It has been controversial whether the use of tacrolimus constitutes a risk factor of perioperative complication. We investigated patients with rheumatoid arthritis used of tacrolimus. [Methods] Seventy eight RA patients were operated from January, 2010 to October, 2011. Twenty four RA patients were treated with tacrolimus (TAC group) and fifty four were not treated with tacrolimus (non-TAC group). We did not discontinue tacrolimus perioperative period. Various biologic agents (INF 1, ETN 2 and ADA2) were used in TAC group and (INF 6, ETN 8, ADA 2, TCZ 1 and ABA 1) were used in non-TAC group. Surgical site infection and delay of wound healing were surveyed. [Results] A case of surgical site infection was seen in both groups. Two cases of both groups had experience of late wound healing. The risk of SSI and delay of wound healing did not show a significant difference. There is not the evidence about perioperative care of tacrolimus, and the guideline of the discontinuation such as MTX is not shown. Tacrolimus have been used in a high dose without discontinuation in the transplantation surgery. Some infection cases of RA were reported during tacrolimus use. Evidence construction of tacrolimus treatment perioperative period is expected in future.

W33-3

The post traumatic shoulder function after conservative treatment of the proximal humeral fractures in RA patients

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Conflict of interest: None

(Objectives) To compare the post traumatic shoulder function after conservative treatment of the proximal humeral fractures in RA patients and non-RA patients. (Patients and Methods) Thirteen proximal humeral fractures with RA patients (1 man, 12 women, mean age of 78 years) were treated conservatively between April, 2005 and March, 2010. Control group were 50 proximal humeral fractures with non-RA patients (10 men, 42, women, mean age of

72 years) who treated conservatively between April, 2005 and March, 2010. Achievement of bone union, pain relief and shoulder ROM were investigated in these patients. (Results) At the last follow-up, bone union was achieved in 73% cases, pain relief, in 18% cases and active shoulder elevation was average 86 degrees in RA patients. On the other hand, bone union was archived in 96% cases, pain relief, in 88% cases and active shoulder elevation was average 130 degrees in non-RA patients. (Conclusion) Shoulder joint damage and dysfunction before trauma was present in RA patients, but post traumatic shoulder function of proximal humeral fractures in patients with RA was poor.

W33-4

The Effect of Biologics on Upper Cervical Spine Lesions in Patients with Rheumatoid Arthritis

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Conflict of interest: None

[Objectives] We examined upper cervical spine lesions (atlantoaxial subluxation, vertical subluxation) in cases with rheumatoid arthritis (RA) and analyzed if biologics can inhibit the progress of the lesions. [Methods] 27 patients (3 males, 24 females), followed for more than 6 months. Mean age was 69.7 years, mean disease duration was 14.4 years, and mean follow-up period was 2.5 years. Lesions were verified on X-ray on the first visit in all cases. Posterior cervical spinal fusion was performed on 5 patients due to progressive instability of the upper cervical spine, severe headaches, or neck pain. 10 patients were treated with biologics for more than 2 years: 6 were treated with ETA, 2 with IFX, 1 with ADM, and 1 with ABT. [Results] Progression of the lesion was verified on 11 of 27 patients (40.7%) on X-ray. Compared with non-progressive patients, progressive patients had significantly longer mean disease duration (18.5 and 11.4 years, respectively); however, there was no significant difference in levels of MMP3, CRP. 4 of 10 cases (40.0%) treated with biologics had progressive lesions, while 7 of 17 cases (41.2%) who did not receive biologic treatment also had progressive lesions. It is difficult to inhibit the progress of upper cervical spine lesions with biologics alone.

W33-5

Management of overwork and misuse in patients with rheumatoid arthritis during biologic therapies

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Conflict of interest: None

[Objectives] To investigate the importance of ADL guidance from the rehabilitation view point, we assessed RA patients with background of overwork and misuse during biologic therapies. [Methods] Seventeen RA patients (2 males and 15 females, mean age: 61.7 years old, mean disease duration: 11.8 years) who showed recurrence of joint symptom in spite of good response during biologic therapies were enrolled in this study. We investigated patterns of daily living and actual motions, and then performed educational intervention. We evaluated VAS, DAS28 and HAQ before and after the intervention. [Results] All patients tended to perform overwork and/or misuse of their joints. VAS in 53% and DAS28 in 73% of the patients improved after educational intervention for the usage of their joints. All patients were satisfied with our educational intervention. [Conclusions] Therapeutic intervention of rehabilitation is very important for patients with RA to improve ADL and QOL under biologic therapies.

W33-6

Usability analysis of music therapy for patients with rheumatoid arthritis

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Conflict of interest: Yes

[Objectives] Recently music therapy is innovated in rehabilitation for dementia and parkinsonism, however, few reports have been made for rheumatoid arthritis (RA). We previously reported that music therapy improved general health condition and pain of patients with RA attending to the patient class. **[Methods]** Music therapy was conducted by a music therapist, a pianist, hospital staffs, and healthcare students. Eight Japanese songs were sung with a piano accompaniment. General health condition, pain, and state anxiety were surveyed by self-rating questionnaire including 10cm VAS, face pain rating scale, and STAI. **[Results]** Twenty-four female patients with RA were participated the survey. mHAQ of the attendee was 0.64±0.80. VAS was improved from 2.9±2.9 to 2.5±2.9 ($P<0.01$), face scale was improved from 5.8±3.4 to 3.6±3.3 ($P<0.01$), and state anxiety of STAI was improved from 38.4±9.4 to 30.4±9.6 ($P<0.01$) by music therapy. **[Conclusion]** Music therapy may improve physical and psychological conditions of patients with RA.

W34-1

Clinical results of surgeries (synovectomy) in RA Patients treated with Biologic agents

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Conflict of interest: None

Clinical results of synovectomy in surgeries performed in rheumatoid patients treated with Biologic agents were evaluated. Twenty surgeries were performed on 17 RA patients(15 woman), with mean age 56.9 years old, treated with biologic agents (etanercept 15, infliximab 2) Surgeries were including 9 synovectomies of the wrist, 7 synovectomies in the elbow, 3 synovectomies of the thumb and 4 endoscopic synovectomy of the knee. Complications like postsurgical infections or poor wound healing were not observed. In 3 of the patients using Etanercept the RA flared up again while the drug was discontinued, but improved after readministration of the preparation. After surgery, the same biologic therapy was continued in all cases. Swelling and pain was not observed in the treated joints. Synovectomy for swollen and tender joints will be useful treatment to control disease activity in RA patients treated with Biologic agents.

W34-2

Orthopaedic surgery in RA patients with biologic agents

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Conflict of interest: None

[Objectives] It has been reported that biologic agents inhibit the progression of the joint destruction in rheumatoid arthritis (RA). For this reason, these agents have been often used for the treatment of RA recently. The purpose of this study is to evaluate

the effectiveness of orthopaedic surgery in RA patients with biologic agents. [Methods] One hundred and forty-two surgeries of RA patients with biologic agents were evaluated (infliximab: 59 surgeries, etanercept: 65, adalimumab: 12, tocilizumab: 6). They underwent orthopaedic surgery from 2004 to 2010. The mean age at operation was 57 year-old. [Results] At the time of follow-up, one deep infectious episode and 4 delayed wound healing related to biologic agents were observed in patients who received orthopaedic surgery. In spite of observed minor complication, the postoperative clinical courses of these patients were good, and the results of the surgeries were excellent. In conclusion, orthopaedic surgery under biologic agents' therapy is thought to be safely performed and useful for RA patients.

W34-3

Perioperative complication in patients with RA undergoing orthopedic surgery treated biologics

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Conflict of interest: None

[Objective] The objective of this study is to examine the effect of biologicas on delayed wound healing and surgical site infections in RA patients who need orthopedic surgery. [Methods] Subjects are 298 RA joints with biologics and 220 RA joints without biologics which underwent surgery at our department from January 2006 to October 2011. Biologics used were ETN for 240 joints, INF for 16 joints, ADA for 17 joints and TCZ for 25 joints. The cases needed resuture after suture removal were defined as delayed wound healing. Also, postoetative infections were examined after categorizing the subjects into two groups, namely, superficial infection group and deep infection group, and the frequency of occurrence of adverse events was examined. [Results] Delayed wound healing was observed at 16 joints in the with-biologics and at 2 joints in the without-biologics. There was no significant difference in the frequencies of occurrence of diseases between the two groups. Four joints were observed with postoperative infection in the with-biologics. [Conclusions] Usage of biological products did not increase the frequency of occurrence of perioperative adverse event.

W34-4

Postoperative complications in patients with rheumatoid arthritis treated with biologic agents

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Conflict of interest: None

【Objective】 Although biological agents have been widely used for the treatment of RA, it is still not revealed that how the agents influence postoperative condition of the patients with RA. We have up-dated the clinical data and postoperative complications of RA patients with or without biological agent therapy. 【Method】 We investigated perioperative CRP levels, disease activity, and postoperative complications in the 84 operation cases of RA treated with biologics compared with 82 operation cases without biologics. The number of cases with each biological agent was 31 with INF, 37 with ETN, 10 with ADA, 6 with TCZ, respectively. 【Results】 In our previous report, the CRP level before and one month after the surgery was significantly higher in biologics group than in non-biologics group, however, there was no significant difference between the groups in this series. It indicate that the disease activities in non-biologics group have been controlled more tight than in the previous report. On the other hand, the CRP levels on the day after the surgery tended to be higher in biologics group, which shows potential increased invasiveness of surgery in the group of patients treated with biologics.

W34-5

surgical treatment under biologic agents

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Conflict of interest: None

[Objectives] Biologic agents is very useful in that they inhibit the progression of joint damage in the patients with rheumatoid arthritis (RA). However, we have performed surgery to the patients under the treatment with biologic agents. The purpose of this study is to investigate which patients under the treatment with biologic patients need surgery. [Methods] The RA patients under the treatment with biologic agents who underwent surgery at our hospital up to April 2011 were included to this study. Demographic data, including disease duration, DAS28-CRP, the time to surgery from the initiation of biologic agents were collected. [Results] The case of surgery were 89 cases, including infliximab 31 cases, etanecept 58 cases. The age in surgery were 60.2 years, disease duration were 14.6 years, DAS28-CRP in the initiation of biologic agents were 5.56±0.98, DAS28-CRP in surgery were 3.63±0.90. TKA were 40 cases, THA were 21 cases, wrist plasty 13 cases, foot surgery were 10 cases, DAS28-CRP in surgery were 3.80±0.88, 3.62±0.79, 3.07±0.90, 3.31±0.76. [Conclusion] Even some of patients with low disease activity need better physical function and undergone surgery. It is important to consider surgical treatment even in the era of treatment with biologic agents.

W34-6

Neutrophil CD64 as a useful marker of infection in perioperative period in patients with rheumatoid arthritis treated with tocilizumab

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Conflict of interest: None

[Objective] Anti-IL-6 receptor blocker Tocilizumab (TCZ) has been reported to increase the incidence of infection, and to mask infection signs such as fever and CRP elevation, derived from immune suppression. We have reported that CD64 expressed on neutrophils was upregulated in infection. It is confirmed that CD64 expression is not affected by the disease activity of RA and is upregulated in infection even in TCZ medicated RA patients. Our study was designed to confirm and extend the utility of CD64 expressed on neutrophils as a marker for detection of infection of TCZ medicated RA patients in perioperative period. [Methods] Before an operation and postoperative on 1, 3, 7, and 14th day, the ex-

pression level of CD64 per neutrophil were measured for 12 orthopedics operationsof the TCZ medicated RA patients. Although there was no case of infection in the operated part, there were two cases of infection in the other part. [Results] In the uninfected patients, the maximum was 1800 molecules per cell, twice less than the value before operations. On the other hand, in the infected patients it was more than 2000 cutoff value and the maximum was 8000. It is summarized that CD64 is useful as a marker distinguishing infection in TCZ medicated RA patients in perioperative period.

W35-1

Mucosal-associated invariant T cells in patients with autoimmune diseases.

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Conflict of interest: None

[Objectives] Mucosal-associated invariant T (MAIT) cells are a subset of innate lymphocytes which express an invariant TCRα chain (Vα7.2-Jα33 in humans). MAIT cells are enriched in intestinal lamina propria and require B cells as well as commensal flora for their peripheral expansion. We previously demostrated that MAIT cells exacerbate disease in arthritis models. In this study, we asked whether MAIT cells are relevant to human autoimmune diseases including systemic lupus erythematosus(SLE) and rheumatoid arthritis(RA). [Methods] Whole blood samples were stained with monoclonal antibodies againt CD3, γΔTCR, Vα7.2TCR, and CD161 to identify MAIT cells. Peripheral blood mononuclear cells were cultured with various cytokines without TCR stimuli. [Results] The percntages of MAIT cells of patinents with RA or SLE were reduced compared with healthy controls. Particularly, the frequency of MAIT cells of SLE patients showed about 5-fold decrease and this was more profound in those with active disease. MAIT cells produced cytokines and proliferated upon cytokin stimulation without TCR stimuli, highlighting their feature as innate lymphocytes. MAIT cells may be related to the pathogenesis of human autoimmune diseases and further studies are required to reveal their roles in autoimmunity.

W35-2

Function of SOCS1 in regulatory T cells under inflammatory conditions

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Conflict of interest: None

Regulatory T cells (Tregs) from T cell specific SOCS1$^{-/-}$ mice were reported to convert into Th1- or Th17-like cells (exFoxp3 cells), which lost the Foxp3 expression and suppressive function. Because these Tregs are constantly exposed to high amount of interferon gamma (IFNγ) from non Tregs in vivo, we analyzed Treg specific SOCS1$^{-/-}$ mice. These mice caused DSS induced colitis more severely compared to wild-type mice, however, EAE was remitted in Treg specific SOCS1$^{-/-}$ mice. Tregs from Treg specific SOCS1$^{-/-}$ mice maintained the Foxp3 expression transferred into *Rag2*$^{-/-}$ mice, differently from Tregs from T cell specific SOCS1$^{-/-}$ mice. In vitro, Tregs from T cell specific SOCS1$^{-/-}$ mice produced IFNγ after 3 days culture with CD3/CD28 stimulation, however, Tregs from Treg specific SOCS1$^{-/-}$ mice did not. When Tregs from Treg specific SOCS1$^{-/-}$ mice were cultured with antigen presenting cells from T cell specific SOCS1$^{-/-}$ mice, which had high expression of CD80 and CD86, these Tregs produced IFNγ. Production of IFNγ from Tregs from Treg specific SOCS1$^{-/-}$ mice were disappeared by anti-IFNγ antibody or anti-IL-12 antibody. These results suggest SOCS1$^{-/-}$ Tregs convert into exFoxp3 cells efficiently under inflammatory conditions, and might protect some disease status by production of IFNγ.

W35-3

Tofacitinib induces CD4$^+$CD25$^-$LAG3$^+$ regulatory T cells *in vivo* and the expression of Egr2 in CD4$^+$ T cells *in vitro*

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Conflict of interest: None

[Objectives] CD4$^+$CD25$^-$LAG3$^+$ T cells (LAG3$^+$ Treg), a novel subset of murine regulatory T cells, express an anergy associated transcription factor, early growth response gene-2(Egr-2) and strongly suppress autoantibody production. Previous study reported that the frequency of CD4$^+$LAG3$^+$ T cells was increased in Jak3-deficient mice. Our objective is to examine the effect of a Janus kinase (Jak) inhibitor tofacitinib on the induction of LAG3$^+$ Treg. [Methods] Tofacitinib was continuously administered to young C57BL/6 (B6) and NZB/W F_1 (BWF_1) mice for 4 weeks. Then splenic LAG3$^+$ Treg were analyzed by flow cytometry. We analyzed the expression of Egr-2 in CD4$^+$ T cells cultured with tofacitinib. [Results] Administration of tofacitinib increased splenic LAG3$^+$ Treg in B6 mice. In BWF_1 mice, splenic LAG3$^+$ Treg showed a decrease at baseline, and tofacitinib did not increase them. Tofacitinib induced the expression of Egr-2 in both B6 and BWF_1 CD4$^+$ T cells *in vitro*. BWF_1 CD4$^+$ T cells required higher concentration of tofacitinib for Egr-2 induction than B6 CD4$^+$ T cells. Our findings may indicate a novel mechanism for the therapeutic effect of tofacitinib. Hyporesponsiveness of BWF_1 CD4$^+$ T cells to tofacitinib may be associated with impaired induction of LAG3$^+$ Treg in BWF_1 mice.

W35-4

The role of complement C3, ATP, and Mincle in the cell death-induced sterile inflammatory response

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Conflict of interest: Yes

[Objectives] When cells die by necrosis *in vivo* they stimulate an inflammatory response. It is thought that this response is triggered when the injured cells expose proinflammatory molecules, referred to as damage associated molecular patterns. This study focuses on evaluating the contribution of three molecules that have been proposed to participate in cell death-induced inflammation: The third component of complement (C3), ATP (and its receptor $P2X_7$), and the C-type lectin receptor Mincle. [Methods] Mice that lack either C3, receptor $P2X_7$ or Mincle were i.p. injected with necrotic cells or challenged with excess amount of acetaminophen. The nuetrophil recruitment to the injured tissue was evaluated. [Results] We find that C3-deficient mice initially have impaired in-

flammatory responses to dying cells. In contrast, at early or later time points there was no reduction in inflammation to cell death in the peritoneum or liver of mice that lack Mincle, the $P2X_7$ receptor or which were treated with apyrase to deplete ATP. These results indicate the complement activation contributes to cell death-induced inflammation but that ATP- $P2X_7$ receptor and Mincle are not required for this response. [Contributing authors of JCR non-member] Zubin Patel and Kenneth Rock of UMass Med School.

W35-5

Significance of follicuar T helper cell (Tfh) in rheumatoid arthritis (RA)

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Conflict of interest: None

[Objectives] Tfh subset plays an important role in the onset of autoimmune diseases and B cell lymphomas. This subset is induced by the oncogene Bcl6. To explore the significance of Tfh in RA onset, collagen-induced arthritis(CIA) mice model was analysed. [Methods] CIA mice with transferred Bcl6 and without Bcl6 were copmared with each other. Tfh cells in their spleen was identified by flowcytometry. Cytokine levels in sera were assayed by ELISA-PCR method. [Results] Bcl6 transferred CIA mice were developed arthritis 5 days earlier, 10% higher Tfh expression in spleen, and higher level of IL-6 and IFN-γ in sera compared to control mice. [Conclusion] Collectively, Tfh expression might induce the CIA in mouse and the RA in human onset.

W35-6

Reconstituted HDL (high density lipoprotein) ameliorates TLR ligands- induced liver toxicity *in vivo*

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Conflict of interest: Yes

[Objectives] Atherosclerosis is recently considered not only a disease of lipid metabolism but also one of inflammatory processes. The danger sisals released from injured cells might facilitate the atherosclerotic inflammation via Toll like receptors. The development of atherosclerosis is correlated with low serum concentration of HDL. HDL was shown to bind and neutralize lipopolysaccharide and exert an anti-inflammatory property. We found that reconstituted HDL (rHDL) can suppress IL-1 beta secretion from cholesterol crystal stimulated macrophages *in vitro*. Thus we aimed to examine the anti-inflammatory activities of rHDL in non HDL binding TLR-lignds induced inflammation *in vivo*. [Methods] Mice were pretreated with reconstituted HDL and challenged with d-N-galactosamine with either poly I:C or CpG-DNA, and then examined for serum cytokine concentrations, ALT levels and liver histology. [Results] rHDL treatment ameliorated the liver damage both in histology and ALT levels, cytokine and chemokine production in the TLR ligands and d-galactosamine treated mice. These results indicate that HDL has an anti-inflammatory properties other than directly binding the TLR ligands. [Contributing authors of JCR non-member] Shihomi Sato of Teikyo University School of Medical Technology.

W36-1

Thrombotic thrombocytopenic purpura (TTP) in patients with rheumatic diseases

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Conflict of interest: None

[Objective] To describe clinical variations of TTP in patients with rheumatic diseases. [Methods] We reviewed hospital records over 9 years for TTP cases, and identified 9 patients(5 SLE, 2 SjS, 1 SSc, 1 idiopathic) after excluding drug- or cytomegalovirus- induced TTP. [Results] TTP manifested at time of the onset of SLE in 2 of 5 SLE cases, or developed after 4-8 disease years of SLE in the remaining 3 cases. Of these, 4 TTP cases had active SLE and were treated successfully with plasma exchange (PE) and steroid monotherapy or combined therapy with intravenous cyclophosphamide. One female case of remitted SLE showed positive anti-ADAMTS13 antibodies and had intractable TTP with multiple hemorrhagic infarction in the brain. She obtained complete disease resolution without sequelae after 30 sessions of PE and rituximab therapy. Two SjS cases and one idiopathic TTP case showed positive antibodies to ADAMTS13 and responded to moderate therapy with PE and steroids. TTP in one SSc case responded to PE monotherapy. All the patients survived. [Conclusion] TTP in rheumatic diseases shows variable clinical courses and intensive immunosuppressive therapy may be required in some patients.

W36-2

The Effect of Saffron (Crocus sativus L.) on plasma level of platelet factor 4 (PF-4) and beta-thromboglobulin (beta-TG), platelet activation markers in patients with chronic autoimmune diseases.

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Conflict of interest: None

[Objectives] The risk for thrombosis is significantly increased in autoimmune diseases, affecting both venous and arterial vessels. Activated platelets are known to participate in thrombus formation and growth. Platelet factor 4 (PF-4) and beta-thromboglobulin (β-TG) are known to be platelet activation markers. Saffron (*Crocus sativus* L.) is classified as a beneficial herb in the treatment of eliminating blood stagnation in Japanese Traditional Medicine. We measured the plasma levels of PF-4 and β-TG for evaluation of the treatment with Saffron. [Methods] 69 patients (63 women and 6 men, mean age 52.3 ± 16.1, SLE;24, RA;8, PMR;7, MCTD;5, Sjögren's syndrome;4, APS;2, other diseases;19) were studied. They were administered saffron (300 mg~900 mg) with traditional Kampo medicine. We measured PF-4 and β-TG in pre- and post-saffron treatment periods. [Results] The plasma levels of PF-4 and β-TG significantly decreased after saffron therapy (PF-4: before 49.6 ± 29.8, after 24.0 ± 19.6 ng/ml, β-TG: before 117.5 ± 64.0, after 64.6 ± 47.1 ng/ml; paired *t*-test, $p < 0.0001$, respectively). No patients experienced side effects to saffron's medication. These results suggest that saffron had a dose-dependent effect in chronic autoimmune disease patients with activated platelets.

W36-3

Report of 6 cases of treatment for pulmonary hypertension related connective tissue diseases, including 1 autopsied case with pulmonary veno-occlusive disease

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Conflict of interest: None

[Objective and methods] We report 6 patients with PH-CTD treated with immunosuppressive therapy and vasodilators. [Result] Cases were 2 SLE and 4 systemic sclerosis (SSc) patients. Functional classification of WHO at baseline was class III in 4 cases, class II in 2 cases, and class I in one. Mean follow-up period was 5.6 years. Median pulmonary arterial pressure was 58 mmHg. Steroid pulse, cyclophosphamide pulse was performed in 1 case of SLE, resulting in the improvement of pulmonary arterial pressure. All cases received oral prostacyclin and Endothelin receptor antagonists (ETA), leading to an improvement of symptoms in 5 (83%) cases. Of these 5 cases, 2 had relapse of PH, but were well controlled by additional administration of phosphodiesterase (PDE) 5 inhibitors. One woman with SSc who did not respond to ETA did not respond to PDE5 inhibitor either. She was given epoprostenol but died of heart failure. Autopsy was done and she was diagnosed with pulmonary veno-occlusive disease (PVOD). 5 of 6 (83%) patients survived during the follow up period [Conclusion] Additional administration of PDE5 inhibitors on ETA even after exacerbation of symptoms improved PH with CTD. PVOD may be a differential diagnosis in patients showing little therapeutic benefit from ETA.

W36-4

Diagnostic value of FDG-PET in patients with fever of unknown origin: retrospective chart review

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Conflict of interest: None

[Objective] To evaluate the diagnostic value of FDG-PET in patients with fever of unknown origin (FUO). [Method] We checked the 272 medical records of the patients who underwent FDG-PET studies that were ordered in our department from January 2006 to December 2010. Sixty eight studies of them were done for detecting the source of fever. [Result] Forty six out of 68 patients met the final diagnoses. One patient with Takayasu arteritis was diagnosed by the FDG-PET, 3 patients (2 Castleman's diseases and 1 SAPHO syndrome) got helpful information from it, and 5 patients (2 polymyalgia rheumatica, 1 reactive arthritis, 1 rheumatoid arthritis and 1 Kikuchi's disease) got compatible observations with their diseases. C-reactive protein of these patients was significantly higher than the others. [Discussion] In this research, 4 studies out of 68 (6%) were diagnostic, and 5 studies (7%) supported the final diagnoses. In Japan, the indication of FDG-PET is limited in daily practice, and therefore any other diagnostic tools should be used prior to it. We should consider whether the FDG-PET study is really diagnostic or not when we cannot reach the final diagnosis after the intensive surveys.

W36-5

Risk factors for the adverse effect in patients with rheumatic diseases treated with azathioprine in Japan.

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Conflict of interest: None

[Objectives] Azathioprine (AZA) is commonly used for the treatments of various connective tissue diseases with corticosteroids. It is well known that adverse effects of AZA include myelotoxicity, liver damage, and infections. The objective of this study is to identify the risk factors for the discontinuation caused by the adverse effect of AZA in patients with rheumatic diseases in Japan. [Methods] We retrospectively analyzed medical records for the patients with rheumatic diseases who had been treated with AZA from January 2006 to December 2010. [Results] The 70 patients included 14 men and 56 women. The mean age was 55.5 years. The median dose of AZA was 50 mg/day (25-100 mg/day). AZA was discontinued in 41% of the patients because of the adverse effects within one year; myelotoxicity (27%), liver damage (15%), and infections (15%). The concomitant use of allopurinol was detected as the risk factor for the myelotoxicity ($P=0.04$), while the drinking habit and performance status was identified as the risk factor for the liver damage ($P<0.01$ and $P=0.02$). Our study showed that a careful interview about the life style, evaluation of the general status and cautions for the drug interaction are need for avoiding the discontinuation of AZA use caused by the adverse effect.

W36-6

Three cases of Wegener's granulomatosis (WG) complicated with hypertrophic pachymeningitis (HP)

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Conflict of interest: None

【Case 1】A 36-year-old man was admitted because of ear fullness in March 2000. He was diagnosed as WG because PR3-ANCA was positive. Although his clinical symptoms were improved by immunosuppressive therapy, headache was developed after the therapy was tapered. Brain MRI demonstrated thickened dura mata. We diagnosed as WG with HP. Administration of PSL and CY improved his symptoms.【Case 2】A 66-year-old woman was admitted because of deafness in January 2001. Although PR3-ANCA was negative, she was thought to be the suspected case of WG according to other examinations. PSL, CY and trimethoprim-sulfamethoxazole (ST) improved her symptoms, thereafter therapy was tapered. She noticed facial nerve palsy in April, and then developed dysarthria from January 2003. Brain CT showed thickened dura mata, and the biopsy specimen revealed WG. She was treated with steroid pulse therapy, followed by oral PSL, CY and ST, and subsequently her symptoms were improved.【Case 3】A 82-year-old woman had gait disturbance from December 2009. She developed fever and deafness in January 2010, and admitted due to positive finding of MPO-ANCA. Brain MRI revealed HP etc., hence she was thought to be the suspected case of WG. High-dose steroid therapy was initiated, and then her symptoms were improved.

W37-1

Assist system designed for electorical medical record in clinic for rheumatoid arthritis

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Conflict of interest: None

[Outline] We developed a solution using with electorical medical records for rheumatologist. The system was developed with Microsoft Visual Basic 2008 and 2010. [Function of this program] The functions of this system are describing joint evaluation, calculating SDAI, CDAI and DAS28, diagnosing patients with ACR 2010 Criteria and supporting for use of new remession critea of ACR 2011. This program is running independently with othe programms such as elecorical medical record system, and so that using with any electorical medical recoed system with runnnig in MS-Windows Operating System. It's easy for input of joint evaluation using with mouse. Also DAS scores and SDAI/CDAI values will be calculated in real time as soon as you enter joint evaluatin, values of CRP or ESR, and etc. It's useful and poweful tool for diagnosing RA and elavation of disease activity of RA patient.

W37-2

Plain knee X ray to diagnose Crowned dens syndrome

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Conflict of interest: None

[Objectives] Crowned dens syndrome (CDS) is diagnosed by the symptoms such as acute neck pain and the radiological findings of calcium phosphate crystal deposition surrounding the odontoid process. [Methods] All patients who underwent cervical spine CT with suspicion of CDS from 9/1/2009 to 9/30/2009 were analyzed. The clinical characteristics and final diagnosis were studied retrospectively. [Results] Thirty-one patients, mean age of 74, were analyzed. All patients experienced acute neck pain. Twelve patients had temperature 99F or higher. Eighteen patients had either elevated WBC or CRP. Eighteen patients were diagnosed as CDS. Thirteen patients were diagnosed as non-CDS: rheumatoid arthritis 5, cervical spondylosis 3, polymyalgia rheumatic 2, temporal arteritis 1, ankylosing spondylitis 1, connective tissue disease 1. Twenty-four patients had plain knee X ray. Chondrocalcinosis was seen in 64% (9 / 14) of CDS group and 10% (1 / 10) of non-CDS group (Fisher's exact test : p=0.047). Other parameters were not statistically significant. The sensitivity, specificity, positive LR, and negative LR were 64%, 90%, 6.4, and 0.4 respectively. In conclusion, CDS is an important differential diagnosis of acute neck pain in elderly. Plain knee X ray will help the differential diagnosis.

W37-3

Relationship between quality of life (QOL) and sleep in rheumatoid arthritis (RA) patients as compared with osteoporosis (OP) patient

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Conflict of interest: None

[Objectives] Effect of sleep status on QOL was analized. [Methods] The subjects were moderate disease activity patients with RA (n=24) which is showed 4.3±0.2 in DAS28 and non-DM severe OP patients (n=21) which is applied to PTH(1-34). Subjective QOL and state of sleep were evalutated by means of SF-36 and Pittsburgh Sleep Quality Index(PSQI). Moreover, correlation between QOL and state of sleep in RA patients was analized and compared with OP patients. [Results] QOL and state of sleep in moderate disease activity patients with RA were as worse as severe OP patients. It was suggested that high disease activity was a factor of difficulty falling asleep in RA patients. On the other hand, it was suggested that dicrease of height and compression fracture was a factor not only of declined physical activity but also of sleep difficulty. The worse state of sleep, the worse mental component score such as vitality, social functioning, and mental health in both group. In both RA and OP patients, state of sleep especially affects mental QOL.

W37-4

Vitamin D_3 deficiency in patients with Rheumatoid Arthritis (RA) in Japan

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Conflict of interest: None

Vitamin D_3 (VD) has multiple physiological function including bone-mineral metabolism, immunomodulation and musculo-skeletal effects. It is surmised that VD could be lack in RA patients because of less UV exposure due to impaired physical activity, in addition to general factors such as aging and low intake. We investigated serum VD concentration in order to disclose the actual situation of VD contentment in RA patients. Blood samples from randomly selected 132 patients in our clinical setting were taken in June, 2011. Average serum concentration of $25(OH)D_3$ was 18.1ng/ml. Amazingly, 60% of the patients showed less than 20ng/ml, which was definitely regarded as VD deficiency. Only 5% of the patients showed more than 30ng/ml, the value which is expected to be effective of bone fracture prevention. Average $25(OH)D_3$ concentration did not showed any correlation with the disease stages, while it was likely to become lower in advanced functional classes. Average $1,25(OH)_2D_3$ was 37.9pg/ml, which was within the reference values. $1a(OH)D_3$ was prescribed in 20 patients, nevertheless, average 1, $25(OH)_2D_3$ value was 35.5pg/ml in these patients. We concluded that RA patients in Japan are having apparent VD deficiency, and appropriate VD supplementation should be considered.

W37-5

Usefullness of 1.5-Anhydro-D-glucitol as a marker of glucose control in the patients using oral corticosteroids

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Conflict of interest: None

[Objectives] Blood glucose fluctuation contributes to oxidative stress, which has been linked to the pathogenesis of the long-term complications of diabetes. Steroid diabetes is characterized by a postprandial hyperglycemia and sometimes shows severe daily fluctuation of blood glucose level. We evaluate the usefullness of the 1,5-anhydro-d-glucitol (1,5-AG) level as a possible marker for glucose excursions. [Methods] Fourty-two patients with more than 5mg daily prednisolone were enrolled. In each patient, 6 point (preprandial and 120-min postprandial for each meal), HbA1c, and

1,5-AG levels were measured. M-value (by Schlichtkrull) were used as indexe of daily glycaemic excursions. [Results] 1: We found a weak negative correlation between 1,5-AG level and M-values (r = -0.35, p=0.02), and positive correlation between HbA1c level and M-values(r=0.428, p=0.005). However, 1,5-AG was not a better marker for a daily glucose excursion than HbA1c. 2: Among 22 patients with HbA1c level lower than 5.8%, 6 patients showed normal fasting blood glucose level (FBG), but over 220 mg/dl postprandial blood glucose levels. Five of these 6 patients showed decreased 1,5-AG levels. Thus the 1,5-AG may be a useful tool for the detection of the diabetes that are missed by the measurement of HbA1c and FBG.

W38-1

Discontinuation of adalimumab after attaining to clinical remission in patients with rheumatoid arthritis; HONOR [HUMIRA discontinuation withOut functional and radiographic damage progressioN follOwing sustained Remission] study

Shintaro Hirata, Kazuyoshi Saito, Ippei Miyagawa, Satoshi Kubo, Koshiro Sonomoto, Shunsuke Fukuyo, Kentaro Hanami, Yasushi Mizuno, Shigeru Iwata, Masao Nawata, Mikiko Tokunaga, Norifumi Sawamukai, Kunihiro Yamaoka, Yoshiya Tanaka
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Conflict of interest: None

[Objectives] We investigated the possibility of the biologics free remission (REM) by adalimumab (ADA) in patients (pts) with rheumatoid arthritis (RA); HONOR study. [Methods] Among 190 RA pts whom initiated ADA with at least 1 year observation, 46 pts whom maintained DAS28 < 2.6 for at least 24 wks without NSAIDs and glucocorticoids were discontinued ADA, and evaluated the ratio of clinical REM after 24 and 52 wks. [Results] All the candidates concomitantly administered MTX or TAC, continued after discontinuation of ADA. Among 39 pts with 24 wks observed, 23 (59%) maintained in DAS28 REM (< 2.6), and 28 (72%) in SDAI REM (≦ 3.3). Among 24 pts with 52 wks observed, 13 (52%) in DAS28 REM and 16 (67%) in SDAI REM. In contrast, 2 (5%) until 24 wks and 8 (33%) until 52 wks required re-administration of ADA, while 5 (55%) out of 9 re-administered pts attained to remission again within 24 wks. Low DAS28 at discontinuation was found as a factor associate to maintaining REM, and when stratified at the cut-off of 2.16, ratio of maintaining REM was higher in deep-REM group (77% vs. 17%). Moreover, all pts who maintained clinical REM kept functional (HAQ ≦ 0.5) and structural REM (mTSS yearly progression ≦ 0.5) as well. [Conclusion] ADA is potent to induce the biologics free REM.

W38-2

Predictive marker for the discontinuation of infliximab in rheumatoid arthritis with clinical remission

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Conflict of interest: None

[Objectives] 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] 51 (7 men, 44 women, average age 50.4 years old) of RA patients were treated with IFX and enrolled in this study. Overall remission rate was 53.1%. 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 remission and without remission. MMP-3 ratio(MMP-3 at initial / MMP-3 at 5th IFX) was the predictive marker for the discontinuation of IFX with clinical remission (4.71+/-5.18 vs1.15+/-0.57, p=0.0279). Results: MMP-3 ratio was the predictive marker to achieve clinical remission with IFX.

W38-3

Discontinuation of infliximab after achieving low disease activity or remission in patients with rheumatoid arthritis

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Conflict of interest: None

Infliximab enable to tight control of disease activity in patients with rheumatoid arthritis. Discontinuation of infliximab after achievement of remission is very important for safety and economical reasons. (Method) We evaluated 100 patients with RA who had received infliximab (IFX), including 12 RA patients (F group) (mean age: 52.0, male/female: 6/6, disease duration: 40.4months, stage I: 5, II: 5, IV: 2, class1: 7, 2: 5) who discontinued IFX after achievement of remission. F group was compared with residual 88 RA patients who continued IFX (N group). All subjects were fullfilled with ACR criteria for RA and examined by ACR core set, DAS 28, mHAQ, and MMP-3 monthly. (Result) 1. F group was shorter disease duration and lower of RA stage and class than N goup. Also, F group was treated with prednisolone rarely. 2. There was no different between F and N group (mean 5.4 vs 5.7) in DAS 28 before treating with IFX. Whereas F group achieved the remission state (DAS28: 2.3) at 10 week after starting with IFX. 3. The remission in F group was continued with administration of MTX, only 1 patient discontinued MTX and flare up. (Conclusion) After attaining low disease activity or remission, discontinuation of IFX was achieved and 66% of patients were continuing this state.

W38-4

Discontinuation of etanercept in rheumatoid arthritis patients in clinical remission: Two-year outcome

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Conflict of interest: None

Objective: We studied 2-year outcome in rheumatoid arthritis patients who achieved clinical remission (DAS28 <2.6) by etanercept (ETN) and maintained without ETN. Methods: The following data were obtained: relapse rate at year 2; the rate of radiographic remission (DTSS ≤0.5) and functional remission (mHAQ <0.5) of patients with continued remission and those with relapse that were based on total sharp score (TSS) and modified health assessment questionnaire (mHAQ). Re-treatment with ETN was considered as relapse. TSS was determined using modified van der Heijde-sharp score. Results: The number of patients who maintained remission was 23. Relapse was observed in 14 patients (60.9%) at year 2. Mean DAS, mHAQ and TSS of patients with continued remission at year 2 were 2.03, 0.09, -2.26 respectively, those of patients with relapse were 3.11, 0.27, 0.37. Radiographic and functional remission rates of patients with continued remission at year 2 were 55.6%, 77.8% respectively, those of patients with relapse were 50%, 64.3%. Some patients could maintain clinical, radiographic and functional remission after 2-year discontinuation of ETN. Even if relapse occurred, remission could be achieved again with monitoring of disease activity and adequate treatment after ETN

discontinuation.

W38-5

Validation of a therapeutic strategy aimed at maintaining remission. (Remission maintenance therapy study with Etanercept (ETN) 25mg Qw)

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Conflict of interest: None

[Objectives] To consider the direction of remission maintenance therapy, we examined how they affect the reduction of ETN usage in maintaining remission. [Methods] In 76 cases the reduction of ETN usage, from 50mg Qw to 25mg Qw, for any reason, we evaluated DAS28ESR, background factors and the achievement ratio of clinical remission(CR)(CR; DAS28ESR<2.6). [Results] In the group performed reduction of ETN usage after reaching CR, the rate of remission was achieved over 60% over one year. On the other hand, the rate of remission remained at less than 20% in the group performed it without achieving CR. Compared both groups, we indicated a statistically significant in treatment responses at 1, 3 and 6 month from initiation therapy used with ETN 50mg Qw. Next, we conducted a study on the maintenance of CR for ETN 25mg Qw by periods of CR achieved. In the group reached CR within 6 months, the maintenance rate of remission(mRR) was about 67%. While, the group took over 6 months to reach CR, mRR was almost 60%. [Conclusion] For use the reduction of ETN usage as remission maintenance therapy, it is important to be achieved CR for the maintenance of remission. As maintenance therapy, the reduction of ETN after remission induction is a useful therapeutic strategy.

W38-6

Effectiveness and safety of etanercept for the treatment of rheumatoid arthritis in patients switching from 25 mg twice a week to 50 mg once a week

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Conflict of interest: None

[Objective] We evaluated the effectiveness and side effects in our patients who switched from etanercept (ETN) 25 mg × 2/w to 50 mg × 1/w. **[Subjects & Methods**] This study included our 44 rheumatoid arthritis (RA) patients (6 males, 38 females) on ETN treatment. Scores of patient-reported visual analogue scale (VAS; 1-100), disease activity score-28 using erythrocyte sedimentation rate (DAS28ESR), simplified disease activity index (SDAI), clinical disease activity index (CDAI), health assessment questionnaire-disability index (HAQ-DI; 0-3) for 3 months before and after switch from ETN 25 mg syringe × 2/w to 50 mg syringe × 1/w were compared. **[Results**] Scores 3 months before, at the time of switch, and 3 months after were as follows: VAS was 32.1, 30.1, 29.3; DAS28 was 3.26, 3.05, 2.94; SDAI was 8.21, 6.19, 5.42; CDAI was 6.80, 5.78, 4.98; HAQ-DI was 1.15, 1.10, 1.18, respectively, with no scale showing a significant change. Mild adverse events were noted in 15 patients (18 events) at 3 months before switch and in 19 patients (19 events) at 3 months after switch; no great difference was seen before and after switch. **[Conclusion**] Switch from ETN 25 mg × 2/w to 50 mg × 1/w in RA patients may accompany no specific concerns on the effectiveness and safety of ETN.

W39-1

Can low-dose etanercept prevent joint destruction in PRECEPT study?

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Conflict of interest: None

[Objectives] The efficacy of etanercept (ETN) in RA has been demonstrated. To reduce the cost of biologics, low-dose ETN has been administered without evidence. To evaluate the prevention of joint destruction of low-dose ETN. [Methods] This prospective, randomized study was registered with the UMIN Clinical Trials Registry (UMIN000001798). 70 patients were randomly assigned to receive either ETN 50mg/w or 25mg/w for 1 year. The primary end point was the variation of total Sharp score (TSS), and the secondary end points were that of DAS28 and mHAQ. No progression was estimated as $\Delta TSS \leqq 0.5$ and no progression rate was compared between groups. [Results] Patients had mean disease duration of 9.2 years, DAS28 of 5.45, and annual progression of TSS of 26.1 at baseline. There were no significant differences between groups. No progression rate of 25 mg/w group (36.7%) was significantly less than that of 50mg/w group (67.7%) ($p = 0.041$). ΔTSS of 25mg/w (1.03) was higher than that of 50mg/w group (-0.13). DAS28 and mHAQ were significantly improved, without significant differences between groups. [Discussion] Low-dose ETN was not inferior to standard-dose ETN in clinical effects. However, from the viewpoint of joint destruction suppression, it was inferior to the effect of standard-dose ETN.

W39-2

Radiographic change and time-course change in cytokine levels of rheumatoid arthritis patients on etanercept treatment

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Conflict of interest: None

【Objective】 To study changes in cytokine levels and radiographic findings (mTSS) in rheumatoid arthritis (RA) patients newly treated with etanercept (ETA). **【Methods】** In our 19 pts who started ETA during Nov/2005 - Jan/2007 (2 men; mean age, 62.0 yo; mean disease duration, 8.7 yrs), cytokine (IL-4, IL-6, IL-8, TNFa) levels were determined at baseline, week 4, 24 to assess relationship of RA activity and radiographic findings. **【Results】** Mean DAS28 (ESR) at baseline, & week 4, 24: 6.7, 5.0, 3.8 respectively. Compared to baseline, TNFa at week 24 significantly increased (2.3 vs 96.9). IL-6 significantly decreased (37.4 vs 9.73). Mean mTSS was 92 ± 62 at baseline and 94 ± 64 at week 24; 9 pts achieved radiographic remission ($\Delta mTSS \leq 0.5$). Analysis of factors affecting radiographic remission showed no significant vari-

able of patient's background. Cytokine levels in the remission group appeared to be lower at week 24: IL-4 (91 vs 351), IL-6 (6.8 vs 12.4), IL-8 (5.0 vs 10.8), TNFa (91.0 vs 102.2), but no significant difference. **【Conclusion】** We evaluated the relationship between radiographic remission and cytokine changes in the course of ETA treatment. Although the remission group had a decreasing tendency of IL-4, IL-6, IL-8, TNFa at week 24, no significant difference was seen.

W39-3

Effect of etanercept in patients with RA comparison of weight-bearing joints and no weight-bearing joints

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Conflict of interest: None

The aim of the present study was to assess the effect of etanercept in patients with RA comparison of weight-bearing joints and no weight-bearing joints. We investigated the changes in radiological findings in 314 joints (86 shoulder joints, 84 elbow joints 77 hip joints, 67 knee joints). Structural damage was assessed using the Larsen scoring method. The progression of joint damage was mostly inhibited in large joints as well as in small joints. While damaged of Larsen grades 3 and 4 at baseline showed progression even in patients with a good response. There was this tendency among weight-bearing joints. Mechanical factor was a potential risk factor for joint destruction.

W39-4

One Year's Results in Humira® (adalimumab) Outcome Study for the Persistent Efficacy under Allocation to Treatment Strategy in Early Rheumatoid Arthritis (HOPEFUL 1) Study

Hisashi Yamanaka[1], Naoki Ishiguro[2], Yoshiya Tanaka[3], Tsutomu Takeuchi[4], Nobuyuki Miyasaka[5], Hartmut Kupper[6], Sourav Santra[6], Hideto Akama[7]
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Conflict of interest: Yes

Purpose: To investigate the inhibition of radiographic progression by adalimumab (ADA) in early active rheumatoid arthritis (ERA), a multi-center, randomized, double-blind, placebo-controlled study (HOPEFUL 1) was conducted in MTX-naive Japanese ERA patients. **Methods:** The study included a 26-week double-blind period (DBP) and a 26-week open-label extension period (OEP) for patients who completed DBP. 334 patients with ERA received ADA+MTX (Group A: n=171) or MTX (Group B: n=163). 306 patients who completed or moved into rescue during DBP were allocated to receive ADA+MTX in OEP and 28 patients were discontinued during DBP. **Results:** The rate of patients without worsening in modified total Sharp score (⊿mTSS, ≤0.5) at Week 52 in Group A (65.9%) was significantly higher than that in Group B (42.9%, $p<0.001$). The remission (DAS28-ESR<2.6) rates at Week 52 in Group A (37.7%) was not statistically different from that in Group B (37.4%, $p\geq0.05$). **Conclusion**: In ERA patients with high disease activity, early introduction of ADA+MTX therapy resulted in greater inhibition of radiographic progression at 1 year compared to introduction of MTX alone followed by ADA add on therapy. These results demonstrated the advantage of early aggressive therapy of RA to minimize the radiographic progression.

W39-5

Analysis on Results of GO-FORTH, Golimumab (Simponi®) Administered in Combination with Methotrexate (MTX), in Patients with Active Rheumatoid Arthritis Despite MTX Therapy (1): Disease Activities and Suppressive Effect on Progression of Joint Destruction

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Conflict of interest: Yes

Objectives: To assess the relationship between disease activities and suppressive effects on joint destruction progress in GO-FORTH Study. **Methods:** Inhibition rates (IR) on progress of joint destruction ($\Delta TSS\leq0$) in 24w-result of GO-FORTH (MTX resistant patients (pts): 261) by baseline disease activity were compared. High disease activity pts (HDA) were defined as DAS28 (ESR)>5.1 or CRP≥1.5mg/dL and low disease activity pts (LDA) were 3.2-5.1 or <1.5mg/dL, respectively. **Results:** Mean ΔTSS (median) in PBO by DAS28 (ESR) (n=57) and CRP (n=40) in HDA were 3.48 (1.0) and 3.41 (1.0) which were higher than those in LDA, 0.76 (0.0) (n=29) and 1.76 (0.0) (n=48), respectively. IR on progression in HDA were 40.4% in PBO (n=57), 43.1% in 50mg (n=51) and 69.8% in 100mg (n=53) by DAS28 (ESR), and 40.0% (n=48), 43.1% (n=52) and 61.5% (n=61) by CRP, respectively, while, in LDA were 69.0% (n=29), 81.8% (n=33) and 70.6% (n=34) by DAS28 (ESR) and 58.3% (n=48), 73.1% (n=52) and 73.8% (n=61) by CRP, respectively. Group differences were only observed between 50mg and 100mg in HDA. ΔTSS over 3.0 was less observed in 100mg than 50mg in HDA. **Conclusion:** Joint destruction progress in HDA was quicker than in LDA. GLM 100mg was more effective on preventing joint destruction than GLM 50mg.

W39-6

Blockade of joint destruction in medium to large sized joints in patients with rheumatoid arthritis (RA) receiving adalimumab (ADA) and methotrexate (MTX) combination therapy

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Conflict of interest: None

[Objectives] To investigate blockade of bone destruction for 1 yr in 28 RA patients resistant to MTX with ADA added to therapy. [Methods] Mean age: 60.1 yr, mean RA duration: 8.4 yr and DAS28-ESR: 6.28. M-L sized joints radiographic evaluation was performed by total Larsen score method at 1 yr after ADA was added. [Results] Among 336 M-L sized joints, 1 Larsen(L) grade progression recognized in 10 (2 elbow, 3 shoulder, 2 hip and 3 knee) joints of 10 patients. Meanwhile, in 7(1 elbow, 1 shoulder, 3 knee and 2 subtalar) joints of 4 patients, 1L grade improvement observed, in 1 joint of 1 patient (1 shoulder) 2L grade improvement observed. The progression details were:L1→L2 in 1 patient, L2→L3 in 4 patients andL4→L5 (artificial joint) in 3 patients. In improved patients, images of bone damage repair were demonstrated via increasing joint space and osteosclerotic changes. Mean yearly M-L sized joint ⊿L grade/joint progression was 0.003. [Conclusion] In a previous study (Mod. rheum:19,513-521,2009), long-term MTX monotherapy in 26 RA patients(mean age 56.2 yr, mean RA disease duration:7.2 yr and DAS28-ESR 5.69), the same

analysis was performed and mean yearly M-L sized joint ⊿L grade/joint was 0.071. ADA+MTX therapy demonstrated marked blockade of bone destruction in M-L sized joints.

W40-1

The efficacy of biologics toward physical disability in RA patients

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Conflict of interest: Yes

[Objectives] We evaluated the efficacy of biologics (four pharmaceuticals) toward physical function in the patients with RA. [Methods] Among 338 patients (IFX 91, ETN 78, TCZ 98, ADA 71) who were started the administration between September 2008 and June 2010 examined the HAQ-DI at entry and after 1 year. [Results] HAQ-DI at the entry and after 1 year; IFX was 1.2±0.8 vs. 1.0 ± 0.9, ETN was 1.4± 0.8 vs. 0.9±0.8, TCZ was 1.5±0.8 vs. 1.2± 0.9, ADA was 1.2±0.8 vs. 1.0±0.8, and significantly improved for all of 4 pharmaceuticals. Functional remission (HAQ-DI ≦0.5) after 1 year; IFX 41cases (45.1%), ETN 34 cases (43.6%), TCZ 29 cases (29.6%), ADA 30 cases (42.3%). The improvement in the HAQ-DI (ΔHAQ <-0.22) after 1 year; IFX 49 cases (53.8%), ETN 50 cases (64.1%), TCZ 57 cases (58.2%), ADA 36 cases (50.7%). Compared to those with switch cases, the mean ΔHAQ with naïve cases tended to improve much better (IFX -0.3 vs. -0.1, ETN -0.6 vs. -0.5, TCZ -0.4 vs. -0.4, ADA -0.4 vs.-0.1).

W40-2

Evaluation of factors which influence HAQ (functional) remission in patients with established Rheumatoid Arthritis (RA) treated with Adalimumab (ADA)

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Conflict of interest: None

[Objectives] Evaluation of effective factors on HAQ remission(HAQ≦0.5). [Methods] 33 advanced bionaïve RA patients treated for 1yr with ADA were assessed for DAS28-ESR(DAS) for activity HAQ index, mTSS in small joints and Total Larson score(TLS) in all 12 medium-large(M-L) joints for damage HAQ index. [Results] Patients background was: mean age: 60.1yr, RA disease duration: 8.4y, DAS:6.28, △mTSS:13.7/y, and HAQ-DI:1.9. At 1yr, 60.9% patients who achieved △mTSS<0.5, DAS and HAQ remission rates were 19.3% and 22.6%. HAQ-DI at 1yr correlated with HAQ-DI (R=0.57, P<0.0001), TLS(R=0.57, P<0.001), mTSS (R=0.54, P<0.01), VAS(R=0.43, P<0.05), CRP(R= 0.38, P<0.05), disease duration (R=0.37, P<0.05) at baseline and TLS (R=0.61, P<0.001), DAS (R=0.62, P<0.0001) at 1 yr. Moreover, none of 16 patients with≧1 M-L sized joint≧L3, achieved HAQ remission, while 8 out of 17 patients with M-L sized joints≦L2, achieved HAQ remission(P<0.01). [Conclusion] Factors which influenced HAQ remission with ADA treatment were not only small joints but M-L sized joints (especially ≧L3) destruction at baseline for damage HAQ index and DAS at 1y for activity HAQ index. These show the benefit of administration of ADA in early stage of RA to achieve remission, before the joint destruction.

W40-3

Comparison of efficacy between four biological agents for with rheumatoid arthritis patients using the Health-Related QoL questionnaire and depression.

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Conflict of interest: Yes

[Objectives] Health-related quality of life (HRQoL) as a patient (pts)-reported outcome in RA has become an important tool in the clinical evaluation of patient preferences and perceptions. The objective of this study was to compare the validity of the HRQoL with respect to depression in RA pts treated with IFX, ETN, ADA or TCZ. [Methods] One hundred six RA pts (IFX, 47; ETN, 17; ADA, 25; TCZ, 17) were assessed prior to treatment and after 30 weeks therapy initiation. The age, gender, and steroid dose were obtained for each participant and the HRQoL questionnaire (mHAQ and Short Form (SF)-36) and depression scale (Hamilton Depression rating scale (HAM-D) and the Self-rating Depression Scale (SDS)) were administered to pts. The primary endpoint was the assessment of clinical improvements, and the secondary endpoints were assessments of the changes in the HRQoL and depression scale. [Results] Although amount of changes in role physical, body pain and role emotion were significantly improved (p<0.05) in the group of pts treated with ETN compared with ADA, other measures of SF-36 and other participant were not significantly different among the 4 treatment groups. Although each biologic agent is highly effective, the degree of improvement in QoL and depression differed among treatments.

W40-4

The investigation of the usefulness of visual analogue scale for the RA patients using FDG-PET/CT

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Conflict of interest: None

[Objectives] In this study, we examined the relationship between changes in patient general VAS or Dr VAS and changes in FDG uptake in patients with rheumatoid arthritis(RA) who underwent biological treatment. [Methods] FDG-PET and the clinical assessments were performed prior to, and 6 months after the initiation of the therapies. The increased FDG uptakes in bilateral shoulder, elbow, wrist, hip, knee, and ankle joints were recorded. Therapeutic response was evaluated by the changes in the sum of the maximal SUV (SUVmax-sum) of all measured joints and the clinical findings. [Results] ΔSUV, the difference of the sum of SUVmax between before and after treatment, significantly correlated with ΔDAS28 (r=0.508), ΔDAS28-CRP (r=0.538), ΔSDAI (r=0.559), ΔCDAI(r=0.534). The changes of Dr VAS significantly correlated with ΔESR (r=0.469), ΔCRP(r=0.346) and the difference of the number of tender and swollen joints (r=0.391 and r=0.416), respectively. However, the difference of the patient general VAS was not significantly correlated with these parameters. In conclusion, the patient general VAS might not reflect disease activity of RA patients.

W40-5

Understanding and acceptance of cost effectiveness of biologics by RA patients

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Conflict of interest: Yes

[Objectives] Biologics have been shown to improve the outcomes in patients with rheumatoid arthritis (RA). Those drugs are so very expensive that the understanding and acceptance of cost effectiveness of those drugs by RA Japanese patients remains unknown. [Methods] We assess the cost-effectiveness of biologics by questionnaire for 194 RA patients taking biologics. [Results] Patients taking infliximab 80, etanercept 49, adalimumab 20, tocilizumab 38, abatacept 15, in each, answered the questionnaire. Monthly cost of biologics is 30-60 thousand Yen. More than half of RA patients perceive that those cost is expensive to effectiveness of those drugs. Patients taking more income by job are minority and more than half of the patients can have more than one hour of working per day after the treatment of biologics.

W41-1

Prognosis of 42 patients with polymyositis and dermatomyotisis after initial treatments

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Conflict of interest: None

[Objective] To evaluate prognosis of patients with polymyositis (PM)/ dermatomyotisis (DM), we analyzed event-free survival (EFS) after initial treatment. [methods] The medical records of 42 patients (PM: 14 patients DM: 28 patients) who were treated at our hospital from 2006 through 2011 were retrospectively reviewed. Event was defined as exacerbation, complications(e.g. infection) or death. EFS was measured from day of initial treatment. Survival rate was calculated by Kaplan-Meier method. [Results] The age was 53.8±13.8 years old(mean±SD). Twenty-nine patients were female, 34 patients had interstitial lung disease. Serum CPK level was 2290±2937 IU/L. All patients were treated with high dosage PSL (50.9±12 mg). Steroid pulse therapy was performed in 19 patients. Cyclosporin A (CyA) and methotrexate were added on 16 patients and 7 patients, respectively. EFS rates (95% at 1 year, 91% at 2 year, 83% at 4 year) in patients treated with CyA tended to be better than EFS rates in patients treated without CyA(95%, 91%, 83%). Our study showed the prognosis of patients with PM/DM after initial treatments, and that CyA may efficacious option for initial treatment for PM/DM.

W41-2

Usefulness of cyclosporine A (CyA) and tacrolimus (TAC) in the treatment of dermatomyositis (DM) and polymyositis (PM). A single center analysis.

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Conflict of interest: None

[Objective] To estimate the efficacy and safety of CyA and TAC for the treatment of DM and PM. [Methods] Usefulness of CyA and TAC using 42 DM and 33 PM patients who were treated with CyA or TAC from 62 DM and 50 PM patients was assessed. [Results] CyA and TAC were administered to 22 and 16 patients in the initial induction therapy, respectively.8 patients were complicated with acute interstitial pneumonitis (AIP). CyA and TAC were used in 5 and 3 cases and 3 were switched to TAC.4 survived, but 4 deceased and 2 of the survival cases were eventually in drug-free remission. For the initial induction therapy of refractory myositis, CyA and TAC were used in 17 and 10 patients, and 10 (59%) and 7 (70%) patients were on CyA and TAC, respectively, at the time of the last observation. For the treatment of recurrence, CyA and TAC were used in 31 and 25 patients, and 15 (44%) and 22 (88%) patients were on CyA and TAC, respectively, at the time of the last observation. Switching to TAC from CyA due to inadequate response was applied in 18 patients and was effective in 17patients. Discontinuation due to side effects was observed in 15 patients treated with CyA and 6 treated with TAC. CyA and TAC appear to be effective and safe for the treatment of DM and PM.

W41-3

Renal involvement in patients with polymyositis and dermatomyositis

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Conflict of interest: None

[Objectives] This retrospective study aims at investigating the incidence and feature of renal disease in patients with PM/DM. [Methods] The hospital records of 172 Japanese patients with PM/DM, examined between 1989 and 2011, were studied retrospectively. [Results] Renal involvement in patients with PM/DM is previously thought to be uncommon. However, tubulointerstitial nephritis related to myoblobulinemia and myoblobulinuria was a well-recognised feature of active PM/DM.

W41-4

Two cases of idiopathic inflammatory myopathies complicated with myocarditis

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Conflict of interest: None

Case 1. 51 year-old woman complained of muscular weakness and pain with elevated CK. She was diagnosed as polymiositis (PM) by muscle biopsy, and administered oral PSL 50mg. Because of the involvement of interstitial pneumonia, she was also administered cyclosporine A (CyA)(3mg/kg). Although her clinical symp-

toms and CK level were improved, pretibial edema was suddenly appeared, and the biomarkers of cardiomyopathy were elevated, suggested that myocarditis was complicated despite the immunosuppressive therapy. An endomyocardial biopsy indicated the injury of myocardium, and that was treated with intravenous immune globulin. Case 2. 67 year-old woman complained of muscular weakness and skin eruption. Heliotrope rash and Gottron sign were positive in the presence of high serum CK. After muscle and skin biopsy, she was diagnosed as dermatomyositis (DM). Although she was administered oral PSL 40mg, the biomarkers of cardiomyopathy got worse during the treatment. CyA (3mg/kg) was administered for myocarditis, resulted in good response. Although it is uncertain how to treat PM/DM involved in myocarditis, we inferred from two cases that the corticosteroid monotherapy might be insufficient to treat. We should consider that myocarditis can be occurred during the treatment of PM/DM.

W41-5

Examination of nailfold capillaroscopy findings at the time of diagnosis of juvenile dermatomyositis

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Conflict of interest: None

[Objectives] To evaluate the characteristic of NFC findings in clinical course of JDM. [Methods] NFC imagings were examined with ten children (2 boys and 8 girls, age 10.2±3.8 years) of 14 JDM patients who visited our hospital from June 2008 to September 2011. NFC findings of the 4 fingers of their not dominant hand, excluding thumb, were recorded in maintaining a constant room temperature of range 24°C-26°C. All childen underwent NFC with videocapillaroscopy at the time of first coming to our hospital. The numbers of end raw loops per millimeter in all 4 digits were summed and then devided by 4 to yield the mean number of ERLs in each patient, then the rate of enlarged capillary and angiogenesis was counted too. [Results] All 10 children with JDM had enlarged nailfold capillaries over the rate of 20 % and end raw capillary densities were decreased (mean 3.9 /mm, range 2-5.5 / mm) in JDM patients comrared with healthy children (6-8 /mm). Four of 5 patients who diagnosed being in early phase (from 1.5 to 6 months) of their clinical course had more capillaries than 5 children had came to our hospital later (from 7 to 88 months). Only 3 patients had angiogenesis, progressing more than three years until diagnosis or receiving effective treatments.

W41-6

Efficacy of intravenous immunoglobulin therapy for patients with refractory myositis due to polymyositis/dermatomyositis: a report of 5 cases

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Conflict of interest: None

OBJECTIVE: To report 5 cases of refractory myositis due to polymyositis (PM) / dermatomyositis (DM) treated with intravenous immunoglobulin (IVIG) Itherapy. **METHODS:** Five cases of PM/DM(2 males, 3 females, ave. age 62.4) complicated with severe muscle weakness. Their myositis were relapsing and was resistant to the combination of prednisolone and immunossuppressants included azathioprine, cyclosporine A, tacrolimus and methotrexate. After informed consent was obtained, IVIG(0.4g/kg) was administered. **RESULTS:** All patients showed high titer of CK levels (ave. 1897.4 IU/L) and severe mescle weakness. Two patients had malignant tumors (1 hepatocellular carcinoma, 1 cholangiocarcinoma). Two had interstitial lung disease. IVIG was efficient in all five cases at the initial treatment, however 2 showed relapse of myositis with elevating serum CK levels slowly. All of two patients with malignant tumor had an effect to IVIG. IVIG was well tolerated without infections and infusion reactions. **CONCLUSION:** However IVIG is expensive, IVIG may be efficient in refractory myositis due to PM / DM especially in patients with malignant tumor.

W42-1

Treatment of CD8 T cell dependent polymyositis model by inhibiting CD28 costimulation

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Conflict of interest: None

[Objectives] CTLA-4Ig modulates T cell activation by inhibiting CD80/86 on APCs to costimulate CD4 T cells via CD28 interaction. While, CTLA-4Ig is reported not to block the activity of CD8 T cells only in an allogeneic mixed lymphocyte reaction, there is no study in an autologous condition or in vivo. By examining the inhibition effect of CD28 to C protein-induced myositis (CIM) mice, which is a polymyositis (PM) model having cytotoxic CD8 T cell engagement in its pathophysiology, we verified whether CD 28 inhibition will suppress the expression of CD8 T cell function in vivo. [Methods] CIM mice were treated with CTLA-4Ig (abatacept) prophylactically or therapeutically or with anti CD80 (RM80) and CD86 Ab (PO3) therapeutically. BSA and rat IgG were used for controls, respectively. Myositis was histologically scored and evaluated 21 days after immunization. [Results] All treatment groups significantly lowered the histological score of myositis compared to its control group. [Conclusions] CTLA-4Ig and anti CD80/86 Ab ameliorated CIM. Generally cytotoxic CD8 T cell differentiation is dependent on CD4 T cell. However, since the therapeutic administration also presented with a treatment effect, CD28 inhibition is suggested to directly suppress CD8 T cell and to be a novel treatment for PM.

W42-2

Increased *BLK* rs13277113A allele frequencies in Japanese patients with polymyositis/dermatomyositis

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Conflict of interest: None

[Objectives] We previously showed the positive asociaton between *STAT4* polymorphisms and Japanese polymyositis/dermatomyositis. To investigate the involvements of the BLK (B lymphocyte kinase) gene polymorphism in the suceptibility to PM/DM.. [Methods] Single nucleotide polymorphism at rs13277113 was genotyped in 273 patients with PM and 187 patients with DM as well as 656 control individuals. [Results] Both in the PM and DM patients, the frequencies of rs13277113A were significantly higher than that in the control individuals of 0.66 (0.73 for PM, p = 0.0045, *pcorr* = 0.027 odds ratio = 1.37, 95%CI = 1.10-1.71 and 0.75 for DM, $p = 3.3\times10^{-4}$, *pcorr* = 0.0017 odds ratio = 1.61, 95%CI = 1.24-2.08). We showed that BLK gene polymorphism was involved in the disease susceptibility to Japanese PM/DM pa-

tients. Results also indicated the genes *STAT4* and *BLK* act additively increase the risk of PM/DM.

W42-3

Importance of vasculopathy in the pathogenesis of dermatomyositis

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Conflict of interest: None

[Objective] Vasculopathy in small vessel of muscle (fascia) is important for the pathogenesis of dermatomyositis (DM). Since the significance of vasculopathy in dermis in DM has not been clarified yet, we pathologically examined the presence of abnormal coagulation and fibrinogenolytic system in skin obtained from DM patients. [Methods] Thirty-eight DM patients were involved to this study. The pathological findings were evaluated in skin samples, and inflammatory signs in muscle were assessed by MRI. Serum levels of thrombin antithrombin (TAT) and von Willebrand Factor (vWF) were measured. [Results] The fiblinoid substance in dermal vessel was observed in 45 % of DM. Elevated level of vWF was seen in the early stage as well as in DM patients with exacerbation. In addition to the presence of fiblinoid substance, increased levels of TAT and vWF, and inflammation in muscle and lung by MRI were concurrently observed in 3 patients. [Discussion] Our data suggest that abnormal coagulation and fibrinolytic systems occur in DM, which lead to the production of fiblinoid substance in small vessels, subsequently developing the circulation disturbance. Our observation might be simultaneously found in fascia and pleura. This aspect would be important for the pathogenesis and therapies in DM.

W42-4

Prognostic factors in interstitial lung disease complicated with polymyositis or dermatomyositis

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Conflict of interest: None

[Background] The prognosis of patients with interstitial lung disease (ILD) complicated with polymyositis (PM) or dermatomyositis (DM) is poor. [Objective] To clarify the prognostic factors in ILD complicated with PM/DM. [Methods] A retrospective analysis consisted of 46 new patients with ILD complicated with PM/DM who admitted to our hospital from January 2000 to October 2011 and were followed up for 35.3(1.0-121.3) months. Primary endpoint was defined as death, relapse of underlying disease or serious infection. Prognostic factors were analyzed by Kaplan-Meier and multivariate COX regression methods. [Results] Three year event free and overall survival were 60.6% and 81.3%, respectively. Independent prognostic factors for events were honeycomb lung (HR 26.7; p<0.001), DM (HR 7.84; p=0.009), amyopathic DM (HR 7.25; p=0.029), the extent of pulmonary abnormalities more than 50% (HR 6.0; p=0.007) and acute progression of ILD within two months (HR 6.0; p=0.003), and those for death were honeycomb lung (HR 24.1; p=0.007), creatinine kinase within normal range (HR 17.5; p=0.014) and age (HR for each 10 year 3.52; p=0.009). [Conclusion] Honeycomb lung, DM, amyopathic DM and extensive and rapidly progressive ILD are prognostic factors in ILD complicated with PM/DM.

W42-5

Serum Angiopoietin-like protein 3 concentrations in rheumatic diseases

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Conflict of interest: None

[Objectives] Angiopoietin-like protein 3 (Angptl3) is one of the angiogenic cytokines that stimulates endothelial cell adhesion, migration, and neovascularization. In this study, we tried to evaluate the possibility that serum levels of Angptl3 can be a useful disease marker in collagen diseases. [Methods] Serum samples were collected from 21 systemic sclerosis (SSc) patients, 10 systemic lupus erythematosus (SLE) patients, 21 dermatomyositis (DM) patients, 5 polymyositis (PM) patients and 11patients with clinically amyopathic DM (CADM). Serum levels of Angptl3 were measured with a specific ELISA kit. [Results] There was significant increase of serum Angptl3 levels in patients with SSc and those of DM. Serum levels of Angptl3 were also slightly higher in patients with ADM, PM or SLE compared with healthy controls, but not statistically significant. Myoglobin levels were significantly higher in DM patients with increased serum Angptl3 levels than those with normal levels. In addition, among patients with SSc, the prevalence of cutaneous ulcers was significantly greater in patients with elevated Angptl3 levels than those with normal levels. Serum Angptl3 levels may be associated with the pathogenesis of muscle involvement in DM patients and microangiopathy in SSc patients.

W42-6

Angiopoietin-1/Angiopoietin-2 ratio is decreased in the sera of patients with dermatomyositis.

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Conflict of interest: None

[Background] Previous studies have reported impaired angiogenesis in dermatomyositis (DM), which in part through hypoxia induces muscle injury. Angiogenesis is regulated by coordinated function of VEGF and angiopoietins (Ang). Ang-1 is important for stabilization of vessels. Ang-2 is natural antagonist of Ang-1 and the effect of Ang-1 is regulated by Ang-1/Ang-2 ratio. We previously reported that IL-6 potentially induces unstable angiogenesis in RA by increasing VEGF and decreasing Ang-1/Ang-2 ratio. [Objective and method] To examine the role of Ang in DM, we measured the concentration of Ang-1, Ang-2, IL-6, and VEGF in the sera of DM patients (n=8) by ELISA, and compared them with healthy controls (n=10). [Results] In DM patients the mean age was 56.9 years old and female was 87.5%. Median of CK was 131 IU/ml. Ang-2 and IL-6 were significantly higher and Ang-1/Ang-2 ratio was significantly lower in DM patients than in control group. Ang-1 and VEGF were comparable between both groups (DM vs cont. Ang-1 33211 vs 44467 pg/ml; Ang-2 3809 vs 2031 pg/ml; Ang-1/Ang-2 ratio 11.7 vs 26.6; IL-6 11.0 vs 0 pg/ml; VEGF 376 vs 194 pg/ml). [Conclusion] These findings suggest that up-regulated IL-6 decreases Ang-1/Ang-2 ratio, which cumulatively in-

duces impaired angiogenesis in DM.

W43-1

IL-18 is a hallmark of juvenile dermatomyositis-associated interstitial pneumonia

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Conflict of interest: None

[Objectives] Dermatomyositis (DM) is an inflammatory disease characterized by weakness in proximal muscles and pathognomonic skin rashes. Serum Interleukin (IL)-18 levels are elevated in adult patients with DM-associated interstitial lung disease (ILD) but have not been evaluated in juvenile DM (JDM) cases. The aim of our study is to evaluate the clinical significance of serum IL-18 levels and other JDM-associated markers in JDM cases with or without ILD. [Methods] 13 JDM patients, 5 with ILD (ILD+) and 8 without ILD (ILD-) followed-up at our hospital from 1990 to 2008 were enrolled. The samples were obtained at diagnosis and remission of ILD or JDM. Serum IL-18 levels were measured by Human IL-18 ELISA kit (BML, Nagoya, Japan). Neopterin, ferritin and soluble (s) IL-2 receptor (R) levels were also measured. [Results] Serum IL-18 levels at diagnosis were significantly higher ($p<0.01$) in ILD (+) cases than in ILD (-) cases. Serum levels of neopterin, ferritin and sIL-2R were not significantly different between both groups. No correlation among tested makers was observed. All of the tested markers significantly decreased at the inactive phase in both groups. [Conclusion] Elevated serum IL-18 levels in JDM-associated ILD suggest involvement of macrophages in the pathogenesis of ILD.

W43-2

Histopathological features of myopathies associated with myositis-specific autoantibodies.

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Conflict of interest: Yes

[Objectives] Myositis-specific-autoantibodies (MSAs) are important because of their clinical usefulness for diagnosis and patient classification. However, their pathogenic role are not established. [Methods] To elucidate the pathological features of MSAs in myositis, we investigated 47 patients with PM/DM, whose muscle biopsy specimen were examined histologically in detail. MSAs were determined using immunoprecipitation assays. Pathological analysis was performed by special staings, including alkaline phosphatase, ATPase, and NADH-TR. [Results] Eleven patients had anti-SRP antibodies: nine of them had muscle fiber necrosis and all had fiber regeneration but only one had inflammatory infiltration, indicating resistance to corticosteroid therapy. Six of these 11 had type 1 fiber predominance. Five patients had anti-U1-RNP antibodies: all of them had muscle fiber necrosis, regeneration and inflammatory infiltrates, consistent with typical finding of inflammatory myopathies. Nine patients had anti-ARS antibodies: a half of them had muscle fiber necrosis, regeneration or inflammatory infiltrates, and one of them showed type 1 fiber predominance with ATPase staining. [Conclusions] These studies clearly demonstrate that specific histological patterns are associated with individual MSA.

W43-3

Myositis-Specific Anti-155/140 Autoantibodies Target Transcriptional Intermediary Factor 1 Family Proteins

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Conflict of interest: None

[Objectives] To identify the 140-kd autoantigen recognized by anti-155/140 autoantibodies that are associated with adult cancer-associated dermatomyositis (DM) and to determine the clinical relevance of anti-155/140 antibodies in a Japanese cohort. [Methods] Sera from 456 DM patients were assessed for the presence of anti-155/140 antibodies in immunoprecipitation using K562 cell extracts as substrate. Then, whether anti-155/140-positive sera recognized transcriptional intermediary factors 1-α (TIF1-α), -β, and -γ was examined by immunoprecipitation and Western blotting. The clinical associations of antigen reactivity were also evaluated. [Results] Anti-155/140-positive sera reacted with 140-kd TIF1-α in addition to 155-kd TIF1-γ. Among 456 DM patients' sera, 52 were reactive with both TIF1-α and –γ, while another 25 were reactive with TIF1-γ alone. Additionally, 7 were reactive with TIF1-β. Malignancy was more frequently found in adult patients with anti-TIF1-α and -γ antibodies than in those with TIF1–γ antibodies alone (73% versus 50%, $p<0.05$). In addition to juvenile DM patients and middle-aged and older DM patients with high percentages of malignancy, 8 "young-adult" DM patients without malignancy possessed these autoantibodies.

W43-4

Anti-CADM-140 Antibody, Ferritin and IL-18 are Associated with Disease Activity of Interstitial Lung Disease in Anti-CADM-140 Antibody-Positive Dermatomyositis

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Conflict of interest: None

[Objectives] To investigate the association between the anti-CADM-140 antibody titer and disease status in patients with anti-CADM-140 antibody-positive dermatomyositis (DM). [Methods] Twenty-seven DM patients with anti-CADM-140 antibody were enrolled. [Results] The complication of rapidly progressive (RP)-ILD was revealed in twenty patients (74%). The ferritin levels were significantly higher ($P = 0.017$) in the dead subset than the living subset, although KL-6, CRP and IL-18 concentrations did not differ significantly between the two subsets. The median value of the anti-CADM-140 antibody titer on admission was higher in the dead subset than the living subset. The anti-CADM-140 antibody titer was significantly lower ($P = 0.0061$) after treatment than on admission in the living subset. The anti-CADM-140 antibody disappeared after treatment in 6 (50%) of 12 living patients. There was no statistical significant difference in the dead subset between the anti-CADM-140 antibody titer upon admission as compared to the antibody after treatment. Moreover, the levels of ferritin and IL-18 were lower after treatment in the living subset. In the dead subset, the levels of ferritin and IL-18 were not significantly lower after treatment.

W43-5

Treatment outcome of anti-CADM-140 antibody positive dermatomyositis with intersititial lung disease.

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Conflict of interest: None

Objective: In a previous report, we described that the prognosis of anti-CADM-140 antibody positive dermatomyositis with interstitial lung disease (ILD) was poor. (Scand J Rheumatol. 2009;38(4):263-7.) We examined treatment outcome of ILD in dermatomyositis with anti-CADM-140 antibody. **Method:** We describe three new patients of anti-CADM-140 antibody positive dermatomyositis with ILD. All patients were treated with prednisolone (PSL) and cyclosporine A (CyA) soon after the diagnosis. We discussed the difference of clinical features and treantments between survivor group (n=5) and non-survivor group (n=6). **Results:** Two patients out of three improved with PSL and CyA. Another patient had elevating the serum revel of ferritin and exacerbation of ILD with mediastinal emphysema. The patient had improved with intravenous cyclophosphamide (IVCY). In comparison of surviver with non-surviver, the level of PaO2/FiO2 at diagnosis and the dosage of CyA were higher in surviver group. ($p<0.05$) **Conclusion:**These results suggest that the serum level of ferritin correlates with the disease activity and early therapeutic intervention with corticosteroid and high-dose immunosuppressant is important in patients with anti-CADM-140 antibody positive dermatomyositis.

W43-6

Analysis of patients with clinically amyopathic dermatomyositis (CADM)

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Analysis of patients with Clinically amyopathic dermatomyositis (CADM)

Conflict of interest: None

[Objectives] To clarify the clinical features of patients with CADM. [Methods] 8 patients with new-onset CADM, who were admitted to our hospital from Dec 07 to Oct 11, were enrolled. We analyzed age of onset, sex, the complications such as interstitial pneumonia (IP) and malignancies, laboratory findings, therapies, response to therapies, infections, and outcome, retrospectively. [Results] 1) Age: 52.2±12.5, sex: M1/F7. All 8 patients were complicated with IP, whereas none with malignancies. CK: 208±127.6 U/l, Ferritin: 2599.5±2878.4 ng/ml, Anti-Jo-1 antibody: all negative. The term between the onset and start of therapies: 3.0±2.1 months. The initial therapies: mPSL pulse+CsA in 4 patients, mPSL pulse in 1, oral PSL+CsA in 1, oral PSL alone in 2. 5 patients were complicated with cryptosporidiosis, 4 with cytomegalovirus, 2 with pneumocystis pneumonia, and 1 with infectious endocarditis. Although 6 patients recovered, 2 patients died because of IP. 2) Comparing the 2 died patients with 6 recovered patients, 2 died patients were over 60 years old, and initial treatments with oral PSL alone were started at 6 months after onset. <Conclusion> Older-onset is the poor prognostic factor in CADM, and we need to initiate combination therapies as soon as possible with regard to infections.

W44-1

Clinical Manifestations and Treatment of 96 patients with Psoriatic Arthritis

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Conflict of interest: None

[Objectives] Psoriatic arthritis (PsA) describes various subgroups in terms of types of psoriasis and psoriatic arthritis with or without enthesitis which sometimes mimic 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 October 31, 2011 were reviewed retrospectively. We analysed age, sex, psoriasis patterns, distribution of arthritis, presence of soft tissue inflammation (such as enthesitis, tenosynovitis and dactylitis), rheumatoid factor (RF) and anti-CCP antibody positivity, and complications. [Results] A total of 96 (45male, 51 female) patients were diagnosed with PsA : mean age 46.8-year old. Dermatological prevalence was 86.5% for plaque psoriasis and 13.5% for pustular psoriasis. At diagnosis, 39.6%, 41.6%, and 18.8% of patients had asymmetric oligoarthritis, systemic polyarthritis, and DIP arthritis, respectively. 33.3% of them had axial joint involvement. Additionally, baseline characteristics and its treatment were also examined. [Conclusion] This information would help to further understand RA mimicking disease.

W44-2

Analysis of 10 cases of psoriatic arthropathy and an example of complete response to a biological pharmaceutical for a case with ocular complications

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Conflict of interest: None

[Objectives] A private guideline for treatment for psoriatic arthropathy [Methods] Analysis of the characteristics and responsiveness in 10 cases in this hospital [Results] Psoriatic arthropathy exhibits various joint symptoms, some half of which cause complicated myelitis occasionally accompanied by serious joint destruction such as of the arthritis mutilans type. Moreover, it can cause tendon symptoms and more uncommonly eye complications, in addition to cutaneous symptoms. Thus, careful and positive treatments are required. I analyzed the characteristics of and the responsiveness to treatment of psoriatic arthropathy in ten cases in this hospital. Patient data were classified by the contraction period, area of the contracted joint, whether one-sided or not, the presence of tendon symptoms, the presence of HLA-Cwb, RF and the anti-CCP antibody, the use of immunosuppressive agents such as MTX, Tac and Biological agent. In addition, I would like to report that I experienced a rare case in which improvement through the use of ADM (adalimumab) was shown, although treatment was difficult in this case due to the presence of ocular complications. I would like this case to be considered as a helpful guideline for the application of Biological agent to treatment of this disease.

W44-3

Traumatic psoriatic arthritis: 2 cases report

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Conflict of interest: None

Case.1: A 60-year-old man had got the bruise of his right hand by hardball for baseball. Soon after that, he had been suffering from mounting contracture of right hand, right knee, and right shoulder for six months. Physical exams showed the erythema of his back with itch and lichen, and spine CT showed Bamboo spine and joint space narrowing of bilateral sacroiliac joints. He was diagnosed Traumatic psoriatic arthritis (PsA), and treated with Infliximab and MTX. His ADL has been improving gradually to play hardball baseball again. Case.2: 68-year-old man had undergone emergency surgery for acute appendicitis and peritonitis, and hospitalized for four months. After discharge, he had been suffering from mounting contracture of both of his hands, knees, shoulders, and neck for two months. Physical exams showed the erythema of his forehead and punctate recessus of hand nails. He was also diagnosed Traumatic PsA, and treated with Adalimumab and MTX. His ADL has been also improving gradually to wear his clothes by himself. These two cases indicate that the specific physical examination for the skin and nail is needed for the diagnosis of PsA, and Biologics is effective for traumatic PsA.

W44-4

The axial involvemnt in psoriatic arthritis and ankylosing spondylitis

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Conflict of interest: None

Psoriatic arthritis(PsA) is an inflammatory arthritis that may affect 15-40% of patients with psoriasis. Some of the patients with PsA suffer from spondylitis. The radiographic features of psriatic spondylitis have been reported to differ from those in ankylosing spondylitis (AS). [Objective] The purpose of this study was to compare the radiographic features of axial involvement between patients with PsA and AS in Japanese patients. [Methods] We collected 70 PsA patients and 19 AS patients. Radiographs of cervical, thoracic, lumbar spine, and sacroiliac joints were obtained and compared. [Results] The mean age/ disease duration at evaluation in PsA without sacroiliitis (SIitis) (n=52), PsA with SIitis(n=18) and AS(n=19) were 50.7 /56.8 /40.6 years, 6.4/12.5/12 years, respectively. Syndesmophyte was the most frequently observed findings in every group. In PsA with SIitis and AS, the frequency of marginal syndesmophyte was higher than that of nonmarginal syndedsmophyte, whereas non-marginal syndesmophyte was high frequency in PsA without SIitis. The severity of axial involvement tended to be high in patients with AS and PsA with SIitis. [Conclusion] It was suggested that radiographic findings of PsA with SIitis was closer to AS than those in PsA without SIitis.

W44-5

Patients with spondyloarthritis on anti-TNF inhibitors; responders with improvement in lower exrimity ultrasonography images can be identified after one week

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Conflict of interest: None

Background/Purpose: Ultrasonography (US) detects inflammatory activity in patients with spondyloarthritis(SpA). The present objective was to follow SpA patients starting anti-TNF inhibitors with US and clinical assessments to explore whether any variable could predict a major decrease in US after 12 weeks. Methods: Patients with SpA starting anti-TNF treatment were consecutively included and examined at baseline and after 1 and 12 weeks with MASEI score system. In addition, the patients were assessed clinically with ASDAS. Patients with ASDAS improvement at the 12 weeks examination was defined as responders. The results of US, clinical and laboratory assessments at baseline and after 1 week were explored by Mann-Whitney tests to examine for associations with the responders. Results: A total of 12 patients were included (with 70% using Remicade, 30% Humira). A total of 65% of the patients were defined as PD responders, and they had significantly lower ASDAS at the 12 weeks examination. At 1 month examination the only variable differing between responders and non-responders was the MASEI score, with a significant reduction in MASEIin the responders versus non-responders 12.6 versus 2.3. Conclusion: US images at 1 week after TNF inhibitors is an advantage to identify responders early.

W44-6

Case presentation; Fluorine-18 fluorodeoxyglucose positron emission tomography(^{18}F-FDG-PET) is very useful for the diagnosis of 2 spondyloarthritis (SpA) cases

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Conflict of interest: None

SpA is subdivided into subtypes consisting of ankylosing spondylitis (AS), arthritis associated with inflammatory bowel disease (IBD), acute anterior uveitis and psoriasis, reactive arthritis and undifferentiated SpA. These SpA features are arthritis, enthesitis, dactylitis, HLA-B27(+), psoriasis, IBD and uveitis. MRI is very important for SpA diagnosis to detect inflammation associated with SpA. Recently, ^{18}F-FDG PET is used as one of diagnostic tools for inflammatory disorder such as infection or collagen disease. Now, we report 2 patients diagnosed SpA using ^{18}F-FDG PET. Case1: 50 y.o. male, chief complaint is joint symptoms including back and chest pain. During the last 2 months he had had joint symptoms in bilateral shoulder, wrists, knee fingers and in the MTP joints with swelling and redness in finger joints. He had negative RF or ACPA, CRP 6.37 mg/dl and ESR of 46 mm/h. Polyarthritis, enthesitis and dactylitis was documented by FDG-PET study. Case2: 41 y.o. female, chief complaint is back pain and walking difficulty. During the last 1 year she had had this symptoms. She had negative RF or ACPA, CRP 5.8 mg/dl and ESR of 64 mm/h. Polyarthritis and sacroiliitis was documented by FDG-PET study. We diagnosed her of SpA with radiographic sacroiliitis.

W45-1

Genetic analysis of Aicardi-Goutières syndrome / Familial chilblain lupus in Japan

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Conflict of interest: None

[Objectives] Aicardi-Goutières syndrome (AGS) is a genetic disease of encephalopathy characterized by calcifications of basal ganglia and elevated interferon-alpha in the cerebrospinal fluid. Approximately 40% of cases suffer from chilblain. Five responsible genes for AGS, *TREX1*, *RNASEH2B*, *RNASEH2C*, *RNASEH2A*, and *SAMHD1*, have been reported. Familial chilblain lupus (FCL) is a genetic disorder of chilblain. Two responsible genes for FCL, *TREX1* and *SAMHD1*, have been reported. Last year we reported the first FCL/AGS family in Japan whose members shared severe chilblain by cold exposure. In this report, we present other AGS/FCL patients in Japan and investigate genotype-phenotype correlation within Japanese cases. [Methods] After obtaining the informed consents, we performed sequencing of the five genes responsible for AGS/FCL and collected clinical information on 33 individuals from 14 families. [Results] By sequencing of *TREX1*, we identified 11 cases from 1 family with a heterozygous p.Asp18Asn mutation, 1 case with a heterozygous p.Asp200Asn mutation, and 1 case with a novel heterozygous variant. We found all the cases with *TREX1* mutations/variant were inherited in autosomal dominant manner, which was rarely reported. We will present the data on the genetic analysis on other 4 genes.

W45-2

Analysis of clinical features in patients with polymyalgia rheumatica

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Conflict of interest: None

[Objectives] We have examined clinical features in patients with PMR. We investigated effective clinical factors of PSL secession. [Methods] We intended for 20 PMR patients we diagnosed from April in 2004 to July in 2011. We have examined sex, age, BMI, smoking/alcohol habit, temperature, Birds criteria item, femoral muscle ache, distal muscle ache, maximum PSL dose, blood examination test (25 items) and proteinuria as an independent valuable, and selected PSL secession as a dependent variable by the logistic-regression analysis. [Results] The average age was 75 years. In the Birds criteria item, there were many three items of shoulder pain and/or stiffness bilaterally, onset of illness of<2 weeks duration, and age>65years. There were 65% of cases with the distal muscle symptom. Mean CRP and mean MMP-3 were 8.7 mg/dl and 305 ng/ml. The mean PSL was 15mg/day. PSL secession cases were only five patients. But there were no statistically significant factors as a predictor of the PSL secession. [Conclusion] PSL was effective by initial treatment of PMR, but PSL secession was only 25%. There were no statistically effective clinical factors for PSL secession.

W45-3

Clinical features of polymyalgia rheumatica in our hospital

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First Department of Internal Medicine

Conflict of interest: None

[Objectives] Our objective is to clarify the clinical features, therapeutic strategy, and prognosis of polymyalgia rheumatica (PMR). [Methods] We analyzed the clinical characteristics of 50 patients diagnosed PMR satisfied with Bird's criteria between 2006 and 2011 in our hospital retrospectively. [Results] Mean age was 73 years old, and the sex ratio (M/F) was 2 to 3. Physical examination showed myalgia (95%), arthralgia (58%), and so on. Only two patients had a complication with temporal arthritis (TA). Six patients were positive for RF, and 18 patients were positive for ANA. Although there were no patients being positive for anti-CCP antibody, all of six RF-positive patients showed morning stiffness (MS). Meanwhile, two patients with anti-SS-A antibody fulfilled the diagnostic criteria of Sjögren syndrome. Mean dosage of 16.2mg/day prednisolone was started for all patients except for TA cases, and the mean dosage was decreased to 6.7mg/day after one year treatment. However, eleven cases needed immunosuppressive agents, mainly MTX. Average of CRP in the patients without MS at 4 weeks after treatment was lower than that in the patients with MS. [Conclusion] Morning stiffness might be a predictive symptom to estimate the sensitivity of steroid therapy in PMR treatment.

W45-4

Hypereosinophilic syndrome with retroperitoneal fibrosis: A case report

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Conflict of interest: None

A 68-year-old woman presented with polyarthralgia in March 2010. She was treated with methylprednisolone (mPSL; 4 mg/day) for rheumatoid arthritis. Although the subsequent blood examination showed eosinophilia (1638/μL), mPSL dosage was tapered and withdrawn in March 2011. She again presented with polyarthralgia in May and epigastralgia in July. Her blood examination showed eosinophilia (13680/μL), and she was admitted to our hospital. According to her medical history and the results of physical and laboratory examination, hypereosinophilic syndrome (HES) was diagnosed. Moreover, abdominal ultrasonography and computed tomography (CT) showed hydronephrosis and fibrosis around the right ureter. Therefore, she was diagnosed with HES that was complicated with retroperitoneal fibrosis (RF). She was given 60 mg/day of prednisolone (PSL) as a result of which the eosinophil number immediately returned to normal. A follow-up CT performed 2 weeks later showed an improvement in the hydronephrosis and a reduction in the fibrosis. Although upper gastrointestinal endoscopy did not show any specific evidence of eosinophilic gastroenteritis before PSL therapy, her epigastralgia also improved after the treatment. This was a rare case of HES with RF.

W45-5

Five cases of paraneoplastic chronic periaortitis

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Conflict of interest: None

[Objectives] Chronic periaortitis is characterized by fibro-inflammatory tissues surrounding the aorta, and it includes idiopathic retroperitoneal fibrosis and fibrosing mediastinitis. Recent studies suggested that chronic periaortitis develops by a systemic immune mediated and inflammatory process. However, the etiology of the disease is not fully understood. [Methods] We retrospectively analyzed five cases of chronic periaortitis associated with cancer. [Results] Four cases were male and one female. Age at diagnosis ranged from 60 to 77 years. Types of cancer included lung (2 cases), prostate, colon, and thyroid. The serum IgG4 levels were increased in three cases. No cases were positive for anti-nuclear antibody or ANCA. Three cases with systemic or abdominal symptoms were effectively treated with oral prednisolone. The other two cas-

es without symptoms were followed without medication, and were in stable condition. The prognosis of cancer was complete remission in three cases, under treatment in one case, and fatal in one case.

W45-6

A case of extra-nodal Rosai-Dorfman disesase

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Conflict of interest: None

A 62-year old man presented with a 3-month history of pharyngeal pain and odynophagia. Elevated CRP, ESR and ferritin were observed and FDG-PET revealed accumulation in soft tissue nodule in the right side of cervical esophagus. Subsequently, pancytopenia developed and the patient sccumb to cachexia. A biopsy specimen obtained from the cervical lesion showed proliferation of histiocytes including karyorrhexis and necrotic materials inside the cytoplasm and these cells were positive for CD68 and S-100 protein. These finding was consistent with Rosai-Dorfman disease (RDD). The patient was treated with steroid therapy and all clinical manifestations improved. In the present case, diagnosis was very difficult because of the absence of lymphadenopathy and the lack of specific findings. Finally, excision biopsy made the diagnosis of RDD. Pancytopenia observed in our case could be caused by macropharge activation syndrome (MAS) or hemophagocytic syndrome (HPS). RDD associated with MAS/HPS was previously reported in only one case. Extra-nodal Rosai-Dorfman disesase is a very rare proliferative histiocytic disease. In our case, the diagnosis was established immunohistochemically by the excision biopsy and the patient dramatically improved by steroid therapy.

W46-1

Echocardiographic screening and diagnosis of pulmonary arterial hypertension in patients with collagen disease

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Conflict of interest: None

[Objectives] To investigate the usefulness of ultrasound cardiography (UCG) in screening of pulmonary arterial hypertension (PAH) in patients with collagen diseases. [Methods] The subjects of this study were 212 patients with collagen diseases (SSc 8, SLE 37, RA 37, vasculitis 21, MCTD 16) to whom UCG was performed from April 2008 to March 2011. We retrospectively reviewed the UCG findings, the diagnosis of PAH and the outcome. [Results] The patients with elevated estimated PA pressure were as follows: 29 patients were 36mmHg or higher, and 19 patients were 41mmHg or higher. Among 29 patients, 6 had already been diagnosed of PAH, and elevated PA pressure was due to congestive heart failure in 8 patients. Cardiac catheterization was performed in 3 patients in this period. Twelve patients (SSc 8, MCTD 2, SLE 1, DM 1) were treated for PAH, and in 4 of them, treatments were started in this period. Eleven patients were followed up without medication of PAH, and in 3 of them, the estimated PA pressure was reducted by following UCG.

W46-2

Clinical examination of pregnancy complicated with connective tissue disease in our hospital

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Conflict of interest: None

【Objectives】Pregnancy complicated with connective tissue disease has a high risk of preterm birth or abortion, and it may cause the exacerbation of primary disease. Therefore, the control of disease activity is important.【Methods】We investigated pregnancy outcome (dose of corticosteroid, pregnancy course, mode of delivery, and complication) in 50 cases with pregnancy complicated with connective tissue disease in our hospital between 2007 and 2011.【Results】Study patients had systemic lupus erythematosus, sjogren syndrome, rheumatoid arthritis, mixed connective tissue disease. The almost half of all patients was positive for anti SS-A antibody, but there were no complication caused by anti SS-A antibody. On the rate of preterm birth, study patients were higher than pregnant women with no complication. About 60% of all patients continued corticosteroid. As the dose of corticosteroid increased, the rate of peripartum complication did not increase. And the rate of LFD(light for date) babies also did not increase. In this study, we suggest that it is possible to manage pregnancy safely with the appropriate treatment of disease and management of peripartum period.

W46-3

Chronic recurrent multifocal osteomyelitis involving the spine: a radiographic and clinical investigation of five cases

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Conflict of interest: None

[Objectives] The objective of this study was to analyze clinical features and radiological findings of chronic recurrent multifocal osteomyelitis involving the spine (CRMO spine). [Methods] Medical records and radiological imagings of five cases (one male and four females) with CRMO spine from June 2002 to October 2011 were retrospectively reviewed. [Results] The average age of onset was 50 y.o. Skin lesions were found in 2 cases. All patients complained of back pain at the initial visit. Radiologically, bony lesions of the spine were observed in all cases. WBC count was within normal limit in all and CRP positive in four cases. Histological examination of biopsy specimens demonstrated chronic inflammation in 3 out of 4 cases. Bacterial cultures were negative in all cases. NSAIDs was used for the pain control in all cases. In one case suffering from severe back pain, etanercept was prescribed. [Discussions] CRMO spine includes multifocal vertebral bodies with radiologically proven osteolytic / sclerotic bone lesions. It is important to distinguish CRMO spine from infectious and tumorous lesions.

W46-4

Rheumatic manifestations of myelodysplastic syndromes: a two-case-report.

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Conflict of interest: None

Myelodysplastic syndrome (MDS) sometimes has inflammatory conditions at presentation. The association of MDS and rheumatic manifestations has been documented in several reports since 1990s. Here we describe two cases. Case 1: A 70-year-old man presented with fever, polyarthralgias and bone pain. RF, anti-CCP antibodies and cultivation surveys showed negative results. He developed cranial nerve palsy caused by epipharynx mass, in which nonspecific infiltrate of mononuclear cells were found on biopsy. He was diagnosed with MDS based on bone marrow dysplasia of 3-cell lineages and chromosome abnormalities. All the symptoms including mass effects were successfully treated by steroid therapy. Case 2: An 82-year-old male was admitted to our hospital because of knee pain and fever. Before referral, he had been treated with steroid for assumed polymyalgia rheumatica. The shoulder pain flared during tapering steroid dose, and the bone marrow examination revealed MDS. The inflammatory conditions subsided by increased dose of steroid therapy. MDS can cause a fever of unknown origin and mimic rheumatic diseases. Even in the settings of no indication for chemotherapy or bone-marrow transplantation, the inflammation may respond to steroid therapy.

W46-5

Relapsing polychondritis diagnosed with biopsy of the unswollen auricular cartilage negative for FDG-PET scan: A case report.

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Conflict of interest: None

A 70-year-old man was admitted to our hospital due to incrementing dyspnea, wheezing, and fever. He had received hemiglossectomy and radical cervical lymph node dissection for his oral tongue cancer 4months before admission. On admission, physical examination revealed no nasal and auricular swelling. Plain chest CT showed thickening of tracheal and bronchial wall. Pulmonary function test demonstrated decrease in air flow through the expiratory phase, indicating the air tract collapse. FDG-PET study showed significant uptake in the trachea and major bronchi, sparing their membranous portion. Although FDG-PET scanning did not show FDG uptake in the nasal and auricular cartilage, a biopsy from the right auricular cartilage revealed eosinophilic degeneration and multinucleated chondrocytes with inflammatory cells infiltration, which was compatible with the diagnosis of relapsing polychondritis. He was successfully treated with prednisolone of 1mg/kg/day. We report the rare case of relapsing polychondritis diagnosed with biopsy of the auricular cartilage which did not show swelling and FDG uptake in a PET scan.

W46-6

A case of refractory aseptic abscess successfully treated by infliximab

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Conflict of interest: None

The patient is a 72-year-old man, who had multiple episodes of culture-negative intraabdominal abscesses with pyoderma gangrenosum without any signs of inflammatory bowel disease. Antibiotics were ineffective and prednisolone, leukocytapheresis, sulfasalazine, azathioprine, tacrolimus, cyclosporin, and methotrexate showed only a partial effect. The abscesses had been repeatedly exacerbated for when prednisolone was tapered < 20 mg/day, but finally resolved after the initiation of infliximab. “Aseptic Abscess” is a recently recognized disease entity and diagnosis and treatment of this emerging disease will be also reviewed.

W47-1

Examination of the discontinuance cases of Biological agent for Rheumatoid Arthritis patients. --- In 1000 cases that installed Biological agent with this hospital ---

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Conflict of interest: None

[Objectives] Examine the discontinuance cases of Biological agent (Bio) for Rheumatoid Arthritis (RA). [Method] We investigated the reason and the time of discontinuance of 1000 RA patients those have been taken 4 types of Bio (Infliximab, Etanercept, Tocilizumab, Adalimumab). 1000 patients are consists with redundancies of 227 Males, 773 Females, Age 57.1+/-13.2, Bio naivety 791, and Switch 209. [Result] The results of Bio is IFX 341, ETN 394, TCZ 105, ADA 160, and Continuance 549 cases, Discontinuance 350 and Hospital transfer 101. The reason of Discontinuance 350 (IFX 162, ETN 111, TCZ 22, ADA 55) were Adverse event (AE) 147, Secondary failure 92, Primary failure 61 and other cases. Infection was 35 cases (Bacterial pneumonia 14, Pneumocystis pneumonia 7, Herpes zoster 3 and other cases). The 57.1% of infection had been appeared within 3 months. The incidence of infection was IFX 5.0%, ETN 2.5%, TCZ 5.7%, ADA 1.3% and drip infusion showed a higher tendency. The age of the infection patients was 63.1 +/- 11.1 and the result was much higher than the age of non-infection 56.9 +/- 13.2. Furthermore, the IFX was remarkable. [Conclusion] AE, especially infection, appear within 3 months after starting medication. Expressly aged patient and the usage of drip infusion should be noticed.

W47-2

Analysis of factors impacting attainment of clinical remission of rheumatoid arthritis in tocilizumab treatment

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Conflict of interest: None

[Objectives] Tocilizumab (TCZ) shows a greater effect on blood examination data rather than the clinical condition due to its mechanism of action. [Methods] Here, we searched for factors that affect attainment of clinical remission of rheumatoid arthritis (RA) with the IL-6 receptor TCZ treatment. HAQ, DAS28ESR, SDAI, CDAI, and various inflammatory cytokines were measured before and after 24 weeks of TCZ administration of 84 patients (M:F ratio 16:68; average age, 56.9). [Results] Seventy-one of 84 patients were achieved clinical remission (DAS28-ESR < 2.6). After main-

taining clinical remission for >24 weeks by TCZ treatment, TCZ was discontinued in 20 patients. Of the 20 patients, 14 patients flared within 1 year (9~47 weeks; average 16.9w), and they had already been re-treated with TCZ. The other 6 were remaining without TCZ at 0.5 year after the discontinuation of TCZ (27~73 weeks; average 47w). Initial "Stage" of RA and DAS28-ESR after 24 weeks of TCZ treatment were correlated with discontinuation of TCZ. [Discussion] In TCZ treatment, discontinuation of TCZ after clinical remission can be expected in cases with lower stage of RA before treatment and lower DAS28-ESR in 24th weeks of treatment.

W47-3

Feature of each analyzed from high survival rate and bio-free remission rate of 1343 patients with rheumatoid arthritis treated with Tocilizumab, Adalimumab, Etanercept, or Infliximab.

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Conflict of interest: None

[Objectives] We treated RA patients with 1343(IFX561, ETN322, TCZ173, ADA212, ABT70, GLM 5) biologics since 2002. We examined the proper use of each Biologics analyzed from high survival rate and bio-free remission rate. [Methods] We compared treatment responses, remission rates, survival rates, adverse effects since July 2008 when these biologics were approved in RA by using Kaplan-Meier method(Log-rank test). [Results] Drug survival rates were as follows; IFX70.6%, ETN83.1%, ADA70.2%, TCZ73.2%, and the rate was highest for ETN. Concomitant MTX rates were as follows; IFX100%, ETN59.3%, and ADA94.6% and TCZ56.2%, and biologics naive rates were as follows; IFX99.3%, ETN74.5%, ADA88.2% and TCZ67.9%. These rates were lowest for TCZ. There was no difference at the adverse effects. The rates of Non-responder were significantly low for ETN. Remission rates(IFX16.2%/ADA13.3%) were significantly high in IFX/ADA.

W47-4

Reducing the dose or discontinuation of methotrexate in patients treated with tocilizumab has no effect on the remission maintenance rate

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Conflict of interest: None

[Objective] Introduction of methotrexate (MTX) with early diagnosis and early remission and maintenance of remission are recommended. However, some patients request reduced doses or discontinuation of MTX because of severe adverse reactions. The effects of dose reduction or discontinuation of MTX on efficacy were studied in tocilizumab (TCZ) +MTZ treated patients. [Method] In the Michinoku Tocilizumab Study Group, DAS28-ESR (DAS28) and Boolean criteria were calculated every 6 months (M) for patients who took TCZ for 24M. [Results] 272 patients were treated with TCZ. Continuation rates were high at 80.2% for 12 M and 70.2% for 24 M. DAS28 was reduced significantly from 5.2 at baseline to 2.6 after 24 M ($p<0.0001$). Remission rate after 24 M was 59.6% for DAS28, 28.3% for Boolean clinical practice. No significant differences in DAS28 remission rates were found with or without concomitant MTX. In 62 patients with reduced doses or discontinuation of MTX, the remission rate was 74.2% after 6M, and remission maintenance rates were 90.9% after 12 M and 79.5% after 24M. [Conclusion] TCZ showed high efficacy with or without concomitant MTX. In patients treated with TCZ+MTX, remission maintenance rates were not affected when MTX was reduced in dose or discontinued.

W47-5

Discontinuation of MTX in RA patients receiving tocilizumab (TCZ) therapy

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Conflict of interest: Yes

[Objectives] To extract clinical characteristics of RA patients to whom MTX was discontinued within 52 weeks after the start of TCZ. [Methods] The subjects were 89 RA patients (11 males, 78 females) in whom TCZ was newly initiated with MTX. [Results] MTX was discontinued on 23 of 89 patients. At the start of TCZ in MTX-discontinued group and MTX-continued group, the mean age was 62.2 and 56.3 years old ($p<o.o5$), the mean disease duration was 119 and 120 months, the mean MTX dose was 7.0 and 7.8 mg/week, the mean DAS-28 (ESR) was 6.20 and 5.50, respectively ($p<o.o5$). At the week 52 in MTX-discontinued group and in MTX-continued group, the mean DAS-28 (ESR) was 2.87 and 2.80, CDAI was improved from 28.6 to 9.5 and from 24.6 to 10.7, CDAI remission ratio was 26% and 21%, HAQ-DI was reduced from 1.68 to 1.10 and from 1.47 to 1.16, respectively. All these values were not significant between 2 groups. [Conclusion] MTX was discontinued more frequently in the elderly patients, which might be useful for the prevention of MTX-induced adverse events. In addition, though MTX-discontinued group patients had higher disease activity, TCZ was equally effective as MTX-continued group patients. TCZ mono-therapy seems to be useful to maintain the low RA activity.

W47-6

Tocilizumab successfully reduced the glucocoriticoids dose at the 28 and 54 weeks after administration in rheumatoid arthritis patients comparing with infliximab.

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Conflict of interest: None

[Objectives] Since long term use of glucocoriticoids(GCs) has adverse events such as osteoporosis, diabetes mellitus, and infection, it is better to taper GCs dose as rapidly as clinically feasible. In the present study, we evaluated sequential GCs dose after initiation of biologics. [Methods] We evaluated DAS28-ESR and prednisolone(PSL) dose before and 28 and 54 weeks after initiation of tocilizumab(TCZ) and infliximab(IFX) in 62 and 48 patients, respectively, with rheumatoid arthritis. [Results] The mean age was 60.4, 58.8years and the mean duration of disease was 14.0, 10.9 years in TCZ and IFX group respectively. The mean DAS28-ESR was 5.01, 3.00, 2.92 in TCZ group, and 4.66, 3.31, 3.06 in IFX group at 0, 28, 54weeks. DAS28-ESR was improved at 28, 54weeks compared with baseline in both group significantly.

DAS28-ESR at 28weeks of TCZ group was more significantly decreased than that of IFX group. The mean PSL dose at baseline and 28,54weeks was 6.19, 2.75, 1.64(mg/day) in TCZ group and 6.19, 4.19, 3.66(mg/day) in IFX group. ⊿PSL dose at 28, 54weeks of TCZ group was significantly higher than IFX group respectively ($P<0.01$, $P<0.05$). [Conclusion] Both TCZ and IFX had a therapeutic effect in RA patients. With TCZ, PSL dose could be decreased more significantly than with IFX.

W48-1

The effect of Abatacept (CTLA-4-Ig) therapy on peripheral Treg in patient with rheumatoid arthritis

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Conflict of interest: Yes

[Objectives] Abatacept (CTLA-4-Ig) prevent the activation of T cell by binding to the CD80 CD86 on APCs, and consequently suppress arthritis in RA patients. However, there are no detailed analysis on the effect of Abatacept on regulatory T cells (Treg) phenotype. **[Methods]** We have examined phenotypic characterization of peripheral Tregs ($CD4^+$ $Foxp3^+$T cell) in RA patients (n=12) before and after(4wks) Abatacept treatment by multicolor flow-cytometry. (The markers we analyzed are as follows: CD25, CD45RA, CD69, CD62L, CD31, CD39, CD127, CD161, CTLA-4(intra), GITR, GARP, LAG-3, HLA-DR, CCR4, CCR6, CXCR3, Helios(intra), Ki67) **[Results]** After 4wks Abatacept therapy, the ratio of $CD45RA^{high}$ $CD25^{low}$ (= resting Tregs) in peripheral $CD4^+$ Tcells dramatically increased compared with pretreatment level, whereas no changes were caused by TNF-α blocking agent. Furthermore, we show that expression level of the functional marker, such as Foxp3, CTLA-4, GITR, and GARP, are decreased significantly in Tregs. Since it is known that resting-Tregs show strong suppressive function and long-survival in vivo, these alteration in phenotypic characterization of Tregs may contribute to the induction of immunotolerance in RA patients, raising the possibility of novel mechanism of Abatacept therapy.

W48-2

Alterations of T cell subsets in bio-naïve RA patients during treatment with abatacept (CTLA4-Ig)

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Conflict of interest: None

[Objectives] Abatacept (CTLA4-Ig) controls T cell activation via competitive inhibition of CD28 binding to CD80/CD86 ligands. However, the mechanism of action of abatacept in human remains inadequately understood. To clarify how abatacept treatment influence on T cell subsets, we examined alterations of T cell subsets in RA patients enrolled in ABROAD test during treatment with abatacept. [Methods] PBMCs isolated from 13 RA patients before and 6 months after treatment were surface stained and analyzed with FACS. Treg cells ($CD4^+CD25^+Foxp3^+$) were measured with intracellular staining with anti-Foxp3 antibody. After *in vitro* stimulation with PMA/Ionomycin for 4 hrs, PBMCs were intracellularly stained with anti-IFNγ, anti-IL-4 or anti-IL17A antibodies. [Results] Proportion of $CD25^+$ in $CD4^+$ T cells significantly decreased 6 months after treatment. Meanwhile, there were no significant differences of the proportions of Th1($CD4^+IFN\gamma^+$), Th2($CD4^+IL\text{-}4^+$) and Treg cells between before and after treatment. The proportion of Th17($CD4^+IL17^+$) cells significantly increased in untreated RA patients and decreased in 8 of 13 RA patients 6 months after treatment. These results suggest that effective treatment with abatacept is achieved by controlling of T cell activation and pro-inflammatory Th17 cells.

W48-3

Different effect of anti-IL-6 and anti-TNF therapy on CD4+ CD161+CD45RO+CCR6+ cells in peripheral blood of RA patients

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Conflict of interest: Yes

OBJECTIVE: An etiological role of Th17 in RA patients remains unclear. Recently, CD161, C-type lectin-like receptor, has been described as a cell surface marker of human Th17. We investigated the percentage of CD4+CD161+CD45RO+CCR6+ cells (defined as human Th17) in total CD4+ T cells in peripheral blood (PB) of RA patients. **METHODS**: Clinical data and PB were collected in 81 RA patients (untreated: 7, DMARDs: 19, TNF inhibitor: 29, tocilizumab (TCZ): 26) and 17 healthy adults (HA). Th17 was measured by flow cytometry. **RESULTS**: The percentage of Th17 in CD4+ T cells in HA and RA was 4.8% and 5.8% respectively, but the percentage of patients with high Th17 (defined as higher than mean+2SD of HA) was 0% in HA and 23% in RA. In untreated patients, the percentage of Th17 was 8.3% and was correlated with swollen joint counts. The percentage of patients with high Th17 was 71%. In patients with less than moderate activity, the percentage of Th17 was 5.8% in TNF inhibitor treatment and 5.5% in TCZ treatment, but the percentage of patients with high Th17 was 3.8% in TCZ treatment and 38% in TNF inhibitor treatment. **CONCLUSIONS**: The percentage of peripheral blood Th17 was higher in untreated RA patients. It is suggested that TCZ treatment could decrease the peripheral blood Th17.

W48-4

Analysis of anti-CCP antibodies concentrations in the treatment of rheumatoid arthritis patients using tocilizumab

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Conflict of interest: None

Objective : To examine the concentrations of anti-cyclic citrullinated peptide (aCCP) antibody in the course of treatment in pa-

tients with rheumatoid arthritis (RA) using tocilizumab(TCZ). Methods : In a 46 consecutive patients with RA treated with TCZ, baseline, 3 months later, and 1 year later aCCP antibodies were measured by ELISA. Results : The aCCP antibody levels decreased at 3 months later (p=0.06), and thereafter the levels of aCCP antibody increased at 1 year after p<0.005). The concentrations (IU/ml) of aCCP antibody at baseline, at 3 months, at 1year, were 201+/-272, 188+/-263, 248+/-333, respectively. These changes of the levels of aCCP antibody were greater in the biologics naïve patients group. Conclusion : TCZ treatment directly influenced aCCP antibody levels. These changes were not associated with the clinical responses to TCZ therapy. These results suggested that TCZ had an effect on aCCP productions in the sera of patients with RA.

W48-5

Analysis of questionnaire survey for the RA patients with biologics treatment

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Conflict of interest: None

[Objectives] To investigate patient satisfaction for biologics treatment via survey with questionnaire. [Methods] We examined efficacy, cost, adverse effect, and hope of continuation on RA patients treated with biologics using questionnaire survey. We also analyzed correlation between the survey and change of DAS-28ESR, HAQ under biologics treatment. [Results] A total of 104 patients responded(response rate 75%, average 63.1 y.o, female 83.7%, mean RA dulation 114.9mths). 84% patients felt to be relieved of symptom and 88% patients were satisfied with treatment, whereas 85% patients suffered from medical expenses, 61% patients cut down on their household expenses such as clothing, recreation and entertainment fee. 23% patients had some adverse effects. The patients who wished to continue biologics treatment were only 60%. Comparison of positive with negative group for continuation of biologics treatment, young age, female, low DAS-28ESR score were predominant in negative group. In negative group, the burden of medical expenses was only factor extracted from the result of multivariate analysis. [Conclusion] Biologics treatment gives high satisfaction for RA patients, whereas medical cost burden seems to be the serious problem in effective, young and female cases.

W48-6

Experience of biologics use on Rheumatoid Arthritis treatment in Osaka university

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Conflict of interest: None

Background/Object: A number of biologics are now available on the treatment of rheumatoid arthritis (RA). To accumulate the experience of each case, we constructed a database about RA treatment, which includes the whole of Osaka University. Method: We retrospectively reviewed charts of patients whom we administrated biologics, and examined the continuation rate and causes of discontinuation of biologics for the treatment of RA. Results: We administrated biologics to 377 RA patients. (All over: 485 counts) Tocilizumab (TCZ), Infliximab (IFX), Etanercept (ETN), Adalimumab (ADA), Abatacept(ABT) was administrated to 92,136,53, and 3 cases respectively. At 2 years, drug continuation rates of TCZ, IFX, ETN, ADA, ABT were 77.0%, 53.6%, 80.0%, 59.3%, and N.A., respectively as the 1st biologics. We stopped administration of IFX, ETN, ADA mainly for the first or the second failure(35%, 38%, and 55% respectively). We stopped TCZ mainly for infection(20%). Conclusion: In our cohort, ETN showed a continuation rate as high as TCZ.

W49-1

Abatacept Research Outcome as a First-line Biological Agent in the Real World

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Conflict of interest: Yes

[Objectives] To investigate the results of ABT therapy in a multicenter setting, in RA patients not previously treated with a biologic. [Methods] The efficacy and safety of ABT were evaluated in 43 RA patients who received the drug for at least 24 weeks out of 104 patients enrolled in the ABROAD Study conducted at 37 institutions (primarily in the Kansai region). [Results] At week 0/12/24, the mean SDAI /DAS28-CRP/ CRP/ MMP-3 scores were SDAI(27.1→12.4→10.0), DAS28-CRP(4.7→3.1→2.8), CRP(2.04→0.96→0.90), and MMP-3(217.1 →130.0→113.2) respectively. At Week 12, SDAI/DAS28-CRP/CRP/MMP-3 scores were significantly reduced from the baseline. The proportions of patients who had low disease activity or remission based on SDAI/DAS28-CRP scores were SDAI (66.7%, 11.9%), DAS28-CRP(53.5%, 39.5%) respectively at week 12. The persistence rate at week 24 was 95.3% with no serious adverse event. 54.8% of patients(17/31) were able to reduce steroids doses by week 24(3.3mg/day→2.1mg/day). [Conclusion] ABT given as a first-line biologic has shown favorable efficacy, with good adherence by patients. The significant improvement of disease activity at week 12 suggests that time to response of ABT is the same as other biological agents.

W49-2

Clinical outcome of abatacept therapy for patients with rheumatoid arthritis: Comparison between patients who did and did not previously received biologics using RA database of multicenter study group

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Conflict of interest: None

[Objectives] To evaluate the clinical efficacy and safety of abatacept for RA patients who did and did not previously received biologic therapy. [Methods] Sixty one RA patients treated by abatacept were extracted from FIT (Fukui, Ishikawa, Toyama)-RA database of multi-center study group in Hokuriku area. Thirteen patients did not received biologics (bio-naïve group) and 48 received other biologics previously (switching group). We evaluated

the retention rate, EULAR response using DAS28-4CRP and occurrence of adverse events for 6 months after abatacept treatment. [Results] Nine patients withdrew from abatacept treatment before 6 months. All of them were in switching group. Six patients were judged as primary failure and 3 patients suffered from adverse events. The retention rate in bio-naïve and switching group were 100% and 81.3%, respectively. Using EULAR criteria, 58.3% of bio-naïve patients had good response after 6 months. However, only 26.4% of patients in switching group showed good response. [Conclusion] Abatacept treatment was effective for patients with RA. The efficacy and safety, however, were superior in biologics naïve patients.

W49-3

Comparisons of clinical efficacy of abatacept between Bio-naïve and Bio-switching 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 since 2010 in Japan. We studied the clinical efficacy of ABT in Bio-naïve and Bio-switching patients. [Methods] Ninety-four RA patients treated with ABT for longer than 24 weeks were included, from the 153 patients with ABT therapy in the Tsurumai Biologic Communication (TBC), which is the multicenter registry for RA patients taking biologics. Disease activities were evaluated by using DAS-28ESR, DAS28CRP, SDAI, and CDAI at 0,4,12 and 24 weeks in Bio-naïve and Bio-switch group. Furthermore, EULAR response criteria and drug survival rate at 24 weeks were evaluated. [Results] Disease activities were significantly decreased at 4 weeks in both groups, and further decreasing were observed at 24 weeks. Bio-naïve group showed 79.4% of EULAR response rate (good 23.5%, moderate 55.9%), while 41.0% in Bio-switching group (good 8.9%, moderate 32.1%). Drug survival rate was 86.5% in Bio-naïve group and 82.5% in Bio-switching group. [Conclusion] Although the clinical efficacy of ABT was superior in Bio-naïve patients, ABT showed significant efficacy also in Bio-switching patients. Further study would be necessary for the best-use of ABT in bio-switching case.

W49-4

Influence of biological history on the effectiveness of Tocilizumab

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Conflict of interest: None

[Objectives] We examined whether the effectiveness of Tocilizumab (TCZ) would have a difference with the number of anti-TNF biologics treated before. [Methods] The clinical results were observed in 37 patients with RA who TCZ was administrated over 24 or more weeks. Mean disease duration was 16 years, 57 years of average age, and 28 patients had the history of biologics treatment, 21 patients with second-bio administration (S group, IFX 18, ETN 3) and 7 patients with 3rd-bio (T group). [Results] Patients of DAS28-ESR<2.6 was 73%, and the significant difference was not accepted by the existence of the bio-treatment history. By the bio-treatment group, DAS28-ESR<2.6 was 72% and high as compared with some literatures (P. Emery et al, 2008). Among bio-treatment groups, DAS28-ESR<2.6 (24 weeks) of S group was 83%, and was significantly high compared with 43% of T group (p=0.04). Moreover, the chronological course (0-12-24-48 weeks) of CDAI of S-group was 23-8-6-4, and was significantly good as compared with T-group (p=0.05). It was suggested that TCZ shows a high effectiveness in patients treated with a single biologic as compared with multiple ones in past.

W49-5

Tocilizumab as the First Biologics: Direct Comparison of Four Biologics in Biologic-naïve Rheumatoid Arthritis Patients

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Conflict of interest: None

[Objectives] We compared treatment response to four biologics, infliximab (IFX), etanercept (ETN), tocilizumab (TCZ) and adalimumab (ADA), in biologic-naïve RA patients who had been started on treatment in the same period in the real clinical setting. [Methods] One hundred and forty-two biologic-naïve RA patients were started on a biologics (IFX 37, ETN 39, TCZ 27, ADA 39) from July 2008 onwards. Baseline, six months later and twelve months later, ESR, CRP, MMP-3, the swollen and tender joint counts, DAS28-ESR and EULAR remission criteria (DAS28-ESR<2.6) were examined. The drug survival rate on each agent was also surveyed. [Results] Patient characteristics showed lower ratio of MTX and high CRP in TCZ. No significant difference was identified at 6 months in ESR, CRP, MMP-3, the swollen and tender joint counts and DAS28-ESR, the DAS28-ESR remission rates and drug survival rate for each biologics. [Conclusion] The present study suggested that TCZ may provide therapeutic efficacy at least comparable to TNF inhibitors in biologic-naïve RA patients.

W49-6

Clinical Benefit of Switching Biologics in Patients with Rheumatoid Arthritis

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Conflict of interest: None

[Objective] Biologics are highly beneficial in the treatment of rheumatoid arthritis (RA), but they sometimes need to be discontinued or switched. I analyzed the clinical benefits of switching biologics in RA patients. [Subjects] At my clinic, biologics were switched in 125 patients. One switch was made once in 101 patients and two or more in 24 patients. Switches were made in 58%, 47%, 37%, 25%, and 25% of 85 patients initially on IFX, 60 on ADA, 175 on ETN, 60 on TCZ, and 8 on ABT, respectively. [Results] In more than 50% of patients initially prescribed IFX or ADA, and approximately 30% patients initially prescribed ETN or TCZ, switches were made due to no response. In the ETN and TCZ groups, side effects or patient preference was the more prevalent reasons. Evaluation of clinical benefit based on the DAS revealed that the remission or good response rate was at least 50% in patients switched from anti-TNF agents to anti-IL-6 agents, and

approximately 30% when switching between anti-TNF agents. Moreover, administration was continued after the switch in at least 80% of patients switched from an anti-TNF agent to an anti-IL-6 agent, but it was continued in 50–70% of patients switched to another anti-TNF agent.

W50-1

Cyclosporine for maintenance therapy in MPO-ANCA-associated vasculitis

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Conflict of interest: None

[Objectives] We investigate the efficiency of cyclosporine (CyA) for maintenance therapy in patients with MPO-AMCA-associated vasculitis. [Methods] Our study included 5 patients with MPO-AMCA-associated vasculitis, who had been given CyA (the mean dose was 87.5mg/day) added to oral prednislone (PSL), for maintenance therapy, following by induction therapy, including streroid pulse therapy, plasmapheresis and/or IVCY. The disease activity was estimated by BVAS. Blood examinations, including ANCA titer, CRP, serum creatinine (sCr), and urinalysis, were also evaluated during the period. [Results] During a mean follow-up of 15.2 months, no patient developed a relapse. A mean MPO-ANCA titer was significantly decreased ($p<0.05$: 935.5 ± 729.4 *vs* 209.6 ± 209.6 U/l) and CRP levels were not obviously elevated in all patients. And, renal involvement did not tend to be progressed. A mean dose of PSL was significantly decreased ($p<0.05$: 26.0 ± 8.9 *vs* 10.8 ± 6.7 mg/day). [Conclusion] These results suggested that cyclosporine therapy might be useful to maintain remission in patients with MPO-AMCA-associated vasculitis.

W50-2

Safety and efficacy of rapid glucocorticoid tapering protocol in severe cases of elderly onset ANCA-associated vasculitis

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Conflict of interest: None

[Objectives] There is no consensus on how glucocorticoid (GC) should be tapered in therapy of ANCA-associated vasculitis (AAV). This study is to examine safety and efficacy of rapid GC tapering protocol in elderly patients. [Methods] Retrospective review of patients diagnosed with severe AAV at age 60 or older from April 2007 to November 2011 was conducted. The cases were divided into two groups based on whether GC was tapered rapidly (0.5mg/kg at first month) or not. Cumulative GC dose, rate of infection, baseline and changes in BADL and rate of relapse were compared between two groups. [Results] Among 29 patients diagnosed with AAV, 13 (5 MPA, 4 GPA and 4 AGA based on classification by Watts et al.) were categorized as severe disease. Seven achieved rapid tapering and 6 did not. Immunosuppressive agent was used in 6 and 3 respectively. Cumulative GC dose at 2 month was significantly lower in the former group. No significant difference in the rate of infection and relapse. Two fatal infections occurred in the latter group but none in the former group. All cases from the former group had preserved or improved BADL while 50 percent of the latter had declined BADL. [Conclusion] In elderly onset severe AAV, rapid tapering protocol, combined with immunosuppressive agent, is preferred.

W50-3

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

To investigate efficacy and safety of European protocol of pulse cyclophosphamide (pCY), we retrospectively investigated 5 Japanese patients with ANCA associated vasculitis (AAV), 4 with granulomatosis with polyangiitis and 1 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 weeks 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. All of our patients had normal creatinine level. The average ± SD of pCY and follow up were 7.4±3.8 and 45±28 (wks), respectively. Remission was achieved in 5/5 within 6 to 12 wks. Leukopenia, oral candidaris, upper airway infection, nontuberculous mycobacterial infection and amenorrhea were observed in 1/5, 3/5, 1/5, 1/5 and 0/1, respectively. Two stopped pCY due to adverse events of lung cancer at W20 and nontuberculous mycobacterial infection at W14. In conclusion, All of 5 Japanese patients with AAV achieved remission with pCY according to CYCLOPS, while two experienced serious adverse events.

W50-4

Utility of mycophenolate mofetil for vasculitides

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Conflict of interest: None

[Objectives] Mycophenolate mofetil (MMF) of antimetabolite inhibiting a nucleic acid composition (purine body) of cells is used as an immunosuppressive drug, however the finding about immunosuppressive effects for the vasculitides is poor. Therefore, we examine the effect of maintenance therapy of MMF on vasculitides. [Methods] Among the patients with vasculitis that came to the hospital from 2007 to 2011 in this hospital, we examined duration of treatment, difference with induction therapy and drop-out rate, in the patients treated with MMF. [Result] Patients (systemic lupus erythematosus, n=7; microscopic polyangiitis, n=4; granulomatosis with polyangiitis, n=3; malignant rheumatoid arthritis, n=4; Sjoegren syndrome, n=1) with 19 vasculitis were treated for MMF. Induction therapy was steroid monotherapy 4 cases, cyclophosphamide intermittent intravenous-injection treatment 6 cases and azathioprine 7 cases. The mean duration of treatment was 639 days, the average dosage was 1421 mg, the relapse case was 1 patient, the activity of other cases did not increase, and remission is maintained. [Conclusion] MMF is a candidate of maintenance therapy of vasculitides.

W50-5

Serum angiopoietin-2 reflects the disease activity and renal function in ANCA-associated vasculitis

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Conflict of interest: None

[Objectives] To examine the serum angiopoietin-2 (Ang-2) levels in patients with ANCA-associated vasculitis (AAV), and investigate the relationship with their clinical and laboratory findings. [Methods] Fifty-nine patients with AAV, who had been referred to Niigata University Medical and Dental Hospital between 2000 and 2011, were recruited. The patients were divided into 2 groups according to their disease activities (active disease group (AD group, n=45) and remission disease group (RD group, n=14)). Serum Ang-2 levels, laboratory markers, and vasculitis activity score (BVAS), were examined in each subject. The data from all subjects were also analyzed using Spearman's rank correlation coefficient to determine the relationship with Ang-2. [Results] The serum Ang-2 level, C-reactive protein (CRP), white blood cell count, and urinary protein excretion were significantly higher in patients with AD group. The serum Ang-2 level was positively correlated with BVAS ($r=0.62$, $p<0.0001$), CRP ($r=0.47$, $p=0.0003$), serum creatinine ($r=0.38$, $p=0.005$), and urinary protein excretion ($r=0.55$, $p<0.0001$), and negatively correlated with estimated glomerular filtration rate ($r=-0.37$, $p=0.005$). These results indicated the possible role of Ang-2 in the development of AAV through endothelial injuries.

W50-6

The prevalence of anti-lysosomal-associated membrane protein-2 antibody levels in rat and human cutaneous polyarteritis nodosa

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Conflict of interest: None

Lysosomal-associated membrane protein-2 (LAMP-2) is an ANCA target antigen. We studied 11 env-pX rats, 25 WKAH healthy rats, 50 patients with cutaneous polyarteritis nodosa (CPN), 8 patients with microscopic polyangiitis(MPA), and 34 healthy persons. Serum of all 50 CPN patients was negative for MPO-ANCA and PR3-ANCA by both direct ELISA and capture ELISA. In contrast, indirect immunofluorescence assay revealed ANCA in 42 (84.0%) of the 50 CPN patients. We found significantly elevated serum anti-LAMP-2 antibody levels in the perinuclear ANCA group detected by indirect immunofluorescence assay compared to the non-ANCA group. The 50 CPN patients were negative for anti-azurocidin antibodies, anti-BPI antibodies, anti-cathepsin G antibodies, anti-elastase antibodies, anti-lactoferrin antibodies and anti-lysozyme antibodies. Serum anti-LAMP-2 antibody levels were not found in 8 patients with MPA. Serum anti-LAMP-2 antibody levels were significantly higher in 11 env-pX rats compared to 25 WKAH healthy rats. Immunohistochemical examination revealed LAMP-2 protein overexpression in necrotizing vasculitis of the CPN patients and env-pX rats. We propose that the anti-LAMP-2 antibody could play an important role in the pathogenesis of CPN.

W51-1

Infliximab therapy in refractory patients with systemic vasculitis

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Conflict of interest: None

【Objective】Systemic vasculitis is sometimes resistant or unresponsive to glucocorticoid and immunosuppressive agents. We retrospectively investigated clinical usefulness of infliximab in such refractory patients with systemic vasculitis.【Patients and methods】Seven patients with systemic vasculitis (Takayasu arteritis: 3, cutaneous type of polyarteritis nodosa: 2, vascular Behçet disease: 1, rheumatoid vasculitis: 1) were enrolled in this study. All patients started to receive infliximab because of clinical symptoms uncontrollable only by glucocorticoid and/or immunosuppressive agents. Clinical information before and after starting infliximab was obtained from their medical record.【Results】Five of the 7 patients showed evident improvement of clinical symptoms in parallel with a decrease in inflammatory reactions. Glucocorticoid could be tapered in these patients. Two patients showed reworsening of symptoms despite increases in the dose of infliximab, and it was changed to tocilizumab. As adverse events bronchopneumonia frequently occurred in 1 patient, who could restart infliximab under prophylactic use of antibiotics after reduction of glucocorticoid.【Conclusion】Infliximab may be a potent therapeutic option in treatment of refractory patients with systemic vasculitis.

W51-2

Am80 ameliorates murine model of vasculitis by suppression of neutrophil and endothelial cell activation

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Conflict of interest: None

<Background> Retinoids are compounds that bind to retinoic acid receptors and have biological activities of vitamin A. In this study, we examined inhibitory effects of Am80, synthetic retinoid, on murine *Candida albicans* water-soluble fraction (CAWS)-induced vasculitis. <Methods> CAWS was injected to Balb/c mice from day 1 to 5. Am80 was administrated from day 1 for 5 weeks (prophylactic administration) or from day 8 for 4 weeks (therapeutic). On day 35, the status of vasculitis on coronary artery was histologically evaluated. Production of reactive oxygen species (ROS) was analyzed by FACS. Chemotaxis was evaluated with optical assay device. Production of inflammatory mediators was measured by ELISA. Phosphorylation of MAPKs was assessed by FACS. <Results> Both prophylactic and therapeutic administration of Am80 attenuated the vasculitis. *In vitro*, Am80 inhibited PMA, Pam3CSK4 or LPS-induced ROS production, chemotaxis by fMLP, fMLP+cytochalasin B-induced elastase release, and phosphorylation of ERK1/2 and p38 by fMLP+LPS in peripheral blood neutrophils. Am80 also reduced production of IL-6 and MCP-1 from human umbilical vein endothelial cells. <Conclusion> Suppression of neutrophil and endothelial cell activation by Am80 might be responsible for the attenuation of vasculitis.

W51-3

Central nervous system involvement in systemic vasculitis

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Conflict of interest: None

[Background] Central nervous system (CNS) could be involved in patients with systemic vasculitis. However, only a few reports are available regarding this issue. [Objective] To clarify the significance of CNS involvements in systemic vasculitis. [Methods and Results] Sixty-two patients diagnosed as systemic vasculitis were enrolled in this retrospective study. Fifteen patients (24%) with systemic vasculitis had the CNS involvement. Eight were diagnosed as MPA, 4 CSS, 1 WG, and 2 PAN. Two had motility disorders, 1 central neuritis, 1 psychosis, 4 acute confusions, 4 cognitive disorders, 1 mood disorder and 1 anxiety disorder. On MRI, 6 out of 13 scanned patients showed some abnormal findings. All patients were treated with intravenous cyclophosphamide and glucocorticoids. Thirteen had clinical remissions within 2 months. The Event Free Survival Analysis showed that the relapse rate of the patients with CNS involvements was significantly higher than those without (Log Rank test: p=0.016). [Conclusion] CNS involvements may lead to a poor prognosis of systemic vasculitis.

W51-4

Benefitial outcomes with Tocilizumab regimen for ANCA- associated vasculitis with renal involvement in older patients; Report of two cases

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Conflict of interest: None

The combination of cyclophosphamide (Cy) and steroid to ANCA associated vasculitis (AAV) often results in poor prognosis in elderly patients due to the adverse effects. We experienced two elderly patients with AAV successfully treated by tocilizumab (TCZ). **The first case** was 82 year-old woman suffering from fever, polyarthritis and myalgia with high titer in MPO-ANCA (218 EU). The histological examination of kidney revealed advanced tubulointerstitial inflammation and necrotizing vasculitis with no crescentic glomerulonephritis. We administered TCZ (8mg/kg/4w) combined with methotrexate and methylprednizolone(16mg) to her. After 4-weeks, fibrinoid necrosis has been observed no longer, though inflammatory cells left. BVAS score has improved from 10 to 0. **The second case** was 77 year-old man hospitalized for walking disturbance with eye conjunctivitis and swelling of knees observed. He had interstitial pneumonia and renal insufficiency with serum creatinine (Cre) as 1.40mg/dl but also high titer in MPO-ANCA (2310 EU) and biopsy proven interstitial nephritis. TCZ treatment with Cy was applied as his renal function worse. His Cre, MPO-ANCA level and BVAS score both had improved subsequently. TCZ could be the alternatives with preferable effect on renal involvement in elderly AAV.

W51-5

Three cases of aortitis syndrome in elderly men diagnosed by FDG-PET/CT

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Conflict of interest: None

Case 1: A 71-year-old man with a 4-month history of headache, neck pain, and fever. Though CRP level was high(7.2 mg/dl), the source of the inflammation was unknown. To exclude malignancy and infection, FDG PET/CT(PET) was performed, which suggested an FDG uptake in the wall of the aortic arch, descending aorta and bilateral common iliac arteries. Enhanced CT also revealed large vessel wall thickening. He was diagnosed with aortitis and administered 45 mg/day of prednisolone(PSL). When PSL was tapered, his aortitis relapsed. Adding on 2.5 g/day of mycophenolate mofetil improved his aortitis. Case 2: A 79-year-old man with a 6-month history of fever. PET was performed and FDG uptake in wall of the aorta and large vessels were observed. Enhanced CT also suggested large vessel wall thickening on the same parts. Combination therapy with 55 mg/day PSL and 8 mg/week MTX was initiated and his aortitis improved. Case 3: A 74-year-old man with an unexplained sore throat. FDG uptake in large vessel walls was observed. His aortitis was improved by 60 mg/day PSL treatment. We report 3 suggestive cases of aortitis syndrome in elderly men diagnosed by FDG-PET/CT.

W51-6

Successful treatment with rituximab to a patient with refractory eosinophilic granulomatous polyangiitis

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Conflict of interest: None

A 44-year-old woman with a history of bronchial asthma was admitted because of fever, and numbness and muscle weakness of the extremities. Laboratory data disclosed increased peripheral blood eosinophil count (6579/ml) and CRP (3.45 mg/dl) as well as presence of MPO-ANCA. The nerve conduction velocity test was decreased in the affected limbs, being consistent with mononeuritis multiplex. She was diagnosed as eosinophilic granulomatous polyangiitis (EGPA). Treatment was started with methylprednisolone pulse therapy followed by oral prednisolone (1 mg/kg). Although peripheral blood eosinophils disappeared and MPO-ANCA became negative, fever and high CRP persisted. Left facial nerve palsy newly developed. Neither two intravenous injections of immunoglobulins nor three cyclophosphamide pulse treatments were not effective. Furthermore, right hypoglossal nerve paralysis appeared. Subsequent rituximab (375 mg/m^2) treatment ameliorated neurological symptoms, fever and positive CRP. Although rituximab has been proven effective in microscopic polyangiitis and granulomatous polyangiitis, it was effective only in eight EGPA cases in the literature. Its sustained efficacy in our case suggests that rituximab could offer an alternative therapy for refractory EGPA.

W52-1

Discrepancy between Boolean remission and DAS28 remission is dependent on the differences in number of swollen joints and global health in daily practice, based on the Institute of Rheumatology, Rheumatoid Arthritis (IORRA) cohort

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Conflict of interest: None

[Objectives] To examine which variables have a strong influence on achievement of new ACR/EULAR remission criteria among RA patients with DAS28 remission in daily practice.

[Methods] The subjects were RA patients who participated in IORRA in October 2010, and were in DAS28 remission. Boolean-based remission for clinical trials (BT)/clinical practice (BP), SDAI and CDAI remission were used as ACR/EULAR remission. Factors that affected the discrepancy between DAS28 and ACR/EULAR remission were analyzed. [Results] We studied 2162 RA patients with DAS28 remission. Among these patients, the numbers achieving BT, BP, SDAI and CDAI remission were 1169 (54%), 1205 (56%), 1602 (74%), and 1536 (71%), respectively. The patient's global health and the number of swollen joints had a significant impact on achieving each ACR/EULAR remission. The combination of these two variables accounted for 74%, 87%, 68% and 69% of the contribution to achieving BT, BP, SDAI and CDAI remission, respectively. [Conclusion] Of the remission criteria applicable to daily practice, Boolean remission is a more stringent than DAS28 remission, and patient management aimed at improving the patient's global health and number of swollen joints is critical for tight control of disease activity targeting to Boolean remission.

W52-2

Successful maintenance of remission defined by the new ACR/EULAR criteria leads to better functional outcome in RA in daily practice, based on the IORRA cohort

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Conflict of interest: None

[Objectives] To evaluate long-term functional outcome in RA patients who achieved the new ACR/EULAR or DAS28 remission criteria in daily practice based on IORRA. [Methods] RA patients with DAS28 remission in IORRA in April 2008 were selected. All patients were evaluated whether they achieved the remission criteria or not at consecutive data collection periods from April 2008 to October 2010. The proportions of patients with J-HAQ score progression during the period was calculated for each group subclassified according to the number of periods in which the patient achieved each criteria from April 2008 to October 2011. [Results] A total of 915 patients with DAS28 remission were selected (females, 80%; mean disease duration, 11.7 years). The proportions of patients whose J-HAQ score progressed during the period in the group continuously achieving remission defined by Boolean trial, SDAI, Boolean practice, CDAI, and DAS28 were 6.2%, 8.5%, 5.7%, 7.1%, and 14.2%, respectively. The proportion of patients whose J-HAQ score progressed was higher in the group which less frequently fulfilled each criteria. [Conclusion] Achievement and maintenance of the new ACR/EULAR remission criteria resulted in better functional outcome in RA compared to those of DAS28 remission in daily practice.

W52-3

Diagnostic performance of the biomarkers in the diagnosis of remission in rheumatoid arthritis (RA)

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Conflict of interest: None

[Objective] To explore the diagnostic performance of C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), and matrix metalloproteinase-3 (MMP-3) in the diagnosis of remission in RA. [Methods] Consecutive 2,136 observations of 268 RA patients from 2004 through May 2011 that included complete data for counts of swollen/tender joint in the 66/68 joints; pain, patient's and physician's global assessment of the current disease activity; and CRP, ESR and were retrospectively analyzed. Data for MMP-3 could be collected in the 2,021 observations in 259 patients. We analyzed diagnostic performances of CRP, ESR, and MMP-3 by receiver-operator curve analyses between contiguous disease activity states below low disease activity states, such as low disease activity, remission states defined by ACR/EULAR definitions in the clinical practice settings using a 28-joint count or those using a full joint count. [Results] Although, diagnostic performances of biomarkers were lower than those of joint count or global assessment to discriminate lower disease activity states, MMP-3 had a highest diagnostic performance in the diagnosis of remission among biomarkers widely available in Japan.

W52-4

Multi-Biomarker Disease Activity (MBDA) score correlates with the disease activity of rheumatoid arthritis in patients treated with tofacitinib

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Conflict of interest: None

[Objectives] We have previously reported that MBDA correlates with composite measures for RA. We herein evaluated the usability of MBDA in patients treated with a JAK inhibitor, tofacitinib (tofa). [Methods] MBDA was evaluated at week-0, -2, -12, -24 and -48 in 47 patients. MBDA combines 12 serum biomarkers (VCAM-1, EGF, VEGF-A, IL-6, TNF-RI, MMP-1, MMP-3, YKL-40, Leptin, Resistin, CRP, SAA) in a pre-specified algorithm resulting in a score between 1 and 100. 1. Primary endpoint: correlation of MBDA with disease activity. 2. Secondary endpoint: correlation of MBDA changes and ⊿MBDA with ⊿DAS28(ESR), ⊿SDAI and ⊿HAQ. [Results] Mean of each measures: age 54.8 years, duration 6.9 years, MBDA 59.5, DAS28(ESR) 6.3, SDAI 36.7, HAQ 1.3. 1. MBDA correlated with both DAS28(ESR) and SDAI. 2. Mean of each measurements at last observation: MBDA 31.3, DAS28(ESR) 3.2, SDAI 8.6, HAQ 0.7, all improved with significant difference and ⊿MBDA correlated with ⊿DAS28(ESR), ⊿SDAI and ⊿HAQ. [Conclusion] MBDA strongly correlated with DAS28 and SDAI. Treatment with tofa improved MBDA score and correlated with improvement of composite measures (⊿DAS28(ESR), ⊿SDAI and ⊿HAQ). Therefore, MBDA score that can be measured with patient serum is an useful tool to evaluate disease activity and also treatment effect.

W52-5

Performance of the new ACR / EULAR remission criteria compared to DAS28 remission, and usefulness of ultrasonography

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Conflict of interest: None

[Objectives] New remission criteria for ACR/EULAR and SDAI remission criteria are more stringent DAS28 remission. Then compare these remission criteria, ultrasonography was performed at the same time investigated the usefulness of. [Methods] 225 cases of patients with rheumatoid arthritis (mean age

59.1±13.0years, 35 men) were examined for the DAS28-CRP, DAS28-ESR, SDAI, CDAI, remission of Boolean, HAQ-DI, ultrasonography performed simultaneously. Ultrasonography results synovial thickening (SH) and power doppler signal (PD) with a semi-quantitative scores to (0-3) was evaluated. For a total of 26 joints of bilateral fingers, wrist, elbow, knee, were evaluated as total SH score and total PD scores. [Results] The rate was achieved remission, respectively DAS28-CRP 38.7%, DAS28-ESR 31.7%, SDAI 24.3%, CDAI 22.6%, Boolean 16.5%. Total SH score and total PD score each showed significant correlation with the DAS28-CRP, DAS28-ESR, SDAI, CDAI. In the example remission DAS28-CRP, the reasons why non-Boolean remission was the most significant factor PtGA. However, total SH score and total PD score were not high. Even if Boolean remission was not provided, it was thought that we should be careful about the case that it was thought synovitis was improved.

W52-6

Imaging residual joint synovitis in patients with rheumatoid arthritis achieving clinical remission in daily practice

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Conflict of interest: Yes

[Objectives] To assessed the presence of residual synovitis detected by power Doppler (PD) ultrasonography (US) in RA patients achieving clinical remission. [Methods] US was performed in daily outpatient clinic when confirmation of physical examination was needed after clinical evaluation. The frequency of intracapsular PD signal was evaluated in patients achieving remission defined by DAS28 or new ACR/EULAR definitions. [Results] US was performed in 92 patients (female 78%, median age 57.6 year and duration 5.0 year) and numbers (%) of patients fulfilling remission in DAS28, CDAI, SDAI or Boolean definition were 46 (50.0), 20 (21.7), 23 (25.0) and 20 (21.7), respectively. Positive PD signal was present in 24/46, 11/20, 11/23 and 12/20 patients, there PD was even detected in clinically non-swollen joint among 7/46, 2/20, 2/23 and 3/20 patients regarding 28 joints, and in 11/46, 5/20, 6/23 and 6/20 patients when including bilateral feet, respectively. [Conclusions] Imaging assessment would be advisable when strictly targeting remission.

W53-1

Pattern classification of rheumatoid foot and ankle destruction

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Conflict of interest: None

The foot and ankle involvement greatly affects the QOL of RA patients. Understanding the pattern of destruction and its natural course is essential to build appropriate treatment strategies. We investigated the RA patients in our hospital cross-sectionally (271 patients and 542 foot, average duration of disease: 15.7y) using X-ray films and checked the Larsen grades for each 12 joints including ankle, subtalar, talo-navicular, calcaneo-cuboid, naviculo-cuneiform, Lisfranc's, IP and MP of great toe and MP of lesser toes. When correlation in Larsen grade was analyzed between every combination in 12 joints and significant correlations were found only in combinations within these subgroups such as ankle&hind foot group, midfoot group and forefoot group. Based on these results, we classified the pattern of destruction into five subtypes, that is, ankle&hindfoot, midfoot, forefoot, combined and normal type. Each type showed individual characteristics radiographically. Average duration of disease is short in normal type (10.0y), long in combined type (23.6y) and intermediate in ankle&hind foot, midfoot and forefoot type (19.7y, 16.4y, 18.8y, respectively). This result suggests the progress of destruction from normal to combined type through partially-destructive subtype.

W53-2

Long-term results of resection arthroplasty with the Swanson implant fo Rhumatoid foot.

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Conflict of interest: None

[Objectives] we report Long-term results of resection arthroplasty with the Swanson implant fo Rhumatoid foot. [Methods] Clinical and radiological analysis were performed in 20 foots, 14 patients (mean age at surgery 51.6 years) after a mean of 14years. The pre and the post operative AOFAS Hallux Metatarsophalangeal-interphalangeal scale, JSSF RA foot ankle scale, standardized radiographs, and pedobarographic analysis was evaluated. [results] Clininal and radiographic results was good. No revision surgery was done.

W53-3

Rsection arthroplasty for hallux valgus deformity in RA patients

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Conflict of interest: None

[Objectives] Rheumatoid arthritis commonly affects the forefoot, and frequently causes hallux valgus. Various types of surgical procedures have been described, including arthrodesis, joint resection, metatarsal shortening and arthroplasty. Satisfactory results have been reported with resection arthroplasty but there are some recurrences of hallux valgus deformity. [Methods] We reviewed 34 feetin 23 RA patients with resection arthroplasty (modified Leliévre procedure). We analyzed radiographic changes of the hallux valgus angle (HVA), first intermetatarsal angle (M1M2A) and medial longitudinal angle (M1Base) and patient rated pain, deformity and overall satisfaction of the surgery. 34 feet were classified into 2 groups (A, B) by the postoperative HVA (Group A: ≧ 20 degrees, B: ≦ 20 degrees). [Results] Postoperatively, HVA, M1M2, VAS for deformity and pain significantly improved in both group A and B. However, preoperative HVA and M1M2A in group A were significantly higher than those of group B. Our results indicated that surgical indication of resection arthroplasty might be limited for patients with severe deformity with regard to recurrence of hallux valgus.

W53-4

Realationship between Hallux-Valgus deformity and the radiological change in the mid-foot in cases of rheumatoid arthritis

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Conflict of interest: None

[Objectives] To investigate the relationship between Hallux-Valgus deformity and the radiological change in the mid-foot in cases of rheumatoid arthritis [Methods] We objected 116 cases including radiograph of foot in the standing position. HV angle, M1-2 angle, M1-5 angle, the grade of dislocation of sesamoid bone, MPV(metatarsus primus varus) angle, diastasis between the base of M1-2 bone, the change of Lisfranc joints, and Internal Arch(IA) were measured and evaluated. [Results] MPV angle and diastasis between the base of M1-2 bone have influence on M1-2 and M1-5 angles, while have no direct influence on HV angle. Furthermore, cases including mobile Lisfranc joint tend to have relatively large MPV angle. Taken together, there is a possibility of recurrence of forefoot deformity after the corrective osteotomy surgeries for Hallux-Valgus deformity in cases which have mobile Lisfranc joint with large MPV angle and diastasis between the base of M1-2 bone.

W53-5

Clinical Outcomes of Patients with Rheumatoid Ankle and Hindfoot Deformity

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Conflict of interest: None

[Objectives] Rheumatoid hindfoot deformity presents with hindfoot eversion and flattening of the longitudinal arch. We investigated that the clinical outcomes of both ankle arthrodesis and selective hindfoot arthrodesis in patients with rheumatoid arthritis (RA). [Methods] 16 foot-and-ankles of 16 patients was included. Mean patients age and disease duration were 57.9years and 21years, respectively. The clinical evaluation was performed by using Japanese Society for Surgery of the Foot RA foot ankle scale (JSSF scale). Radiographic evaluation was also performed for medial longitudinal angle, calcaneal pitch, and Meary's angle on the lateral radiograph. [Results] JSSF scales improved in both groups, especially in pain. Medial longitudinal angle and Meary's angle improved significantly in each group. Calcaneal pitch improved on ankle arthrodesis group than selective hindfoot arthrodesis group. Slight loss of correction was observed in some cases of selective hindfoot arthrodesis. [Conclusion] Clinical outcomes of selective hindfoot arthrodesis are equivalent to that of ankle arthrodesis. Selective hindfoot arthrodesis is a reliable procedure to relieve pain and to preserve range of ankle joint motion in RA, although careful attention must be paid to loss of correction.

W53-6

Clinical result of selective hindfoot arthrodesis for rhumatoid arthritis

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Conflict of interest: None

[Objectives] We performed selective hindfoot arthrodesis for rhumatoid arthritis patients, and we present the results. [Methods] We intended for 12 feet that were performed selective hindfoot arthrodesis until from 1999 to 2006, and were able to followed up more than five years. It was one man, 11 women. The age was 47-70 years old (an average of 59 years old), postoperative follow up period was from 5 to 12 years (an average of 7 years and 6 months). Operative methods were talocalcaneal and talonavicular joit fusion: 4 feet, talocalcaneal and calcaneocuboid joit fusion: 3 feet, tripl (talus--calcaneus-cuboid) arthrodesis: 5 cases. We evaluated Ankle-Hindfoot Scale (AOFAS scale), calcaneal pitch from X-ray. [Results] AOFAS scale was 53.2 points before operation, 77.7 points postoperatively, 70.3 points at the final follwo up. Calcaneal pitch was 10.8° before operation, 14.2° just after operation, 5.8° at the final follow up. The destruction of talocrural joint was recognized in 5 cases, the destruction of Chopar joint was recognized in 8 cases. [Discussion] The selective hindfoot arthrodesis for rhumatoid arthritis patits was superior in improvement of pain, but several cases were destroied in adjacent joint..

W54-1

Changes of the incidence of falls in patients with rheumatoid arthritis after orthopaedic lower limb surgery.

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Conflict of interest: None

[Backgrounds] Many studies reported that patients with rheumatoid arthritis (RA) have a high risk of falls. The incidence of falls might decrease after lower limb surgery because pain or deformation of the joints is improved. The aim of current study was to examine the incidences of falls in patients with RA in association with orthopaedic lower limb surgeries. [Methods] Self-reported questionnaires about the frequency of falls and walking ability were performed for 141 patients with RA. The incidences of falls in patients who underwent lower limb surgeries (71 cases) were compared to patients with no history of surgery (70 cases). [Results] to patients with no history of surgery (9.6% vs. 38.6%, $p<0.01$). Among the patients who underwent surgery, the frequency of falls decreased after surgery in 29.6% of the patients, on the other hand, it increased in 4.2% of the patients. 33.8% of the patients answered that walking ability was improved after surgery. In contrast, 4.2% of the patients answered that walking ability was impaired after surgery. [Conclusion] It was supposed that walking ability and stability might improve after surgery, which resulted in decreased incidence of falls. [Results]

W54-2

Comparison of RA with OA for the prevention of venous thromboembolism and risk for bleeding after total joint arthroplasty

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Conflict of interest: None

[Objectives] In this study, the prevention of venous thromboembolism and risk for bleeding after total joint arthroplasty was assessed and compared between patients with RA and those with OA. [Methods] Subjects comprised 879 patients with THA and 1309 patients with TKA. We compared the prevention of DVT between the RA and OA group. All patients underwent Doppler ultra-

sonography to assess DVT on postoperative day 10. The data collected were age, sex, BMI, comorbidity, operation time, intraoperative hemorrhage volume, D-dimer, antibodies against platelet factor 4/heparin complexes, and hemorrhage event. [Results] The incidence of postoperative DVT was equivalent in the two group. In RA group, the incidence of postoperative DVT with factor Xa inhibitor was 11.7%, with no factor Xa inhibitor was 26.3%. Anti-PF4/H Ab seroconversion was more frequently in OA group(13.5%) than in RA group(8.1%) Hemorrhage event was more frequently in the RA group. [Conculusions] In this study, there was no significant difference in the prevention of DVT between the RA group and OA group. However factor Xa inhibitor was more effective than others in RA group. We should keep in mind the hemorrhage event in the RA group.

W54-3

Total Knee Arthroplasty in Rheumatoid Arthritis with Biologic Agent`s Therapy-Comparison between Arthloplasty before Biologic and Biologic before Arthroplasty-

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Conflict of interest: None

Objectives: The objective of this study was to demonstrate clinical outcome between Surgery before Biologic and Biologic before Surgery for Total knee Arthroplasty (TKA). **Materials and Methods:** Thirty patients were the subject of the study. There were 29 joints in Arthroplasty before Biologic and 19 joints in Biologic before Arthroplasty, respectively. We estimated the patients characteristics, the laboratory data, the clinical outcomes, DAS 28 and complications after surgery. **Results:** No significant difference was noted in the patients characteristics, the clinical outcomes, DAS 28. Conversely, the laboratory data (Hemogronbin and CRP) have a significant difference ($P<0.05$). There was one deep infection in AB group. In BA group, three were the superior infections. **Discussion and Conclusion:** This study showed that Biologic before surgery for TKA supposed to be more effective in the perioperative care than Arthloplasty before biologic.

W54-4

Long term clinical results of rheumatoid arthritis patients with total knee arthroplasty

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Conflict of interest: None

[Objectives] The purpose of the present study was to evaluate long term clinical course of rheumatoid arthritis (RA) patients with of total knee arthroplasty (TKA). [Methods] 53 RA patients with 85 TKA were enrolled in this study. Within 10 years after TKA 19 patients in 30 knees were died or bedridden, and 1 patients had moved. 33 patients in 53 knees were able to evaluate clinical course of RA including TKA over 10 years. The average age at TKA was 69.2±6.4 (mean ± SD) years old. Range of motion of the knee (ROM) and Knee Society Score (KS) were evaluated. In addition, we investigated medical treatments for RA until last follow-up. [Results] There was no revision case or infectious case. The mean ROM before TKA was 102.0°±3.0°and it significant improved after TKA until last follow-up. The mean KS was also significant improved from 34.5±14.7 point before TKA to 97.9±17.3 point at last follow-up. All patients received DMARDs at TLA. At final follow-up, 3 patients received biologics and 7 patients received MTX. 7 patients were remission. [Discussion] We evaluated long term clinical course of RA patients who received TKA. We recognized good clinical results of TKA for RA. At final follow-up, some patients received BIO or MTX. However, most patients were remission or nearly condition.

W54-5

Results of the total knee arthroplasty to the patients with rheumatoid arthritis

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Conflict of interest: None

[Objectives] In rheumatoid arthritis, a knee joint destruction causes a serious impairment to ADL. And the destructed knee joint exerts a harmful influence upon the other joints. We have performed 240 total knee arthroplasties (TKA) against RA patients in this hospital from 1992. We report the clinical results of TKA and course of RA. [Methods] TKA (GENESIS I, II; Smyth&Nephew) of 170 patients and 240 joints were done in 18 men, 152 women, and 64 years of average age (range 21-83). Follow-up periods were an average of 7 years and a maximum of 19 years. [Results] Revision was done in 7 joints (2.9%) in an average of 9.87 years after primary TKA. The revision of femoral, tibial and HDP component was done in 3 joints (loosening :2, late infection:1), femoral and HDP component in 2 joints (loosening) and only HDP in 2 joints. There was no case of a revision of patellar component. Survivorship of TKA was at 98.3% in 10 years, at 82.3% in 15 years and at 75.9% in 19 years. TKA under the administration of biologics was 20 patients, 22 joints, and there was no complication in term of operation. The 84 patients(49.4%) were treated with the biologics after TKA. Of RA patients with TKA, THA were done in 39, total ankle arthroplasty 4, and arthrodesis of ankle 17 joints.

W54-6

Changes of the background in patients undergoing total knee arthroplasty for the last 10 years

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Conflict of interest: None

[Objectives] The aim of this study was to analyze the clinical background in patients undergoing total knee arthroplasty (TKA). [Methods] We retrospectively investigated the background of 867 primary TKA performed in our hospital from July 2001 through June 2011. [Results and Conclusions] In these 10 years, 644 TKA (74.3%) were performed in patients with rheumatoid arthritis (RA) patients. However, the number of TKA for osteoarthritis (OA) patients gradually increased every year, and the rate of RA TKA was 62.8% in the last year. The average age at TKA was 75.0 years old in 2001 and also 75.0 years old in 2010, respectively, in OA Patients. On the other hand, it was 60.5 years old in 2001 and 65.4 years old in 2010, respectively, in RA patients, indicating that the age at TKA got older in RA group. Interestingly, these trends seemed to plateau in the last 5 years, suggesting that the recent therapeutic strategy including several biologics could not be enough to prevent destruction of knee joints in RA patients.

W55-1

Investigation of influence on the outcome of inferior scapular osteophytes following reverse shoulder arthroplasty

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Conflict of interest: None

[Objectives] Osteophytes developing at the inferior aspect of the scapular neck following reverse shoulder arthroplasty (RSA) are rarely described in the literature. The goal of this study was to identify the incidence of scapular osteophytes following RSA, and to evaluate their influence on the clinical outcome. [Methods] Two cohorts with more than 100 patients were radiographically and clinically evaluated at the 2 year follow-up following RSA. Radiographic assessments were identification of osteophytes distinguished from heterotopic ossifications, classification of scapular notching, and measurement of the prosthetic scapular neck angle. Clinical assessment included the Constant Score (CS) in combination with patient reported outcomes (Quick-/DASH, SPADI). [Results] Scapular osteophytes were identified in 36% and 22%, respectively. No significant differences were seen with and without osteophytes regarding shoulder function and pain (SPADI), function of the upper extremity (Quick-/DASH), range of motion or with the CS (p>0.05). A higher scapular angle was significantly associated with the development of osteophytes (p<0.01). Glenoidal notching greater than grade II was also frequently seen (50% and 37% resp.), but without any correlation to the presence of osteophytes.

W55-2

Mid-term results of unlinked elbow arthroplasty for stiff elbows with rheumatoid arthritis

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Conflict of interest: None

[Objectives] We retrospectively review the mid-term results about the unlinked elbow arthroplasty for stiff elbows due to rheumatoid arthritis. [Methods] The inclusion criteria into the study was patients with a preoperative passive arc of elbow motion of 30 degrees or less. The elbow with radiological change of Larsen grade 5 and painful stiffness was excluded. 9 elbows in 7 patients were treated with unlinked elbow implant, Osaka University Model Elbow System. All patients were women with the average age of 54 years. The clinical assessment was performed by elbow scoring system of Japanese Orthopaedic Association (JOA). Radiographic evaluation was done for implant position, radiolucency and ectopic bone formation. [Results] Follow up averaged 8 years (range 5-9 years). The mean JOA score improved from 42 % preoperatively to 74% after the surgery. Mean flextion improved 83 degrees to 128 degrees, and mean extension improved -59 degrees to -43 degrees. No patients developed infection and ectopic bone formation. Radiographically, there were no radiolucent lines at the bone-metal interface of any of the humeral or ulnar implant. Our study demonstrated that for stiff elbows due to rheumatoid arthritis with satisfactory results can be achieved by the unlinked elbow arthroplasty.

W55-3

Clinical and radiographic evaluations of Sauve´-Kapandji procedure for rheumatoid arthritis

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Conflict of interest: None

[Objectives] Several operative procedures have been reported for repairing destruction of the distal radio ulnar joint (DRUJ) in patients with RA. In our hospital, we have been applying the S-K method to the most of cases with DRUJ disorders in RA. For severely damaged DRUJ, we have been applying the S-K method with some modification. We report the clinical and radiographic results of two methods and compare the result of them. [Methods] Thirty seven patients (41wrists) underwent the original S-K method and 9 patients (10 wrists) underwent the modified S-K method from 2007 to 2009. The mean follow up period was 24months. ROM, DAS-28 and DASH were evaluated for physical assessments before and after the surgery. The radiographic evaluation was performed by assessment of the carpal height ratio (CHR), the carpal translation index (CTI) and radioulnar width ratio (RWR). [Results] DAS-28 and DASH showed better score in the original S-K method group. Radiographic examination revealed significant change regarding to CTI of the modified S-K group showed better result in both MTX and biologic group. Although clinical result in the original S-K group was better than modified method group, it should be considered that the modified method was applied to the more severely damaged wrist.

W55-4

Comparison of the absorbable screw in the Sauve-Kapandji procedures for the wrist disorders of rheumatoid arthritis

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Conflict of interest: None

[Objectives] We compared the results among 3 types of absorbable screws in the Sauve-Kapandji (S-K) procedures for rheumatoid arthritis. [Methods] We examined 60 RA patients with 61 wrists were operated from 2003 to 2011 with S-K procedures who were able to be followed up at least 6months after surgery. The average follow up period was 19 months and the average age at operation was 51.8 years old. The patients were divided into 3 groups according to the type of screws: group A (n=24) is partial thread screw made of poly-L-lactic acid (PLLA), group B (n=16) is partial thread screw made of unsintered hydroxyapatite (u-HA)/PLLA, group C (n=21) is full thread screw made of u-HA/PLLA. [Results] The patients who could not obtain complete bony union was 12.5% of group A, 6.3% of group B, 9.5% of group C. However, there were no statistically significant differences. There was a trend toward the group B fixation being less stable, because of high rate usage of Kirshner wire. There's a possibility that intraoperative fixation was less stable in B group, however, there were no statistically significant differences between 3 groups for bony union. We conclude absorbable screws are useful, because screw removal was unnecessary and there were no major complications.

W55-5

Modified Thompson-Littler procedure for swan neck deformities due to rheumatoid arthritis

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Conflict of interest: None

[Objectives] We evaluated a modified Thompson-Littler procedure (modified Littler procedure) for the treatment of swan neck deformities due to rheumatoid arthritis. In this procedure, the ulnar side of the lateral band that was rerouted to the radial side between flexor sheath and neurovascular bundle, was sutured to the proximal part of the radial side of the lateral band to obtain dynamic tenodesis effect. [Methods] 11 modified Littler procedures were performed on 3 patients (3 females, 0 male). The mean age of the patients was 61 year-old. The mean follow-up period was 9 months. The evaluations were performed pre and post-operatively in terms of extension degrees of the PIP and DIP for clinically. [Results] Post-op PIP extension was significantly improved (pre-op 26° to post-op -3°). Post-op DIP extension was significantly improved (pre-op -47° to post-op -7°). [Discussion] In the modified Littler procedure, spiral path lateral band acts as a dynamic tenodesis, extending the DIP joint as the PIP joint is extended and relaxing with PIP flexion to allow full DIP flexion. This procedure is provided useful for swan neck deformities of Nalebuff type I, Zancolli's articular type.

W55-6

Analyses between the range of motion and the function deficiency in typeI thumb deformity due to rheumatoid arthritis.

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Conflict of interest: None

[Purpose] TypeI deformity makes up about 70% of rheumatoid affected thumbs. An ROM is limited gradually progressing with the deformity. Adequate timing for therapeutic intervention is unknown. We evaluated typeI deformity and assessed the indicator to preserve hand function. [Methods] We could assess 27 thumbs in 18 patients who had typeI deformity and completed evaluations among our outpatients. The average age was 65.0 and the average affected duration was 21.8. We measured the ROM of the MP joint (MPJ) and the IP joint (IPJ), and performed the functional evaluations with questionnaires and manual tests. [Results] There was a strong correlation between the MPJ extension and the IPJ flexion. The thumbs with over -30° of MPJ extension could preserve IPJ flexion over 30°. In contrast, the IPJ flexion became impossible in the thumbs with less than -30° of MPJ extension. There were strong correlations in "MPJ extension and upper limb function" and "IPJ flexion and finger function". [Discussion] From the results of this study, the decrease of working space in the hand impairs upper limb function when the MPJ extension becomes less than -30°. Then the IPJ flexion becomes impossible. We considered that "MPJ extension less than -30°" may be a indicator for therapeutic intervention.

W56-1

One-hour infusion of infliximab: Report of 15 cases

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Conflict of interest: None

[Objectives] To assess the practice pattern of infliximab infusion over one hour. [Methods] Rheumatoid arthritis patients receiving biologics under our care were registred to Cohort of Arthritis, Biologics Users of Kameda Institute(CABUKI) registry. There have been reports of infliximab safely administered over 1 hour after several 2-hour administration, and it was officially approved in Europe in 2006. We assessed utilization of this administration method. [Results] Between July 2003 and April 2011, 102 patients received infliximab, of whom 102 were first-line biologic users, whereas 3 were second- and 2 were third-line users. One-hour administration was found in 15 patients. One of them had experienced minor infusion reaction with two-hour administration, however, none of the 15 experienced infusion reactions with one-hour infusion. Nine of the patients were switched to one-hour infusion within one year. The earliest transition was at the fourth infusion. For premedication, 2 received acetaminophen, 2 received prednisolone, and 11 received none. Establishing a protocol for transition may be efficient.

W56-2

The effects of dose of methotrexate and infliximab on remission induction rate during infliximab therapy in patients with rheumatoid arthritis

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Conflict of interest: None

[Objective] To investigate the effects of dose of methotrexate (MTX) and infliximab (IFX) on the remission induction rate during the treatment with IFX in patients with rheumatoid arthritis (RA). **[Subjects and methods**] Eighty-four patients with RA (20 males and 64 females) treated with IFX in our hospital were stratified by the pre/post time, when we could use high dose of IFX by health insurance treatment, and by high (MTX>8mg/week) /low (MTX≦ 8mg/week) dose of MTX. That is, subjects were subdivided into 4 subgroups (pre/high group; PrH (n=13), post/high group; PoH (n=17), pre/low group; PrL (n=24), post/low group; PoL (n=30)), and the subgroups were compared for remission induction rates at year 1 based on DAS28 and SDAI. The LOCF method was used in each analysis. **[Results**] The remission induction rates in PrH, PoH, PrL, and PoL were as follows: 31%, 53%, 17%, and 30% for DAS28 ($p<0.05$ for PoH vs PrL); 46%, 47%, 13%, and 20% for SADI ($p<0.05$ for PoH vs PrL). **[Conclusion**] The remission induction rate during IFX therapy can be expected to be increased when MTX and/or IFX is used at higher doses.

W56-3

BIO switch among anti-TNF treated patients, disease duration, & remission rates

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Conflict of interest: None

[Objectives] Evaluations are dependent on disease background and biologics. Stratified analysis was conducted to see if anti-TNF treated-patients switched biologics, disease duration, and remission rates. [Methods] We selected patients who'd used anti-TNF for

>1yr: (infliximab(IFX);127, etanercept(ETN); 209, adalimumab(ADA);57. Stratified analyses; conducted on rates of patients with >2yr. history, <2yrs. In comparison, rates using only 1 biologic or using >2 were analyzed with DAS28, CDAI, SDAI and Boolean. [Results] IFX, ETN, ADA, early stage achieved higher rates, highest rise 12mo. after initiation. Remission rates; DAS>CDAI=SDAI>Boolean with rate difference 7x higher between DAS28 (CRP) / Boolean. Rates of LDA: significant difference according to duration. Using IFX, ETN and ADA, rates among BIO naïve was high, no significant difference dependant on timing of evaluations. Rates among early-stage patients; higher compared to stable patients. Almost none who'd switched achieved remission using Boolean. Achievement rates of LDA activity: higher among the BIO naïve. Disease duration needs consideration in evaluating anti-TNF drugs or deciding when to switch. It's quite likely those who don't achieve remission around initial phase, even using CDAI and/or DAS should switch.

W56-4

Analysis of clininal remission, functional remission, and structural remission in Bio-switching therapy from IFX used effectively to ADA in RA patients with moderate and high disease activity

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Conflict of interest: None

[Objectives] In RA patients with high disease activity, we have estimated the efficacy of Bio-switching therapy from IFX to ADA in clinical remission, functional remission, and structual remission. [Methods] The mean administration of IFX was 5.1 before Bio-switching to ADA. The mean age was 70.3 years old in 7 patients. The mean follw-up period was 80.6 weeks. We have evaluated the change of DAS28-ESR, serum level of MMP-3, HAQ scoring and either bony destructions or bony erosions by X-ray in the wrist and MP joints. [Results] The difference between effective treatment by IFX used previously and treatment by ADA induced after more than 64 weeks was significant in DAS28-ESR ($p < 0.01$). There was no difference between IFX treatment and ADA treatment in MMP-3. The difference between pre-treatment and induction of Bio-therapy combined with IFX and ADA was also significant in HAQ scoring ($p < 0.01$). The radiographical remodelling change of bony destruction and erosion was seen in 5 patients, and there was no radiographical destructive change of the wrist and/or MP joints in 2 patients. We have concluded that this Bio-switching therapy with ADA was clinically effective for RA patients under good response to IFX used previously.

W56-5

Drug survival rate of etanercept (ETN) in the patients with a previous biologics history in the Tsurumai Biologics Communication Registry (TBCR)

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Conflict of interest: None

[Objective] The mechanism of ETN for inhibiting TNF is different from anti-TNF antibody agents, infliximab (INF) and adalimumab (ADA). Therefore ETN is often used as second line after INF and ADA therapy. In this study, we studied drug survival rate of ETN in the patients with a previous biologics history. [Methods] 134 patients taking ETN therapy, as a second line, for longer than 52 weeks were included, from the 2072 patients with biologics therapy in TBCR. We retrospectively reviewed the clinical data. [Results] Eleven cases stopped taking ETN within 52 weeks, and drug survival rate was 91.8% at 52 weeks in all cases. Primary biologics were INF in 114, ADA in 18, and tocilizumab (TCZ) in 2 cases. The survival rates according to primary biologics were 92% in INF, 88.9% in ADA, and 100% in TCZ at 52 weeks. The survival rates at 52 weeks according to the reasons for primary discontinuation were 91.6/ 87.9/ 83% (LOE/ AEs/ others, respectively). [Discussion] ETN therapy showed quite high survival rate even when used as a second line. It was regardless of primary biologics agents and reasons for primary biologics discontinuation. This study suggested that ETN would be considered as the second line as well as the first, in the strategy of biologics treatment in RA patients.

W56-6

Efficacy of golimumab among BIO naïve patients and patients who've switched their treatment

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Conflict of interest: None

(Purpose) According to clinical trials, golimumab, the 6th biologic launched in Japan, is equal or superior to other anti-TNF agents. But, it's difficult to use golimumab on BIO naïve patients clinically; unlike other drugs, PMS was a bit restricted. We analyzed efficacy of golimumab between two groups; BIO naïve patients and those who'd switched biologics. (Method) Twenty-two patients were analyzed; 15 BIO naïve, and 7 that had switched. Remission induction rates were analyzed for 6mo. after initiation with DAS 28, CDAI, SDAI and Boolean. Achievement rates using ACR20, 50 and 70 were analyzed. (Result) Mean age BIO naïve; 48yrs.,>6yr. disease duration, mean age BIO switching; 62yrs., duration >10.7yrs. BIO-switching; 3 used humira, 3 used enbrel, and 1 used orencia. At 6mo. after initiation, remission induction rates for BIO naïve; 20% with DAS 28 and 10% with SDAI; rates were lower for BIO-switching. Remission rates using CDAI or SDAI were about as high as rates using ACR 70 while the remission induction rates using DAS28 were about equal to rates with ACR 50. (Conclusion) It's important to consider patient background in expecting response to treatment because with golimumab or other types of anti-TNF agents, the remission induction rates are lower among BIO-switching patients.

W57-1

Infections during Infliximab therapy for rheumatoid arthritis patients in our hospital.

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Conflict of interest: None

[Objectives] To evaluate rate of infections during infliximab (IFX) therapy for rheumatoid arthritis (RA) patients. **[Patients]** All patients were received IFX between June 2004 and April 2011 and patients with infections were divided into two groups and com-

pared with them. **[Results]** Among 158 patients, 23 patients (14.5%) were stopped or done rest IFX. In the 23 patients,15 patients (16.9%) were the first half group and 8 (11.6%) were the last half group. The patients with infections within 6 months after receiving IFX were tend to less in the last half group compared with the first half group. Respiratory infections were 17 patients with infections and the rate was over 60% in both groups. Two patients in each group were developed pneumocystis carinii pneumonia over one year after receiving IFX. Mean ages of patients with infections were higher than that of non-infection patients. In the last half group, mean durations were shorter and rate of stage III and IV was lower than that in the first half group. T. **[Conclusions]** The most causes of infections during IFX for RA patients was respiratory infections. Although posterior half group was tend to receiving IFX before stage development compared with first half group, the rate of infections were no difference in two groups.

W57-2

Reintroduction and continuation of biologics after episodes of infectious diseases

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Conflict of interest: None

There are reports regarding infectious diseases after introduction of biologics (BIOs), however, only a few reports describe the drug use after the episode of infection. We here report how the patients were treated after the episodes of infection. Fifty-nine patients were analyzed in whom episodes of infection developed which needed specific treatment after introduction of BIOs in patients with rheumatic diseases. The number of infectious episodes was 103, and they were 75 respiratory infections including pneumonia in 10, PCP in 3 and cryptococcosis in 3, pyelonephritis in 3, 20 skin and connective tissue infections including HZ in 3, bacterial arthritis in 3 and cellulites in 7, and others. The episodes which needed hospitalization ware 17, including pneumonia, PCP, cryptococcosis, bacterial arthritis, etc. One patient died of infection. Nine patients stopped receiving BIOs after the episodes, whereas 10 patients stopped BIOs temporarily and restarted them. Other patients continued BIOs during the episodes of infections without any big troubles. In conclusions, BIOs can be reintroduced or continued in patients in whom episodes of infection developed.

W57-3

The influence of biologics on the incidence of tuberculosis in Japanese patients with RA

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Conflict of interest: None

[Objectives] To evaluate the influence of biologics on the incidence of tuberculosis (TB) in Japanese patients with RA. [Methods] We calculated the standardized incidence ratio (SIR) of TB from the post-marketing survey of 4 biologics; infliximab (IFX), etanercept (ETN), adalimumab (ADA) and tocilizumab (TCZ), and compared them with the SIR of TB in biologics-naïve RA patients from National Database of Rheumatic Disease by iR-net in Japan (*NinJa*). [Results] Among 7832 biologics-naïve RA patients registered *NinJa* from 2003 to 2004, 7 patients developed TB. The SIR of TB in biologics-naïve RA patients was 3.98 (95%CI:1.22-6.74). According to the post-marketing survey of 4 biologics in Japan, among 5000 patients treated with IFX, 13894 patients treated with ETN, 7468 patients treated with ADA and 7901 patients treated with TCZ, 14, 10, X and 5 cases of TB had reported, the SIR of TB were 21.5 (15.8-27.1), 4.75 (3.28-6.23), Y and 5.72 (3.22-8.23), respectively and were increased in each 5.4 times, 1.2 times, 2.6 times and 1.4 times when compared with the SIR of TB in biologics-naïve RA patients. [Conclusion] The incidence of TB in patients with RA was increased by biologics, especially with the anti-TNFα antibodies. We have to recognize the risk of TB when we start biologics.

W57-4

Study of association between biologics therapy and β-D-gulucan levels in patients with rheumatoid arthritis

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Conflict of interest: None

[Objectives] To study the association between β-D-gulucan (β-D) elevation and fungus infection in rheumatoid arthritis (RA) patients. **[Methods]** Among 378 RA patients (TNF inhibitors: 359, TCZ: 10, ABA: 9), β-D levels were monitored before and after Bio and studied the association with infection. **[Results]** β-D levels (normal range: <5 pg/ml) were elevated in 37 patients (9.8%); 13 patients were elevated before Bio (average: 42.3±32.1; 21.9-92.1), 9 were elevated after Bio within 6 months (average: 49.1±50.1; 22.0-260), 15 were elevated after Bio over 6 months (average: 42.8±33.8; 23.6-167). One of the patients among tye group was treated with hemodyalisis. ST mixture was admitted with 7 patients in β-D elevation group before Bio and 5 patients in β-D elevation group after Bio. Two patients who were not admitted ST mixture were developed pneumocystis carinii pneumonia (PCP) and rapid β-D elevation were monitored in onset of PCP regardless of β-D negative until just before onset. No patients with β-D elevation were developed fungus infection despite PCP during Bio. **[Conclusions]** There was no association between β-D levels and fungus infection except PCP in RA patients during Bio. It is suggested that the necessity of ST mixture for asymptomatic β-D elevation is further considered.

W57-5

Interferon gamma release assay in prophylaxis of tubeculosis infection of RA patients with biologics therapy of RA

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Conflict of interest: Yes

[Objectives] In biologics therapy in RA patients, prophylaxis of tuberculosis infection is very important. Recently, in addition to tuberculin test, Interferon release assay (QFT test) is used for detection of latent tuberculosis infection. The purpose of this presentation is to estimate the efficacy of Interferon gamma release assay in prophylaxis of tuberculosis infection of RA patients with biologics therapy. [Methods] QFT test was performed in patients with induction of biologics and in patients with long time biologic therapy. [Results] At the time of induction of biologics for RA, tuberculin test and QFT test were performed in 11 patient. 8 patients were negative for both tests and 3 patients were positive only

for tuberculin test. In 56 patients under long time biologic therapy, who do not reveal abnormal chest X-ray and do not have infectious symptoms were performed QFT test. In 4 patients, QFT test were positive and in one patient, CT scan of chest showed tuberculosis infection. QFT test may be useful in screening of latent tuberculosis infection for patients with long time biologics therapy.

W57-6

The assessment of the safety of the biologic agents against RA patients with resolved hepatitis B infection (2nd report)

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The Rheumatic Disease Center, Konan Kakogawa Hospital

Conflict of interest: None

[Objectives] At 51st meeting of this congress, we reported two cases of RA patients who developed acute type B hepatitis during etanercept therapy. One case was the HBV-carrier but the other was though to be a patient with resolved HBV infection. At 53rd meeting, we reported 23 patients with previous resolution of HBV infection (negative test for HBsAg and positive for anti-HBc) who were using biologic agents (average administering period is 12 months), all of them had no symptom of the hepatitis B recurrence. When de novo hepatitis B develops, it is known to become fulminant easily. So it is important to know the frequency of HBV reactivation for the safe use of biologics. [Methods] 61 cases were registered and their HBV-DNA were measured during the clinical course. [Results] No case of the reactivation of the hepatitis B virus has been observed (average administering period is 21.6 months) at this time. So the risk of HBV reactivation by the biologics is estimated to be quite low. According to the recent report from Japanese institutions, the evaluation of the risk is conflicting. More extensive investigation is needed to obtain accurate data.

W58-1

Quantitation of peripheral blood Epstein-Barr virus DNA load in four cases of methotrexate-associated lymphoproliferative disorder (MTX-LPD)

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Conflict of interest: None

[Objectives] Epstein-Barr virus(EBV) reactivation is more likely to occur in immunocompromised patients with subsequent higher susceptibility to EBV-associated lymphoproliferations. In contrast to several malignancies, limited data are available concerning the EBV load in methotrexate-associated lymohoproliferative disorder(MTX-LPD). [Methods] We measured the peripheral blood EBV load of four cases in MTX-LPD. [Results] Patients profile was age 59-66, female 1, male 3. All patients were treated with prednisolone(2-9mg/day) and MTX(8-12.5mg/week). Two patients were treated with tacrolimus or biologics (adalimumab and infliximab). Cessations of MTX, tacrolimus and, biologics except for PSL led to regression of the tumor. One patient received chemotherapy for remaining lymphadenopathy and had complete clinical remission. In all cases, EBV DNA was detectable at diagnosis. It paralleled the clinical course. Only one case showed high titer of EBV specific VCA IgG antibody. [Conclusion] Monitoring of EBV load may be a usefle indicator for assessing treatment response in patients with MTX-LPD.

W58-2

The Effect of Methotrexate and Biologics to the Elevation of Antibodies to Ebstein-Barr Virus in Patients with Rheumatoid Arthritis

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Conflict of interest: None

[Objectives] Activation of Ebstein-Barr virus (EBV) are common in patients with rheumatoid arthritis (RA), and the concern is raising that intensive therapy with methotrexate (MTX) or biologics might accelerate the activation and cause complications. This study is to investigate the effect of biologics or moderate dose of MTX to immune response to EBV in RA patients. [Methods] Four antibodies to EBV: VCA-IgG, VCA-IgM, EBNA, EA-IgG, were examined by EIA in 130 patients with RA. We analyze the correlation between titer of each antibody and CRP, RF, serum immunoglobulin levels, and compare average titers of the antibody between patients treated with low dose MTX (LMTX), <6mg/week, and intensively treated patients: ones treated with moderate dose MTX (MMTX), 8-12mg/week, TNF blockade (TNFB), IL6 receptor blockade (IL6RB). [Results] Number of patients who showed elevation of VCA-IgM, EA-IgG and both, above 0.5, were 25, 37, and 21 respectively and 63.8% of all subjects as a whole. Weak positive correlation was found between VCA-IgM and RF (r= 0.401). The average titers of EA-IgG in patients with LMTX, MMTX, TNFB and IL6RB were 1.57, 1.02, 0.62, 1.58, and VCA-IgM were 1.07, 0.68, 1.46, and 0.53 respectively. There were no significant differences between LMTX group and other three groups.

W58-3

55 renal biopsy findings of RA patients with nephropathy

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Conflict of interest: None

Histology in patients with rheumatoid arthritis of 55 patients who underwent nephritis kidney biopsy at our hospital. RESULTS: Sixteen men. In the 39 women, those presenting with nephrotic syndrome in 14 cases, out of nephrotic membranous nephropathy (MN) 7 patients, focal glomerulosclerosis (FSGS) 3 cases, 2 cases of amyloidosis, minimal change type (MCNS) were two cases. In other interstitial nephritis (TIN) in 4 patients, one case nephropathy IgA, one case of lupus nephritis, 2 cases focal glomerular sclerosis, eg amyloidosis 4, 7 membranous nephropathy, crescent formation ANCA associated four cases nephritis, one case was unknown. Merger of membranous nephropathy to RA in various reports a similar trend was observed in our many facilities, especially in recent years while relatively few amyloidosis, FSGS also showed many mergers. Genesis of FSGS is still unclear, is thought to be suggestive of involvement are considered part of the immune system

W58-4

Comparison of bucillamine-induced MN and non drug-induced MN in RA patients.

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Conflict of interest: None

[Objectives] Membranous nephropathy (MN) is famous as extra articular lesion of rheumatoid arthritis(RA). Most of them are caused by Disease-modifying antirheumatic drugs(DMARDs), especially bucillamine. We compared bucillamine-induced MN with non drug-induced MN in RA patients. [Methods] 39 rheumatic patients who had a diagnosis of membranous nephropathy by renal biopsy in our hospital between January 1985 to December 2009 were enrolled in this study. [Results] Bucillamine-induced MN was 26 cases and non drug-induced MN was 13 cases. The amount of proteinuria after follow-up was dominant in non drug-induced MN group than bucillamine group, because proteinuria disappeared after discontinuance of medicine in all cases of bucillamine group. On the other hand, proteinuria of non drug-induced MN group followed various course, and some of these cases decreased the amount of proteinuria after RA treatment. [Conclusions] In bucillamine group, proteinuria disappeared in all of cases after discontinuance of medicine. In non drug-induced MN group, the course was various. In some cases of this group, proteinuria disappeared after decrease of RA activities by RA treatment, and it is possible that the control of RA contribute the improvement of MN in RA patients.

W58-5

Gastroesophageal reflux disease (GERD) in patients with RA

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Conflict of interest: Yes

[Objectives] Patients with RA frequently complicate gastric mucosal injury. In 2011, ACR/EULAR announced the new remission criteria of RA based on radiographic outcome with SDAI/CDAI. The purpose of this study is to investigate gastroesophageal reflux disease (GERD) in patients with RA. **[Methods]** Patients with RA were investigated for GERD with self-administered frequency scale for the symptoms of GERD (FSSG). The correlation between GERD and clinical characteristics of RA was analyzed. **[Results]** Two hundred and eleven patients (178 females and 33 males) were investigated. The prevalence of GERD in RA (24.6%) was significantly higher than that in Japanese population (11.5%). A positive correlation between FSSG and mHAQ was observed. mHAQ, Pt-VAS, Dr-VAS, TJC, DAS-CRP, DAS-ESR, SDAI, and CDAI were significantly higher in the GERD positive group than the negative. Patients achieving remission criteria with SDAI, CDAI, DAS-CRP, or DAS-ESR had lower prevalence of GERD. **[Conclusion]** GERD should be considered as a complication of RA especially in the patients with low ADL score and high disease activity.

W58-6

The investigation of the initial dose and adverse effects of Pregabalin for the RA patients

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Conflict of interest: None

[Objectives] The purpose of this study is to examine the appropriate initial dose and adverse effect of pregabalin for peripheral neuropathic pain in patients with rheumatoid arthritis (RA). RA patients have peripheral neuropathic pain and nociceptive pain. [Methods] We examined 17 RA patients (5 men,12 women, the average age: 69.5 years, the average disease duration: 13.6 years) who were prescribed pregabalin. We checked the body weight, CRP, Cre, eGFR, and the adverse effects of the medication. [Results] The average body weight was 51.8 (37-65) Kg, CRP; 0.51(0.01-2.54) mg/dl, Cre; 0.82 (0.4-1.25) mg/dl, eGFR; 64.2 (33.3-117), the initial dose of pregabalin; 76.5 (25-150) mg/day and the dose of pregabalin at the last observation; 127.3 (25-300) mg/day. Six of 17 patients discontinued the treatment. The reasons of the discontinuations were improving pain, exacerbation of pain, dizziness, nausea, inadequate responses. In conclusion, high initial dosage of pregabalin may read to the discontinuation of the drug in RA patients.

W59-1

Association of Human Leukocyte Antigen with Interstitial Lung Disease in Rheumatoid Arthritis

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Conflict of interest: None

[Objectives] Interstitial Lung Disease (ILD) is frequently associated with Rheumatoid Arthritis (RA) as one of the extra-articular manifestations. Many studies for HLA allelic association with RA were reported, but few have been validated in RA subpopulations. In this study, we investigated the association of HLA with ILD in RA. [Methods] An allelic association study was conducted on HLA-DRB1, DQB1, and DPB1 in Japanese RA patients that were diagnosed to be suffering from ILD or not, based on the findings of computed tomography images of chest. [Results] HLA-DR*04 and DQ*04 are associated with protection against ILD in RA. HLA-DR*16 and DQ*06 are associated with susceptibility to ILD in RA. SE was associated with decreased risk of ILD.

W59-2

Using genome-wide SNP analysis to investigate the possibility of the CYB5R gene promoting interstitial pneumonia in RA patients

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Conflict of interest: None

【Objectives】 Interstitial pneumonia (IP) is a serious complication for RA. However, the pathogenesis of IP remains to be elucidated. We investigated SNPs which seem to be closely correlated with the pathogenesis of IP using genome-wide SNP analysis of IP in RA patients. **【Methods】** A total of 306 RA patients from 6 hospitals in different regions of Japan were enrolled in the study. There were 57 IP patients and 249 non-IP patients. Genome-wide SNP genotyping was performed by HumanHap300K chip. Case-control analyses between 285,548 SNPs and the association with IP were examined by Fisher's exact tests and Bonferoni's correction. **【Results】** We detected one SNP which is strongly associated with IP and located adjacent to the cytochrome-b5 reductase (CYB5R) gene (p value: 0.0000000117, $p<0.05$, after Bonferoni's correction). It is reported that CYB5R plays an important role in the resolution of superoxide. In this present analysis, we propose a hypothesis of the functional and/or quantitative reduction of the CYB5R gene which promotes the resolution of superoxide, according to the SNP detected in this study, and the increase of superoxide may lead to the high susceptibility of IP in RA patients, even though further investigation is required to confirm this.

W59-3

Clinical characteristics of patients with rheumatoid arthritis (RA)-related bronchiolitis

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Conflict of interest: None

Objectives: To clarify clinical characteristics of bronchiolitis occurring in RA. Methods: We reviewed the medical records of 7 RA patients with bronchiolitis detected by high-resolution CT of the chest, together with 30 RA patients without finding of small-airway disease. Results: Compared with RA patients without small-airway disease, dry mouth and anti-SS-A antibody were significantly frequent in patients with bronchiolitis. No significant difference was found in sex, mean age, duration of RA, activity of synovitis between patient with bronchiolitis and those without small-airway disease. Conclusion. Salivary hypofunction may closely associated with bronchiolitis occurring in RA.

W59-4

Nodular lesions and methotrexate (MTX) treatment in patients with rheumatoid arthritis (RA): from the histopathological point of view

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Conflict of interest: None

Objective: To elucidate the relation between histopathological patterns of nodular lesions and MTX treatment in patients with RA. **Methods**: We performed histological examination on nodular lesions in 5 patients who showed versatile lesions during RA disease course and analyzed the correlation between histological changes in nodular lesions and treatments, their rheumatoid disease activities. **Results**: The histological diagnosis of the nodules were; 1) rheumatoid neutrophilic panniculitis without vasculitis, 2) reactive lymphoadenitis, 3) palisading granuloma, 4) lymphomatoid granulomatosis with EB-virus reactivation, and 5) follicular lymphoma. The histological broad spectrum seemed to be connected with the variety of pharmacological actions in MTX and the extent of each disease activities. Iatrogenic action of MTX was suggested. **Conclusion**: We should place our close eyes on nodular lesions in patients with RA. The differences in morphological changes of nodular lesions in patients with RA would correlate not only with disease activity but also with pharmacological action of MTX, including lymphoproliferative character.

W59-5

Tocilizumab impvores arterial stiffness than methotrexate in remission.

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Conflict of interest: None

[Objectives] Reduction in cardiovascular events in rheumatoid arthritis is a treatment goal. We reported the possibility of a reduction in cardiovascular events in the tocilizumab. In this study, we investigated the differenciation of reduction in cardiovascular events between tocilizumab and methotrexate at the time of clinical remission. [Methods] In remission (> 3 months, SDAI <CDA and 3.3 <2.8) state, we compared CAVI and AIx75(as surrogate cardiovascular marker) with tocilizumab and methotrexate monotherapy. [Results] We investigated 42 patients in methotrexate group, and 19 patients in tocilizumab group, Disease duration, activitiy, and ages at baseline were corrected. ΔCAVI and AIx75 were were significantly improved with tocilizumab group than methotrexate group.

W59-6

A Rheumatoid arthritis case of Tocilizmab improve mitral valve regurgitation

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Conflict of interest: None

Tocilizmub has anti -nflamatory effect and affect to Rheumatoid arthritis or castleman syndrome or so many diseases. We have a case of not only rheumatoid arthritis activity but also imprpve the degree of mitral regurgitation or left ventricular function after initiation of tocilizmab. We report this interesting case. [case] 69 y.o japanese male. He has a history of HTN, Diabetes mellitus and diabetes nephropathy and 4year history of rheumatoid arthritis. 2009/10 he admit for mild congestive heart filure and treated diuretics. cardiac US shows moderate to severe mitral valve regurgitation and mild inferior wall hypokinesis. CAG was not done. MTX was quited for creatinine elevation.(Cr2.6mg/dl) sulfasalazine was started, but clinical and laolatory indicator shows no benefit,2010/4 we started etanercept. It makes little clinical improvement but ESR is over 100mm/1hr,2011/1 change to tocilizmab After initiating Tocilizmab, His clinical symptom was slowly improve. But same time, His mitral regurgitation was gradualy improve, Body weight and BNP and CTR was dramatically improve. CTR was 64% to 51%, BNP was over 800mg/dl to 127mg/dl. cardiac US shows mitral reguritation become very mild. We check fat pad biospy shows no evidence of amyloidosis. [Results] Tocilizmab may have another pleomorphic effect.

W60-1

Increased serum levels of IL-18 and impaired NK cell function in an infant from the mother with adult-onset Still's disease

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Conflict of interest: None

(Introduction) Interleukin(IL)-18 is closely associated with the pathogenesis of adult-onset Still's disease (AOSD). IL-18 is also the most effective regulator for NK cell activity and plays an important role of the pathogenesis of hemophagocytic lymphhistiocytosis (HLH). (Methods) Serum IL-18 levels were serially monitored in a pregnant patient with AOSD and her infant. NK cell numbers and function were serially monitored in this infant. (Results) The mother had relapses of AOSD twice and high levels of serum IL-18 persisted during pregnancy. Serum IL-18 level of her infant at birth was markedly increased. High serum levels of IL-18 persisted for about one month. At birth, his NK cell number was significantly decreased and NK cell function was impaired. Decreased number of NK cells and impaired NK cell function closely correlated with serum IL-18. (Conclusions) The pregnant patient with AOSD could show markedly increased level of serum IL-18 even in clinically inactive condition. The infant from the mother with AOSD might have transient NK cell dusfunction and have a risk for HLH. The careful monitoring with serum IL-18 is necessary for the pregnant patients with AOSD and newborn.

W60-2

Serum procalcitonin levels in patients with adult-onset Still's disease

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Conflict of interest: None

[Objectives] Procalcitonin (PCT) has been reported as a diagnostic marker in bacterial infection. [Methods] We measured serum PCT levels in 14patients with adult-onset Still's disease (AOSD) without infection. [Results] Serum PCT levels were 0.02 – 13.6 ng/ml (median 0.38 ng/ml) in 13active patients and were above cut-off value for bacterial sepsis (0.5 ng/ml) in 6 patients. PCT levels were within normal range in 2 inactive patients. PCT values correlated with CRP and WBC in AOSD patients. Serum PCT levels may increase in active AOSD without any bacterial infection.

W60-3

A case of flare-up of adult-onset Still's decease (AOSD), which was thought to be triggered by adalimumab.

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Conflict of interest: None

Biological therapy, such as TNF inhibitors has been reported to be effective on refractory cases of AOSD to conventional therapy; however, we experienced a patient with AOSD, who was thought to be flared by adalimumab. A 74-year-old woman was diagnosed with AOSD and was treated with prednisone 15~30 mg/day. At the age of 77, she was referred to our hospital because she had been febrile with skin rash and high level of CRP. Although adding MTX 6mg/week relieved her symptoms, CRP level remained positive. Subcutaneous injection of adalimumab 40 mg/2week was started. At 13 days after the second injection, she had high fever with rash, polyarthralgia, and elevated liver enzyme (ALT 535U/L, AST 1401U/L) and ferritin (561 ng/ml). Her symptoms and abnormal data improved after the cessation of adalimumab and treatment with high dose of steroids and MTX 6 mg/week. Even though the details are not clear, adalimumab might trigger a flare-up of AOSD in this patient.

W60-4

The choice of primary treatment for adult-onset still's disease (AOSD)

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Conflict of interest: None

[Objectives] Moderate-dose corticosteroid(CS) is often chosen as the primary treatment of AOSD, but the disease aggravation was experienced even after starting the treatment. We examined appropriate primary doses of CS according to serological evaluation after primary treatment. [Methods] We experienced 14 AOSD patients who admitted to our hospital from January, 2006, to November, 2011. Before and after primary treatment, we examined CRP and AST, ALT, LDH, ferritin, leukocyte, lymphocyte, platelet, and D dimer. [Results] Moderate-dose CS was administered in 10 of 14 patients, and 4 of them were induced and maintained clinical remission only with the primary therapy. The other 6 patients, who needed to intensify immunosuppressive treatment, tended to show the higher value of CRP. Methotrexate(MTX) was administered in 8 of 14, and all of them were induced the remission. 4 patients who was administered methylprednisolone pulse therapy for primary therapy showed the higher value of CRP(20.4 vs 7.6, p=0.013), and fewer lymphocytes(426 vs 895, p=0.031). The higher value of CRP in AOSD before primary treatment may show higher disease activity. MTX is effective for AOSD treatment. We analyzed the reactivity to primary treatment and report the early prediction models of treatment resistance.

W60-6

Infliximab was effective to macrophage activation syndrome developed after treatment of adult onset still's disease with tocilizumab: Case report

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Conflict of interest: None

A-30-year-old woman was referred to our hospital with high spike fever, polyarthralgia, myalgia, and rash. Three years before admission, she developed similar symptoms. Two years ago, she developed fulminant hepatic failure and underwent liver transplantation, followed by administration of tacrolimus(TAC) and mPSL. A month before admission, she developed above symptoms, after the cessation of mPSL 4 months ago. Since a restart of mPSL was not effective, she was admitted to our department. By spiking fever, rash, arthritis, myalgia and neutrophilic leukocytosis, she was

diagnosed as adult onset still's disease (AOSD) according to Yamaguchi's criteria. After failure of intravenous mPSL (1g/day), tocilizumab (TCZ, 8mg/kg) was introduced. She showed dramatic improvement of fever, arthralgia and myalgia with a normalization of serum CRP level. However, paradoxically, serum levels of liver enzymes and ferritin were sharply raised. Liver biopsy showed neutrophilic infiltrates. We switched TCZ to infliximab (IFX, 200mg/body) with etoposide and granulocyte adsorption apheresis. Her clinical symptoms and laboratory abnormalities were dramatically improved. Eight months later, she was maintained on IFX, mPSL and TAC. The mechanisms of the effects of biologics on MAS need to be clarified

W61-1

Clinical Significance of Anti-CADM-140 Autoantibody in Patients with Juvenile Dermatomyositis

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Conflict of interest: None

[Objectives] Anti-CADM-140 autoantibody is specifically detected in patients with adult dermatomyositis(DM), especially with clinically amyopathic DM(CADM) and is known to have a strong association with rapidly progressive interstitial lung disease(RP-ILD). We have examined the clinical significance of this antibody in patients with juvenile DM(JDM). [Methods] Sera from 25 patients diagnosed as having JDM(19 with classic JDM and 7 with JCADM) were screened for autoantibody using an enzyme-linked immunosorbent assay. [Results] Sera from eight of 25 with JDM were found to contain anti-CADM-140(each 4 with classic JDM and JCADM). All 8 patients had ILD, of which 5 developed RP-ILD. Four of 5 with RP-ILD died. The frequency of RP-ILD was significantly increased in anti-CADM-140 positive JDM compared with that in anti-CADM-140 negative($p<0.01$)). The mean antibody titer before treatment was higher in those who had RP-ILD than in those who did not(768.4 vs. 44.1, $p=0.16$). In JDM with RP-ILD patients, the mean antibody titer did not decrease significantly and was maintained at a high level as was observed in adult DM(981.9 vs. 511.8, $p=0.15$). These results suggest the clinical utility of anti-CADM-140 antibody to predict the development of RP-ILD in patients with JDM as well as adult DM.

W61-2

A clinical and cutaneous pathological study of 11 patients with juvenile dermatomyositis

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Conflict of interest: None

【Background】Juvenile dermatomyositis(JDM) is a vasculopathy with muscle weakness and dermatologic eruptions. The cutaneous histopathology isn't included in DM criteria, while muscle histopathology is included in it. Amyopathic dermatomyositis with interstitial pneumonia has recently been reported in adult cases and isn't often good prognosis. Skin biopsy is very useful for a diagnosis of amyopathic dermatomyositis. We report the histological features of JDM.【Methods】Fifty-eight patients were diagnosed as JDM at the Department of Pediatrics, the Yokohama City University Hospital between 1991 and 2010. Skin biopsies from 11 patients were studied by Hematoxylin-eosin stained sections. The Skin biopsy sites selected by dermatologists were thighs(n=3), elbows(n=3), upper arms(n=2), trunk(n=2), the Gottron's papules of PIP joint(n=1).【Results】Ten of eleven patients (91%) had muscle weakness or CK elevation. The High frequency of histological findings are vascular fibrin depositions(82%), perivascular lymphocytic infiltration(82%). The findings were also seen in one patient of amyopathic dermatomyositis with interstitial pneumonia.【Conclusions】Microvascular abnormalities of JDM were characterized in our report. Skin biopsy is important for amyopathic dermatomyositis.

W61-3

6 cases of articular-type juvenile idiopathic arthritis with onset before age of 3 years

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Conflict of interest: None

[Objectives] The purpose of this study is to investigate of features in patients with articular-type JIA, who have disease onset less than 3 years old. [Methods] We studied 6 patients with articular-type JIA. 5 patients were oligoarticular JIA, 1 was polyarticular JIA. The average age in disease onset was one years and eight months old. We investigated features of physical examination, blood examination, MRI. [Results] The average durations from disease onset to consultation in our hospital were 92±81 days. At first examination in our hospital, all patients had limitation of range of motion in joints with arthritis. In blood examination, WBC was normal in all patients, CRP was slightly elevated in 1 patient, RF was negative in all patients, ANA was positive in 5 patients. In blood examination except one patient, anti-CCP antibody was negative in all patients, MMP-3 was elevated in 1 patient. MRI was performed in 5 patients with oligoarticular JIA, and indicated synovitis in all these patients. [Conclusions] In this study, the patients didn't have difficulty in joint disorder, but all of them had limitation of range of motion in joints with arthritis. In blood examination, ANA-positive patients were 83%. MRI for examination of synovitis was useful to diagnose as articular-type JIA.

W61-4

PET assessment in children with juvenile idiopathic arthritis

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Conflict of interest: None

[Background] In juvenile idiopathic arthritis(JIA), it is thought that pathophysiolosy is deferent between systemic-onset JIA(s-JIA) and polyarticular JIA(p-JIA). Degree of 18-fluorodeoxyglucose (FDG) uptake is previously reported to correlate with physical examination and laboratory tests for evaluating disease activity in patients with rheumatoid arthritis. [Objective] To assess the relationship between ^{18}F-FDG positron emission tomography (PET) uptake and disease activity in children with JIA. [Method] ^{18}F-FDG administered intravenously 3 to 5 MBq/kg in the hungry state, scanned the whole body 1 hour afterward. 15 children with proven JIA who were evaluated for disease activity using PET between 2007 and 2008 were retrospectively enrolled. [result] In 9 s-JIA patients, FDG accumulation was seen at each joint of the 17 shoulders, 6 elbows, 4 hands, 4 hips, 10 knees, and 7 ankles. In 6 p-JIA, the 7 shoulders, 4 elbows, 5 hands, 4 hips, 10 knees, and 6 ankles, respectively. In s-JIA patients, accumulation was seen in all

of shoulder joints. Clinically evaluated by pediatricians, arthritis involved in 36 joints, however the FDG accumulation was seen in 84 joints, at the same day. It reports also including the relation between an SUV value, symptoms, laboratory findings.

W61-5

Etanercept in the treatment of disease modifying anti-rheumatic drug (DMARD) -refractory polyarticular course juvenile idiopathic arthritis: experience from Japanese clinical trials

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Conflict of interest: Yes

[Objectives] The efficacy, safety and pharmacokinetics results from 4 studies; 3 open-label (OL) and 1 randomized double-blind (DB) provided data for the approval of etanercept for treatment of DMARD –refractory juvenile idiopathic arthritis (JIA) in Japan; results from the 3 shorter-term (2 OL and 1 DB) studies are reported. [Methods] Subjects (4 to 17 years) enrolled in the OL studies had active JIA, ≥5 swollen joints and ≥3 joints with limitation of motion and pain or tenderness. Subjects enrolled in the primary OL study received etanercept 0.4 mg/kg subcutaneously twice weekly; in the lower dose OL study subjects received etanercept 0.2 mg/kg. Subjects in the primary OL study who completed ≥48 weeks could continue into a 12-week DB dose-down extension study, where subjects received etanercept 0.4 mg/kg or 0.2 mg/kg twice weekly. [Results] The primary endpoint in all 3 studies, ie 30% improvement in the American College of Rheumatology criteria for JIA (ACR Pedi 30) at 12 weeks, was achieved by ≥80% of subjects by week 2 and sustained to week 12. Common adverse events reported were injection site reactions, nasopharyngitis, and gastroenteritis. These results provide further evidence that etanercept is effective therapy for DMARD –refractory polyarticular JIA patients.

W61-6

Safety and efficacy of long-term etanercept in the treatment of methotrexate-refractory polyarticular-course juvenile idiopathic arthritis in Japan

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Conflict of interest: Yes

[Objectives] The aim of this study was to evaluate the long-term safety and efficacy of etanercept in Japanese children with JIA. [Methods] Patients (4 to 19 years) who received etanercept in one of three short-term studies continued on to this long-term open-label study. [Results] Of 32 patients enrolled, 18 (56.3%) completed 192 weeks of the study and 14 (43.8%) were discontinued; 7 (21.9%) for "patient refusal", 2 (6.3%) for adverse events (AEs), and 5 (15.6%) for lack of efficacy. All patients reported AEs; 31 (96.9%) reported infections and 6 (18.8%) reported serious AEs. Main efficacy assessments included change from baseline in the American College of Rheumatology Pediatric core components including mean improvements from baseline in the physician global assessment (90.7%), patient/guardian global assessments (54.1%), the Childhood Health Assessment Questionnaire (CHAQ; 84.6%) and median improvements in C-reactive protein levels (92.7%). No unexpected safety results were reported and early efficacy responses were sustained in the long-term. This study provides further evidence that etanercept is an effective therapeutic option for Japanese children with polyarticular-course JIA.

W62-1

Musculoskeletal ultrasonography assists the diagnostic performance of 2010 rheumatoid arthritis criteria

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Conflict of interest: None

Objectives. To investigate whether musculoskeletal ultrasonography (MSKUS) assists the diagnostic performance of 2010 RA criteria. *Methods.* Sixty-nine early arthritis patients were consecutively enrolled. None of the patients were treated at entry. In MSKUS of bilateral wrist and finger joints including the 1st – 5th MCP joints, 1st IP joint and 2nd -5th PIP joints, the findings obtained by gray scale (GS) and power Doppler (PD) were graded on a semi-quantitative scale from 0 to 3. Plain MRI of both wrist and finger joints was also examined. The diagnosis of RA was defined by the initiation of DMARDs within the first 3 months. Classification of the patients was evaluated at entry using the 2010 RA criteria in conjunction with MSKUS. *Results.* The 2010 RA criteria classified RA at a sensitivity of 59.5 %, a specificity of 87.5 %, and a positive predictive value (PPV) of 84.6 %. The best MSKUS finding for differentiating RA was the presence of PD grade ≧ 2 that was superior to MRI-proven bone edema. We have found that the decision tree algorithm of 2010 RA criteria with PD grade ≧2 reveals the best discriminative ability. *Conclusion.* MSKUS, especially the strong PD signal, is very useful to assist the diagnostic performance of the 2010 RA criteria in the early recognition of RA.

W62-2

Improved accuracy of 2010 ACR/EULAR rheumatoid arthritis classification criteria by evaluating synovitis with ultrasonography

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Conflict of interest: None

Synovitis was evaluated with ultrasonography (US) in 38 joint regions in 117 cases with possible diagnosis of RA. US-synovitis was defined as gray-scale grade of 1 or greater and/or power Dop-

pler grade of 1 or greater. The clinicians were blinded to the US findings. RA was defined as a condition which required MTX treatment during a one-year observation period. The mean age was 51.6 years, 25 patients were male, and the median duration of articular symptom was 6 months. RF and anti-CCP antibody were positive in 56 and 41 cases, respectively. 49 cases required MTX treatment during one year, and the sensitivity and specificity of ACR/EULAR criteria for development of RA were 71.4% and 68.2%, respectively. Ten cases who fulfilled the criteria with US evaluation, but not with clinical examination were identified, and six cases among them (60.0%) developed RA within a year. On the other hand, 12 cases who fulfilled the criteria with clinical examination, but not with US evaluation were identified, and only one case among them (8.3%) developed RA within a year. The sensitivity and specificity of US-combined ACR/EULAR criteria for development of RA were 81.6% and 79.3%, respectively. In conclusion, US evaluation of synovitis improves the accuracy of ACR/EULAR RA classification criteria.

W62-3

Gray-scale ultrasonography represents accumulated joint damage and predicts residual physical findings of joints during DAS28-based clinical remission of RA

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Conflict of interest: None

[Objectives] To clarify the roles of gray-scale (GS) ultrasonography (US) during clinical remission of rheumatoid arthritis (RA). [Methods] GSUS were monitored in 22 RA patients who were in persistent DAS28 remission for 2 years. GS images were scored semiquantitatively from 0 to 3 in each joint, and total GS score (ΣGS) was calculated as the sum of scores of individual joints. To determine the associations of ΣGS with clinical features and radiological findings, patients were divided into two groups, the lower ΣGS group (ΣGS ≤ 6) and the higher ΣGS group (ΣGS ≥ 7) at entry. [Results] The higher ΣGS was associated with advanced clinical stage and high value of total Sharp score at entry, though ΣGS was not affected by disease duration, duration of remission, and therapies. Tender joint count was comparable between the lower and higher ΣGS groups at entry, whereas swollen and/or tender joints were found in 67% of patients in the higher ΣGS group at 2 years, with completely disappeared in those belonged to the lower group. These results suggest that GSUS finding not only represents accumulated structural damage but also predicts persistent joint swelling and/or tenderness after reaching DAS28-based remission of RA. The parameter may be essential for judgment of "true remission".

W62-4

The findings of musculoskeletal ultrasonography in patients with rheumatoid arthritis achieving clinical remission

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Conflict of interest: None

Objectives. To investigate the findings of musculoskeletal ultrasonography (MSKUS) in patients with RA achieving clinical remission.*Methods.* Thirty-five RA patients were enrolled. All of the patients achieved in clinical remission (SDAI≦3.3) for at least 3 months at MSKUS examination. In MSKUS of bilateral wrist and finger joints including the 1st – 5th MCP joints, 1st IP joint and 2nd -5th PIP joints, the findings obtained by gray scale (GS) and power Doppler (PD) were graded on a semi-quantitative scale from 0 to 3. *Results.* The mean of age was 55.8 years and that of disease duration was 32.1 months. The mean of SDAI was 0.82. The percentage of abnormal findings of MSKUS presented at any joint are GS grade≧1; 74.3%, GS grade≧2; 45.7%, GS grade 3; 14.3%, PD grade≧1; 65.7%, PD grade≧2; 42.9%, PD grade 3; 5.7%, respectively. Regarding to the patients with synovitis determined by PD grade≧2 as compared with the patients without those, the usage of biologic DMARDs was low (p=0.036) and the presence of MSKUS-proven bone erosion was high (p=0.020). *Conclusion.* Abnormal findings of MSKUS still present in the patients with RA achieving in sustained SDAI remission. Biologic DMARDs may lower the appearance of abnormal MSKUS findings.

W62-5

Assessment of clinical disease activity of rheumatoid arthritis (RA) by power Doppler ultrasonography (PDUS)

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Conflict of interest: None

[Objectives] We aimed to clarify the association between PDUS and clinical disease activity. [Methods] We studied 72 RA patients (28 men and 44 women) with mean age of 62.5 yrs and mean disease duration of 5.6 yrs. Twenty-two joints including PIP, IP, MCP and both hands were assessed by PDUS with 4 grades (0-3), the sum of which was defined as "PD22 score". Clinical disease activity was also assessed by SDAI, CDAI, DAS28CRP, and Boolean criteria. We analyzed correlations between PD22 score and the activity scores. The correlations with tender joint count (TJ), swollen joint count (SJ), serum CRP, patient global assessment (PGA), and evaluator global assessment (EGA) were also analyzed. [Results] PD22 score was significantly correlated with SDAI, CDAI, and DAS28CRP, especially most significantly with SDAI ($r=0.77$, $p<0.01$). The correlations with SJ, PGA, and EGA were more significant compared with TJ or CRP. In 6 (43%) of 14 patients satisfying Boolean remission criteria, PD22 score were equal or more than one. [Conclusion] PD22 score was correlated well with conventional activity scores and thus considered useful for assessing RA disease activity. It is suggested that PDUS is so sensitive that we assess "true" clinical RA remission.

W62-6

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

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Conflict of interest: None

Purpose: In the treatment of rheumatoid arthritis (RA), early diagnosis, treatment and tight control increased their importance by the appearace of biologic therapy. Ultrasonography (US) of the

various joints enables an evaluation of synovitis and bone erosion in real time. The purpose of this study is to investigate whether the image of US at the operated joint reflect synovium pathology or clinical indicators. Materials and methods: 23 joints in 21 patients with RA were operated. Preoperatively, US was performed and grade of Power Doppler (PD) signal was weighed. Rooney score of the synovium pathology, Larsen grade at the operated joint, DAS28-ESR(4), MMP-3, CRP were investigated. The operated site was 1 shoulder joint, 5 elbow joints, 12 wrist joints and 5 fingers. Results: 11 joints were in grade 0,1 (group L) in PD signal and 12 joints were in grade 2,3 (group H). CRP in group L (0.26±0.55:mean±SD) was significantly lower than that in group H (0.04±1.31, p=0.050). Rooney score in group L (26.1±10.7) was significantly lower than that in group H (36.0±6.9, p=0.016). There was an association between grade of PD signal and CRP, and between grade of PD signal and synovium pathology. Conclusion: PD signal in the US image was one of the indicators to reflect CRP and synovium pathology.

W63-1

Underwater ultrasonography using an acoustic board for finger joint evaluation

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Conflict of interest: None

[Objective] Finger ultrasonography for rheumatoid arthritis has been attracting attention with regard to the diagnosis and evaluation of the disease state, but evaluations on the horizontal axis, severity of swelling, and blood flow using the power Doppler method markedly vary depending on the measurement techniques. In this study, we employed underwater ultrasonography using a special acoustic board, and obtained favorable measurement results. [Methods] The conditions were the same as those for conventional joint ultrasonography regardless of the device model or probe. A vat filled with water sufficient to immerse the hand-wrist joint was used, instead of jelly. [Results] <Advantages> 1) The image sharpness increases, 2) the cross-sectional assessment range is wide, 3) no probe compression-induced change occurs in the swollen region, 4) evaluation is not influenced by finger contracture or deformity, 5) the results are reproducible because a constant skin temperature can be maintained, and 6) there is no stickiness with jelly. <Disadvantages> 1) A special vat is used, and 2) it is inconvenient for carrying. [Discussion] Weaknesses of the previous method were improved; particularly, the evaluations of changes in swelling, deformed fingers, and blood flow were markedly simplified.

W63-2

Programs of automatic acquisition of appropriate PD gain and real-time calculation of PD signal area in MSUS

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Conflict of interest: None

[Objectives] MSUS is useful for assessment of joint lesions in RA. However, difficulties in being familiarized with techniques and evaluation methods are obstacles to popularize MSUS. We assessed the efficacy and validity of two newly developed-programs; automatic acquisition of the most appropriate power Doppler (PD) gain and real-time calculation of PD signal area. [Methods] Joints of RA patients were evaluated with Aplio XG possessing the two new programs by 2 experts in MSUS blindly each other; one conventionally evaluated PD signals in joints by semi-quantitative scoring method after manually adjusting PD gain, whereas the other examined the same joints using these new programs. [Results] Automatic gain adjustment in each examination was completed within a second. The gain value was not significantly different from those adjusted manually. The program of real-time PD signal calculation was useful for acquisition of the best point to evaluate PD signal, and data of the program were well correlated with semi-quantitative scores. These new programs enable MSUS operators to evaluate arthritis objectively, efficiently, and accurately. Quantitative evaluation of PD signal may contribute to more detailed analysis of arthritis than using a conventional evaluation method.

W63-3

Relationship between finger joint cartilage evaluated by ultrasound and clinical characteristics in rheumatoid arthritis (RA)

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Conflict of interest: None

[Objectives] To clarify the relationship between the finger joint cartilage evaluated by ultrasound (US) imaging method and clinical characteristics in RA. [Methods] We examined 16 RA patients with low disease-activity or remission The cartilage layer of MCP and PIP joints for fingers 2-5 was bilaterally visualized from a posterior view, with joints in approximately 90 degrees flexion. Cartilage thickness (CT) was measured with integrated tools on static images, and thickness was compared with other clinical and laboratory parameters. [Results] CT in MCP joints ranged from 0.1 to 0.8 mm, and CT ranged from 0.0 to 0.4 mm, respectively. The sum of total 8 fingers CT ranged from 2.7 to 6.8 mm (average 4.7 mm). CT measured by ultrasound did not correlated with age, duration of RA, DAS28-CRP, HAQ score or positivity of rheumatoid factor or anti-CCP-antibody. CT was modestly reduced in RA patient whose had had high serum MMP-3 value at diagnosis of RA (before treatment). [CONCLUSION] The US method of direct visualization and quantification of cartilage in MCP and PIP joints can be valid and useful in RA. Further study should be needed to clarify the relationship between the finger joint cartilage evaluated by US and clinical characteristics.

W63-4

Ultrasonographic study of seronegative rheumatoid arthritis (RA) and Osteoarthritis (OA)

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Conflict of interest: None

[Objectives] To evaluate the ultrasonography(US) of patients with seronegative arthritis. [Methods] Twenty patients with seronegative RA and twenty five patients with OA were underwent laboratory tests, radiographs of the hands, and US imaging of both MCP and PIP and wrist. [Results] The grading average of power doppler (PD) of both MCP, PIP, wrist with seronegative RA was 1.57±0.12, and 1.06±0.03 with OA($p<0.0002$). The grading average of gray scale synovial thickness (GS) with seronegative RA was 1.56 ±0.12, and 1.24 ±0.07 with OA($p<0.01$). In 20 seronega-

tive RA, 10 patients were satisfied with ACR/EULAR criteria, and 10 were not. If we had substituted the number of US positive joints for criteria,15 patients were satisfied with criteria. 4 of 5 patients who were not satisfied with criteria had only wrist joints swelling. The grading of PD and GS of there wrists were more than 2. [Conclusion] US is useful when we diagnose seronegative RA.

W63-5

Ultrasonographic remission is useful for predicting long-term clinical remission and successful dose-reduction of etanercept in patients with rheumatoid arthritis

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Conflict of interest: None

[Objectives] To identify usefulness of US assessment in the prediction for long-term clinical remission and dose-reduction of etanercept (ETN) in patients with remitted RA. **[Methods]** Included were 14 RA patients who were treated with ETN (50mg/ week) and achieved DAS28 CRP <2.3. US assessment was conducted within 3 months after achieving clinical remission and total power doppler signals (t-PDS) of bilateral wrists and knees were recorded. Correlation between t-PDS and clinical outcome and laboratory indexes were analyzed. Subsequently 7 patients attaining long-term clinical remission were attempted to reduce the dose of ETN (25mg/ week) after US evaluation. **[Results]** Among 14 patients, 8 were t-PDS (+) and 6 were negative t-PDS (-). T-PDS (+) group tended to have fewer CCP-positive patients and higher HAQ score as compared with t-PDS (-) group. Three t-PDS (+) patients relapsed at 3, 8, 14 months, respectively and all of t-PDS (-) patients attained long-term clinical remission. Three out of 4 patients with PDS (-) successfully reduced the dose of ETN over 6 months or more, while 2 of 3 patients with PDS (+) relapsed at 2 and 4 months, respectively. **[Conclusion]** US remission may be a strong predictor for long-term clinical remission and successful dose-reduction.

W63-6

Ultrasonography is useful for monitoring of therapeutic response to abatacept in rheumatoid arthritis.

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Conflict of interest: None

[Objective] To evaluate therapeutic response of abatacept in patients with rheumatoid arthritis (RA) by ultrasonography (US). [Methods] We assessed 10 patients with RA patients (female 10 cases, 59.1 y.o.) who were treated with abatacept. Bilateral MCP, PIP, wrists, and knees were examined by US in which synovitis was graded with 0-3 gray scale and power Doppler. [Results] The mean disease duration was 10.8 years. Baseline mean disease activity index of DAS28-ESR, DAS28-CRP, SDAI and CDAI were 4.4, 3.8, 21.5, and 21.2, respectively. All clinical and laboratory parameters as well as the US scores were significantly reduced in response to treatment with abatacept. [Conclusion] A favorable response to treatment with abatacept was demonstrated by US evaluation as well as clinical and laboratory findings.

W64-1

Association of *PRDM1-ATG5* region with clinical subsets of systemic lupus erythematosus

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Conflict of interest: None

[Objectives] Association of *PRDM1-ATG5* region with systemic lupus erythematosus (SLE) has been identified in the Caucasians and Chinese. PRDM1, also known as Blimp-1, is a transcription factor involved in plasma cell differentiation. ATG5 is essential for autophagosome formation. In this study, we examined whether the *PRDM1-ATG5* region is associated with SLE in Japanese population. [Methods] Three SNPs (rs548234, rs2245214, rs573775) located in the *PRDM1-ATG5* region were genotyped, and were tested for their association with SLE in 506 Japanese SLE patients and 466 healthy controls. [Results] In the whole SLE group, a tendency toward increase of rs548234C/C genotype was observed (SLE: 14.6%, control: 10.9%, P=0.087 odds ratio [OR] 1.39). When the association with clinical subsets of SLE was analyzed, rs548234C/C was significantly increased in SLE with nephritis (18.9%, P=0.0026, OR 1.89), when compared with healthy controls. In addition, the same allele was associated with SLE with anti-Sm antibodies (P=0.013, OR 1.74). On the other hand, evidence for association of the SNPs in *ATG5* (rs2245214 and rs573775) was not observed. These findings suggested that the *PRDM1-ATG5* region may genetically contribute to nephritis and anti-Sm antibody production in SLE.

W64-2

Association of *NLRP3* polymorphisms with systemic lupus erythematosus

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Conflict of interest: None

[Objectives] Mutations of *NLRP3,* a component of inflammasome, cause CAPS, and its common SNPs have been associated with immune diseases such as Crohn's disease. In this study, we examined its association with SLE. [Methods] Association of 5 tagSNPs, previously associated with other immune disorders, was examined in 440 patients and 515 healthy controls. [Results] rs1539019A/A genotype was significantly increased in SLE (P=0.030, odds ratio [OR] 1.45, 95% confidence interval [CI] 1.04-2.03). The association was more striking in the patients with renal disorder (P=0.011, OR 1.67, 95%CI 1.13-2.46). rs4612666C allele was also increased in SLE with renal disorder (P=0.040, OR 1.27, 95%CI 1.01-1.60). These results suggested that *NLRP3* polymprphisms are associated with susceptibility to SLE.

W64-3

Integrative gene expression analysis in subpopulation of peripheral blood mononuclear cells from untreated active systemic lupus erythematosus patients

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Conflict of interest: None

[Objectives] Although gene expression abnormalities, such as interferon (IFN) signature in peripheral blood from active systemic lupus erythematosus (SLE) patients have been reported, contribution of each subpopulation is still unclear. [Methods] Peripheral blood from five cases including three untreated active SLE patients and two healthy controls was collected and sorted to four subpopulation (CD4+, CD8+, CD19+, CD14+). We quantified gene expression in subpopulation by DNA microarray. These datasets were analyzed by bioinformatics methods. [Results] In SLE, various differences including IFN signature were found and thus enhanced IFN inducible gene pathway may be different in subpopulation. Gene ontology analysis revealed various immune related gene groups in subpopulation. One interesting example is here, proteasome and HLA class I expression was significantly upregulated both in CD14+ and CD19+ subpopulation. In SLE CD14+ and CD19+ subpopulation, after IFN signal activation, increase of degradation of endogenous antigen by proteasome and subsequent induction of antigen presentation by HLA class I may be indicated. Information on integrative gene expression analysis in subpopulation was considered to be useful for focusing on the pathogenesis and therapeutic target of SLE.

W64-4

Expression of BCMA and BAFF-R on RP105 negative B cells in SLE and systemic autoimmune diseases

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Conflict of interest: None

[Objectives] RP105(-) B cells produce autoantibodies, including anti-dsDNA antibodies, in SLE. To clarify the difference of its phenotype between SLE and other autoimmune diseases, we investigate expression of BBRs, including BCMA, BAFF-R and TACI, on B cells in various autoimmune diseases. [Methods] The phenotype of RP105(-) B cells from 42 cases were investigated by 4-color flow cytometry. [Results] Analysis of phenotype of RP105(-) B cells shows that the cells are several subsets of late B cells differentiating towards plasma cells. Preferentially expressed BCMA was characteristic of RP105(-) B cells compared with RP105(+) B cells. The ratio of BCMA/BAFF-R was the highest in SLE patients among various systemic autoimmune diseases. In case of sCD40L induced cell death, RP105(+) B cells were not rescued by BAFF or APRIL. However, survival of RP105(-) B cells was found. In vitro activation with sCD40L and BAFF resulted in reduction of BAFF-R and increase of BCMA expression on RP105(-) B cells. These results suggest that RP105(-) B cells are possibly regulated by BCMA and BAFF/APRIL.

W64-5

Characteristics and significance 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 show that increased expression of IL-21 mRNA in peripheral blood mononuclear cells (PBMC) of patients with SLE, and reveal the phenotype of IL-21 producing cells. **[Methods]** PBMC were obtained from patients with SLE and healthy subjects (HS) and IL-21 mRNA expression was quantified by RT-PCR (TaqMan assay). After isolation of CD4+ T cells from PBMC of patients with SLE and HS, these cells were analyzed on ICOS and CXCR5 expression by Flow Cytometory. **[Results]** In the peripheral blood of SLE, IL-21 production was increased, because IL-21mRNA expression was higher in PBMC of SLE patients. Further examination will be necessary to clarify the characteristics on IL-21 producing cells, CD4+ ICOS+ CXCR5- T cells was one of the candidate hallmark of IL-21 producing cells in peripheral blood of SLE patients.

W64-6

The role of Syk in activation of human B cell subsets and its relevance to SLE

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Conflict of interest: None

[Objectives] B cells play a pivotal role in pathology of SLE. Spleen tyrosine kinase (Syk), a key molecule in BCR-mediated signaling, is prerequisite for optimal induction of TRAF6, thereby allowing efficient propagation of CD40 and TLR9 signaling and robust activation of human B cells. We aimed to clarify the relevance of Syk to pathogenesis of SLE. [Methods] PBMCs were isolated from SLE patients and analysed by FACS. [Results] p-Syk and TRAF6 expression in $CD19^+$ cells of patients with SLE (n=58) were significantly increased compared to healthy donors (n=27). Moreover, both p-Syk and TRAF6 expression correlated with the disease activity score, SLEDAI. Compared to $CD19^+CD27^-$ naïve B cells, TRAF6 expression was higher in $CD19^+CD27^+$ memory B cells and correlated with the increased ratio of memory B cell subset among the total B cells. When PBMCs from SLE patients were

cultured with a specific Syk inhibitor (BAY61-3606) in vitro, p-Syk and TRAF6 expression was suppressed. Taken together, our results suggest that dysregulation of Syk-mediated TRAF6 signal transduction leads to expansion of memory B cell subset and is involved in pathological processes of SLE. Therefore, we underscore the potential role of Syk in B-cell-mediated pathological processes in autoimmune disease such as SLE.

W65-1

The role of Btk in human B cell differentiation and class switching

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Conflict of interest: None

[Objectives] B cells play a pivotal role in pathological processes of autoimmune disease such as RA and SLE. Btk is well known for its importance in B cell signaling and recent reports showed the efficacy of Btk (Bruton's tyrosine kinase) inhibitors on mouse CIA., However, underlying mechanisms of Btk in human B cells remain elusive. [Methods] Human pan B cells were isolated from healthy donors and SLE patients. [Results] When B cells were stimulated with IL-21, a cytokine important for B cell differentiation and Ig class switching, only a slight induction was observed. Likewise, BCR and/or CD40/BAFF stimulation were with similar results. However, combinatorial stimulation with BCR, CD40/BAFF and IL-21 caused robust AICDA (coding gene of AID) gene expression and IgG production. A specific Btk inhibitor(ONO-A) significantly abrogated these expression to the extent of IL-21 alone in a dose-dependent manner. Taken together, these findings suggest that Btk-mediated BCR/CD40/BAFF signaling is prerequisite for efficient propagation of IL-21-signaling critical for differentiation and class switching of human B cells. These results also underscore the potential role of Btk in B cell-mediated pathological processes in autoimmune disease.

W65-2

Restoration effect of TCR zeta expression in patients with systemic lupus erythematosus by calcineurin inhibitors

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Conflict of interest: None

[Objectives] It's been reported that TCR zeta protein expression is decreased in T cells from patients with systemic lupus erythematosus (SLE). Aim is to clarify whether calcineurin inhibitors (CNIs) have any effect for recovery from low TCR zeta protein expression in T cells from SLE patients and the recovery effect is relating to clinical response by these drugs or not. [Methods] Peripheral blood cells were obtained from 26 SLE patients before and after the commencement of CNIs. The expression level of TCR zeta protein compared with β-actin was examined by western blot analysis. Disease activity of SLE was accessed by SLEDAI and its relation to TCR zeta recovery was statically analyzed. [Results] Mean age of patients was 44.7 years old and 88.5% of them were female. Before start of CNIs, all patients had active disease status, including arthritis, skin eruption, cytopenia, and nephritis. Tacrolimus was used for 20 patients and ciclosporin for 6, respectively. TCR zeta protein was significantly decreased in SLE patients as compared with healthy age matched controls (45% decrease; p value <0.001). Interestingly, the TCR zeta was significantly restored after treatment with CNIs ($p<0.01$). Moreover, the recovery of TCR zeta was correlated with the clinical response ($p<0.05$).

W65-3

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

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Conflict of interest: None

[Objectives] The efficacy of B-cell depletion therapy in autoimmune diseases highlights a pivotal role of B cells in their pathogenesis. Elimination of B cells, however, occasionally leads to exacerbation of these diseases, suggesting the existence of regulatory B cells (Bregs). B cell activation is required for Breg induction, and regulatory mechanisms of Bregs underscore the production of IL-10. In this study we have tested the effects of CpG, a TLR9 ligand, on Breg induction in normal subjects and SLE patients. [Methods] IL-10 production was evaluated at mRNA and protein levels by using quantitative RT-PCR and ELISA/intracellular staining, respectively. [Results] CpG was the potent inducer for IL-10 production in normal B cells, and in particular memory B cells exhibited high levels of its production. Combined stimulation of BCR and TLR9 enhanced IL-10 production in B cells. The signaling pathways such as MAPK, NFkB, PI3K and STAT were involved in TLR9-induced IL-10 production. Notably, TLR9-induced Breg induction was significantly impaired in B cell subsets from SLE patients, albeit high levels of IL-10 expression in freshly isolated B cells. We are now elucidating a possible explanation for the difference in Breg induction between normal subjects and SLE patients.

W65-4

CIN85 regulates BCR signaling and plays a role in aberrant functions of SLE B cells

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Conflict of interest: None

<Purpose> The efficacy of B cell depletion therapy highlights a key role of B cells in the pathogenesis of autoimmune diseases such as SLE. Fate decisions of autoreactive B cells are made by fine-tuning of positive and negative signals downstream the BCR. Cbl is an E3 ubiquitin ligase highly expressed in self-tolerant B cells. In this study, we sought to clarify a role of a novel Cbl adaptor CIN85 in the function of normal and SLE B cells. <Methods> BCR signaling was biochemically assessed using CIN85-overexpressing/knockdown B cell lines. Role of CIN85 in B cell survival, growth and differentiation was evaluated using CIN85-knockdown

primary B cells. Expression and function of CIN85 in SLE B cells were tested. <Results> CIN85 strongly associated with Cbl and BLNK. CIN85 enhanced Cbl phosphorylation, which in turn inhibited BCR-induced calcium flux and activation of Syk and PLCg2. CIN85 negatively regulates survival, proliferation and differentiation of primary B cells via altering expression of respective genes. CIN85 expression and Cbl phosphorylation in SLE B cells were reduced compared with normal controls. Collectively, these suggest that aberrant expression of CIN85 causes impaired Cbl function, culminating in tolerance breakdown of autoreactive B cells in human SLE.

W65-5

Antibodies to NR1 subunit of N-methyl-D-aspartate receptor in the sera of patients with systemic lupus erythematosus

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Conflict of interest: None

【Objective】It has been reported that antibodies to NR2 subunit of N-methyl-D-aspartate receptor (NMDAR) were involved in the pathogenesis of lupus psychosis. However, it remains unclear whether antibodies to NR1 subunit of NMDAR is involved in systemic lupus erythematosus (SLE). The current studies were performed to explore the presence of anti-NR1 antibodies in the sera of human SLE.【Method】Sera from 85 patients with SLE, 11 patients with RA and 98 healthy individuals were analyzed for anti-NR1 antibodies with ELISA, using the N-terminal 100-amino acids of NR1 subunit of murine NMDAR.【Results】Serum level of anti-NR1 in 98 healthy individuals were 4.224±2.035 units/ml (mean±SEM). Serum anti-NR1 levels were significantly elevated in patients with SLE (22.45±6.030 units/ml, p=0.0049) compared with healthy individuals. None of the 11 patients with RA showed elevation of serum anti-NR1 over the upper limit of normal, which was defined as 3SD above the mean of anti-NR1 levels in normal healthy individuals.【Conclusion】The results indicate that serum anti-NR1 antibodies are elevated in patients with SLE. Further studies to determine whether anti-NR1 might be involved in central nervous system manifestations would be important.

W66-1

IL-17 affects destruction of cartilage but not joint inflammation in the K/BxN arthritis mouse model

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Conflict of interest: None

[Objectives and Methods] To clarify the role of IL-17 in arthritis, we generated IL-17 deficient K/BxN mice. [Results] Interestingly, cartilage destruction in IL-17 deficient K/BxN mice is less than those in IL-17 heterogeneous K/BxN mice although the arthritis severity was similar to each other. We examined the expressions of several proteinases, which may contribute to the cartilage destruction and their inhibitor in the synovium of arthritis mice. Proteinase expressions including MMP (matrix metalloproteinase)-3 and MMP-13 in the synovium of IL-17 deficient K/BxN mice were less than those in IL-17 heterogeneous K/BxN mice. The serum anti-glucose-6-phosphate isomerase (GPI) antibody titer was not different between IL-17 deficient K/BxN and IL-17 heterogeneous K/BxN mice. Thus, IL-17 plays a pivotal role for the destruction of joint cartilage, but not joint inflammation, in the K/BxN arthritis model. IL-17 may regulate the expression of MMPs which leads to the cartilage destruction and may not control the antibody production.

W66-2

The crucial role of TNFα-induced adipose-related protein (TIARP) in autoimmune arthritis

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Conflict of interest: None

Objective We found that TNFα-induced adipose-related protein (TIARP) is dominantly expressed in macrophages (Mφ) and joints of arthritic mice, although the pathogenic mechanisms of arthritis remain unclear. To elucidate the role of TIARP in the development of arthritis, we have generated TIARP-deficient ($TIARP^{-/-}$) mice in C57BL/6 background. **Methods** (1) We investigated several organs in aged (12-month-old) $TIARP^{-/-}$ mice. (2) Peritoneal Mφ were cultured with TNFα, and the production of IL-6 was measured. (3) We examined the susceptibility of $TIARP^{-/-}$ mice to collagen-induced arthritis (CIA). (4) The level of IL-6 and TNFα in the serum on day 60 were measured. (5) We examined the effects of anti-IL-6R mAb (MR16-1) on the development of arthritis in $TIARP^{-/-}$ mice. **Results** (1) Aged $TIARP^{-/-}$ mice spontaneously developed weak synovitis with enthesitis. (2) Mφ from $TIARP^{-/-}$ mice produced high amount of IL-6 by TNFα. (3) The severity of arthritis score in $TIARP^{-/-}$ mice was higher than that in WT mice. (4) The serum IL-6 was significantly increased in $TIARP^{-/-}$ mice. (5) Administration of MR16-1 significantly suppressed the progression of arthritis in $TIARP^{-/-}$ mice. **Conclusion** TIARP should be a negative regulator against autoimmune arthritis via suppression of inflammatory cytokines.

W66-3

Detection of *PADI4* gene expression in the joint and serum anti-CCP antibody at very early stage of arthritis in the knock-in mouse gp130F759

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Conflict of interest: None

[Objectives] A knock-in mouse gp130F759 is a rheumatoid arthritis (RA) model having gp130 with Y759F mutation and spontaneously develops arthritis at 8 months old (M.O.). The analysis of the gene-expression profiles of the joint of gp130F759 at 5 M.O., when the earliest and subtle symptom of arthritis was detectable, revealed the increased expression levels of *peptidyl arginine deiminase type IV* (*padi4*). A SNP of *padi4* is reported to correlate with susceptibility to RA in Japanese. Citrullination by PADI4 could cause the production of autoantibodies detected as anti-cyclic citrullinated peptide (CCP) antibody (Ab), a reliable diagnostic marker for RA. [Methods] Sera and the joint RNA from gp130F759 or C57BL/6(B6) at 4, 5, 8, and 12 M.O. were collected. Serum anti-CCP Ab was measured with ELISA. Expression levels of *padi4* gene were determined using quantitative RT-PCR. [Results] At 5 M.O, serum levels of anti-CCP Ab (IgM class) in gp130F759 were higher than those in B6. Gp130F759 with the increased expression levels of *padi4* gene compared with those of B6

belonged to the age group of 5 M.O. These data suggest the correlation between the expression of *padi4* gene in the joint, production of anti-CCP Ab, and the development and/or pathophysiology of RA-like arthritis in gp130F759.

W66-4

Effect of antigen-specific B cell depletion using toxin-conjugated peptide tetramers on collagen-induced arthritis

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Conflict of interest: None

B cell depletion therapy is effective in the treatment of various autoimmune diseases. Rituximab is an effective treatment for human RA. However, this therapy is shown to be associated with increased risk of adverse effects such as opportunistic infections. In order to minimize the risk of adverse effects of B cell depletion therapy in autoimmune diseases, we selectively depleted arthritogenic B cells using peptide tetramers in collagen-induced arthritis. We developed toxin-conjugated peptide tetramers, which contained citrullinated epitope (CIA1) of mouse type II collagen(CII). The male DBA/1J mice were injected with peptide tetramers twice after first CII immunization. The incidence of arthritis was significantly lower in the tetramer-treated group than in the control one. And there were significant differences in the titer of anti-CIA1 antibodies over time between the two groups. We show that toxin-conjugated peptide tetramer is effective in the selective depletion of antigen-specific B cells and in the treatment of arthritis without global immunosuppression. This approach might be applied to various autoimmune diseases, using autoantigen-derived peptides.

W66-5

Establishment of a novel collagen-induced arthritis model by manipulating dendritic cells

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Conflict of interest: None

[Objectives] Rheumatiod arthritis (RA) is a progressive, destructive systemic autoimmune disease, and collagen-induced arthritis (CIA) is a useful model to analyze the pathogenesis of human RA. Dendritic cell (DC) is thought to be involved in autoimmune diseases such as RA. However, the role of DCs on the induction of RA has not been investigated in CIA model since conventional CIA model is induced by intradermally (i.d.) injection of chicken type II collagen (CII) with adjuvant, but not by directly stimulating DCs. Therefore, we tried to establish a novel CIA model to analyze the role of DCs. [Methods] C57BL/6 mice were primed with intravenous injection of CII-loaded DCs as priming, followed by i.d. injection of CII with complete Freund's adjuvant and killed *Mycobacterium tuberculosis*. [Results] A few weeks after boosting, we observed inflammation characterized by synovial infiltration of immune cells and subsequent damage of cartilage. Furthermore, we found Th1 or Th17 cells infiltrating into the inflammation sites in the joints. In summary, we have established a new CIA model useful for analyzing the role of DCs in the induction of CIA.

W66-6

Establishment of FcγRIIB-deficient mice with spontaneously occurring severe rheumatoid arthritis

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Conflict of interest: None

[Objectives] FcγRIIB is a negative regulator of B cell activation. Thus, the decrease in FcγRIIB expression level may induce aberrant B cell activation and autoantibody production. To examine the effect of FcγRIIB deficiency on autoimmune phenotypes, we established FcγRIIB deficient B6 mice. [Methods] We established two lines of FcγRIIB-deficient B6 mice (KO1 and KO2) by selective backcrossing of the originally constructed FcγRIIB-deficient mice on a hybrid (129 x B6) background into a B6 background. [Results] Unexpectedly, KO2 mice did not produce autoantibodies; however, KO1 mice developed severe RA with high serum levels of RF and anti-CCP antibodies. Genotyping revealed that KO1 mice carried 129-derived ~6.3 Mb telomeric chromosome 1 region including *Slam* family genes, but this region was B6 origin in KO2 mice. These result suggest that epistatic interaction of FcγRIIB deficiency and 129-type *Slam* polymorphism may confer the predisposition to RA.

W67-1

Pirfenidone ameliorates the development of interstitial pneumonitis in rheumatoid arthritis model, D1CC mouse

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Conflict of interest: Yes

[Objectives] D1CC mouse showed chronic and systemic inflammation together with interstitial pneumonia as an extra-arthicular manifestation (PNAS, 103:14465, 2006). We analyzed histological features in lung disease and measured the concentration of serum surfactant protein-D, SP-D. We also assessed the effects by Pirfenidone for the development of interstitial pneumonitis in D1CC mice. [Methods] We established a novel rheumatoid arthritis mouse model called D1CC mouse, in which CIITA transgene was introduced as a master switch for MHC class II gene expression. Inflammatory arthritis was induced by injection of lower dose of type II collagen (Col2, 0.05mg/mouse/injection), because D1CC mice had high susceptibility to arthritogenic stimuli. Serum SP-D was measured by ELISA. Pirfenidone was administrated orally. [Results] D1CC mice showed chronic inflammation and fibrosis in lung to differ from transient symptoms in bleomycine-induced pulmonary fibrosis. We found that primary nodules were consist of T, B and plasma cells, bur no infiltrated neutrophils and fibrosis its surrounding in the early stage of interstitial pneumonitis. Oral administration of pirfenidone inhibits the increasing of serum SP-D.

W67-2

Dendritic cell-specific depletion of protein-tyrosine phosphatase Shp1 causes autoimmunity

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Conflict of interest: None

[Objectives] Dendritic cells (DCs) promote immune responses to foreign antigens and immune tolerance to self-antigens. Dysregulation of the function of DCs is through to cause abnormal immune responses, which in turn cause autoimmunity. Spontaneous mutations in the protein tyrosine phosphatase *Shp1* gene in mice produce the *motheaten* phenotypes that exhibit multiple inflammatory and autoimmune defects. Previous studies suggest that Shp1 negatively regulates the function of lymphocytes. But, physiological roles of Shp1 in DCs remain to be elucidated. [Methods] To investigate the Shp1 function in DCs *in vivo*, we generated Shp1 conditional knock out (CKO) mice, in which the *Shp1* gene was specifically deleted in DCs. [Results] CKO mice develop splenomegaly associated with an increased number of CD11c+ DCs. Splenic DCs from the mutant mice showed up-regulation of CD86 expression as well as of production of proinflammatory cytokines. The mice manifested an increased number of activated T cells and the serum immunoglobulins were also increased in the mutant mice. Moreover, aged mutant mice developed glomerulonephritis and interstitial pneumonitis together with increased serum concentrations of autoantibodies. Shp1 is thus a key regulator of DC functions that protects against autoimmunity.

W67-3

Functional interaction between synovial mast cells and fibroblast-like synoviocytes via IL-33 and its receptor ST2

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Conflict of interest: None

[Background] Mast cells (MCs) have been recognized as potential participants in inflammatory arthritis. We have recently demonstrated that Fibroblast-like synoviocytes (FLS)-derived IL-33 contributed to joint inflammation via MC granule maturation and activation. The expansion of synovial MCs in established arthritis has been observed and MCs are usually in close proximity to FLS. Thus, we speculate that FLS and their products, such as IL-33 regulate MC survival. We elucidate the mechanism of functional interaction between MCs and FLS. [Methods] Co-culture of WT or IL-33 receptor ST2-null mouse bone marrow-derived MCs (mBMMCs) and FLS was performed. MC viability was examined using Alamar blue dye and apoptosis was quantified by Annexin V stain. IL-6 was measured by ELISA and transcripts for IL-6 and IL-33 were evaluated by RT-PCR. [Results] IL-33 promoted MCs viability by reducing apoptosis. The IL-6 content of the co-culture supernatant was higher than that of the FLS or mBMMCs monoculture. WT but not ST2-null MCs induced FLS to express IL-6 as well as IL-33, constituting a positive feedback circuit. In conclusion, FLS-derived IL-33 contributes to MC biological function by promoting survival. Besides, we define a MC-FLS amplification loop dependent on IL-33 and its receptor.

W67-4

The role of T-bet overexpressing T cells in PD-1 KO mice

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Conflict of interest: None

[Background] Programmed cell Death-1 deficient mice (PD-1KO) develop strain-specific autoimmune phenotypes. Although past reports showed that lupus-like glomerulonephritis was observed in PD-1KO C57BL/6, the function of $CD4^+$ T cells was not fully elucidated. [Objectives] To clarify the effect of T-bet overexpressing T cells in PD-1KO. [Methods] 1) PD-1KO x T-bet Tg (P/T) mice were generated by crossing T-bet Tg with PD-1KO. 2) In P/T, the pathological evaluation of kidneys was performed. 3) The histologic of analysis were evaluated on several organs. 4) FACS analysis was performed to evaluate proportion of lymphocytes subset, the expression of cytokine and transcription factor expression on $CD4^+$ T cells in spleen and thymus. [Results] 1) Most of P/T died within 10weeks. 2) Lupus-like glomerulonephritis was not observed in P/T. 3) Splenomegaly and infiltration of mononuclear cells in liver and pancreas were observed in P/T. 4) FACS analysis showed higher IFNγ production and lower Foxp3 expression on $CD4^+$ T cells in P/T compared with PD-1KO. [Conclusion] In P/T, short lifespan was related with systemic inflammation, which might be due to upregulation of IFNγ producing from T cells and the suppression of $Foxp3^+$ regulatory T cells.

W67-5

Thymic differentiation pathway for self reactive $CD4^+$T cells in central tolerance

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Conflict of interest: None

[Background] In the thymus, most T cells expressing high-affinity receptors for systemic self-antigen are eliminated by clonal deletion and become unresponsive to self -antigen before their release to periphery. On the other hand, some self-reactive T cells differentiate into $Foxp3^+$ regulatory T cells (Treg) in the thymus. However, it is still unclear whether there is a novel differentiation pathway for self-reactive $CD4^+$ T cells. [Method] We have created "Rag-DBL" mouse strain by crossing Rag-2 deficient DO11.10 mice with the mice expressing OVA systemically in the nuclei. In the current study, we generated the mouse strain by crossing Rag-DBL mice with scurfy mice (RDBLSf), in which T cells have a single TCR against systemic autoantigen, and lack both TCR revision and the expression of Foxp3. [Results] RDBLSf mice developed dermatitis, whereas they did not develop inflammation in other organs. In RDBLSf mice, $CD4^+CD8^-$ T cells with a single TCR specific for self-antigen were found in the thymus and periphery. These $CD4^+$ T cells were anergic in vivo. We also confirmed the presence of this novel $CD4^+$ T cell differentiation pathway paralleled with Treg and TCR revision in WT mice. [Conclusion] We found a novel differentiation pathway of self-reactive T cells in the thymus.

W68-1

Age at corticosteroid administration is associated with development of osteonecrosis in SLE patients

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Conflict of interest: None

[Objectives] To clarify whether age at corticosteroid adminis-

tration is a risk factor for corticosteroid-associated osteonecrosis in SLE using MRI. [Methods] We used MRI to prospectively study 676 joints, including 72 joints (36 hips, 36 knees) in 18 pediatric SLE (<15 years old), 100 joints (50 hips, 50 knees) in 25 adolescent SLE (15-20 years old), and 504 joints (252 hips, 252 knees) in 126 adult SLE (>20 years old), beginning just after corticosteroid administration, for at least 1 year. The follow-up rate was 100%. [Results] Osteonecrosis developed in 4 joints (6%) including 4 hips in pediatric, 49 joints (49%) including 18 hips and 31 knees in adolescent, and 207 joints (41%) including 95 hips and 112 knees in adult. The rate of osteonecrosis was significantly lower in pediatric than in adolescent or adult (p=0.0001). Logistic regression analysis revealed that age at corticosteroid administration was an independent risk factor for osteonecrosis with an odds ratio of 10.3 (p<0.0001). The youngest patients with osteonecrosis in the hip and knee were 14.9 and 15.5 years old, respectively. Osteonecrosis did not develop in patients under 14 years old. We suggest that age at corticosteroid administration is associated with osteonecrosis in SLE.

W68-2

Treatment of macrophage-activation syndrome in systemic lupus erythematosus

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Conflict of interest: None

[Background] The treatment for SLE-assocated macrophage-activation syndrome (SLE-MAS) has not been established so far. [Method] The clinical data, treatment regimens, and clinical courses of SLE-MAS patients from 2007 to 2011 in our hospital were examined retrospectively. [Results] Eight cases(2 male and 6 female) with SLE-MAS were detremined. They were 24-59 years old (mean age was 38.9), and the follow-up duration was 6-192 months (mean 52.6). All the cases were treated with high-dose steroid, and 7 cases with steroid pulse therapy. Five cases were treated with steroid alone, and 2 cases among them were additionally treated with immunosupressants (cyclosporine, and cyclophosphamide) later because of the steroid-resistant disease. Three patients were treated with both steroid plus cyclosporine early in the courses. MAS was improved in all the caes. One patients treated with steroid alone showed a relapse of MAS. Severe adverse events due to the therapies occured in 3 cases (2 cases of cytomegalovirus infections, and 1 case of osteonecrosis), and all of them were treated with stroid alone. [Conclusion] The combination therapy of steroid and immunosuppressant is strongly recommended from the early courses of SLE-MAS to avoid the adverse events and relapses.

W68-3

Study on the safety and efficacy of hydroxychloroquine (HCQ) in patients with systemic lupus erythematosus (SLE) complicated with active skin lesion

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Conflict of interest: None

[Objectives] Although HCQ is widely used for the standard treatment in SLE, it is impossible to use HCQ in Japan. We evaluate the efficacy and safety of HCQ in SLE patients with active skin lesion. [Methods] The subjects are the patients who were diagnosed with SLE but were not complicated with retinopathy. The IC was obtained. The primary endpoint was the CLASI improvement and the secondary endpoint were SLEDAI, the dose of CS tapered at 24 weeks. [Results] Case 1: A 37-year-old female who had been administered CS for 10 years. After HCQ treatment, CLASI decreased from 18 to 6, and SLEDAI decreased from 8 to 4, and CS was tapered from 10 to 2.5 mg. Case 2: A 54-year-old female who had been administered CS, CsA, TAC, MTX and AZ for 5 years. After HCQ treatment, following improvement of rash and arthritis, CLASI decreased from 10 to 2, and SLEDAI decreased from 8 to 2 and CS was tapered from 4.0 to 3.0 mg. Case 3: A 29-year-old female who had been administered CS, CsA, TAC, MTX and AZ for 7 years. After HCQ treatment, following improvement of rash and leukocytopenia, CLASI decreased from 11 to 3, and SLEDAI decreased from 3 to 0 and CS was discontinued. No adverse event was observed. HCQ can be a tolerable and effective option for SLE complicated with active skin lesion.

W68-4

Efficacy of oral thrombopoietin in intractable thrombocytopenia complicated with systemic lupus erythematosus

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Conflict of interest: None

Thrombocytopenia is one of the most important symptoms of systemic lupus erythematosus (SLE). We report 2 SLE patients with intractable thrombocytopenia who were treated by an oral thrombopoietin, eltrombopag. They were resistant to various therapies including glucocorticoid (1.0mg/kg/day), immunosuppressants (azathioprine, cyclophosphamide, tacrolimus, and cyclosporine A), a biological agent, rituximab, and a testosterone derivative, danazol. Case 1 (46 y.o., female) responded, whereas Case 2 (58 y.o., female) did not responded to eltrombopag. Reasons for differences in response to this drug will be discussed with references of the previous reports.

W68-5

Treatment of refractory SLE with combination of tacrolimus and mizoribine.

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Conflict of interest: None

As induction therapy for refractory SLE, such as lupus nephritis and cytopenia, we have focused on combination therapy with tacrolimus(TAC) and mizoribine(MZR). There were 8 patients (average age: 43 years, 8 women) treated with this protocol since April 2009. Five cases were affected with lupus nephritis, two were with refractory cutaneous involvement with hypocomplementemia, and a case with refractory cytopenia. All cases showed improvement of clinical findings, decrease of autoantibodies, and elevation of complement after initiation of this treatment. We could reduce the initial dose of predonisolone and also taper it rapidly, so it made their hospitalization shorter. One case presented cardiac hypertrophy which was due to TAC administration (and it resolved with discontinuation of this drug), and another case died from

cryptococcal meningitis 9 months after the initiation of the therapy. It seems that the combination therapy with TAC and MZR is effective for induction of SLE. We discussed the efficacy and safety of this therapy based on the clinical outcome of 8 cases.

W68-6

Clinical Trial for the prevention of steroid-induced osteonecrosis of femoral head in systemic lupus erythematosus by anticoagulant and statins

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Conflict of interest: None

[Objectives] Osteonecrosis of femoral head (ONF) is one of the serious complications in systemic lupus erythematosus (SLE) associated with corticosteroid therapy. We performed prospective study to prevent ONF using anticoagulant and statins. [Methods] Warfarin and statins were given to SLE patients who were newly diagnosed and treated with 40mg or more prednisolone. Prophylaxis continued for three months, and the development of ONF was evaluated by MRI. [Results] In 35 patients (male 5, female 30, average age at diagnosis 36 years), ONF developed in eight patients (23%), which tended to be fewer than that in non-prophylactic control in the previous trial (34%). Six patients showed MRI abnormality in 3 months. Serum total cholesterol levels at first month after the treatment were higher in patients who developed ONF than those in patients who did not develop ONF. Prophylactic use of warfarin and statins tended to reduce the incidence of ONF, although not statistically significant, in patients with SLE.

W69-1

Soluble Form of Herpesvirus Entry Mediator (HVEM) Is Elevated in Sera of Active Connective tissue diseases; a Candidate of New Biomarker of Disease Activity

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Conflict of interest: None

Purpose: To determine whether there exists soluble form of herpesvirus entry mediator (HVEM), a receptor of LIGHT and a ligand for BTLA and CD160, in sera from connective tissue diseases (CTDs), and to clarify clinical importance of sHVEM in CTDs. **Methods:** We developed a EIA system for detection of soluble HVEM (sHVEM) and examined sera from SLE (n=44), RA (n=63), scleroderma (SSc)(n=21), vasculitis(n=21), and healthy controls(n=42). Clinical features of the patients were examined by reviewing medical records. **Results:** Serum levels of sHVEM in controls were 1.93+0.85ng/ml. Serum sHVEM levels were elevated in sera from SLE, RA, SSc and vasculitis compared to controls. In SLE, patients with low complement levels or high anti-DNA titers showed high sHVEM levels. In RA, sHVEM levels from patients with moderate to high disease activity were higher than those with remission or low disease activity. Moreover, immunosuppressive therapy reduced sHVEM levels significantly in active CTDs. **Conclusion:** sHVEM exists in human sera. Serum levels of sHVEM were elevated in varieties of CTDs compared to controls. The elevation of sHVEM reflects disease activity and treatment reduced titer of the molecules. Soluble form of HVEM could be a candidate of new biomarker of disease activity of CTDs.

W69-2

Analysis of DNase1 in autoimmune diseases

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Conflict of interest: None

【Introduction】Deoxyrubonuclease1(DNase1) is the primary enzymes for the metabolism and clearance of DNA, and involved in the process of apoptosis. In addition, it has been reported the serum DNase1 activity was significantly decreased in patients with systemic lupus erythematosus (SLE) compared with healthy controls. We examined DNaseI activity among various autoimmune diseases.【Methods】We measure the serum DNaseI activity in patients with rheumatoid arthritis (RA), Sjogren's syndrome (SjS), vasculitis and SLE using single radial enzyme-diffusion (SRED) method.【Result】The serum DNase1 activity was significantly decreased in patients with active SLE compared with those with inactive SLE or healthy controls. The serum DNaseI activity of RA and SjS patients was normal level. The serum DNaseI activity decreased inpatients with vasculitis compared with healthy controls.【Conclusion】The serum DNaseI activity decreased in patients with activity SLE and vasculitis, and it was suggested to be related to the onset and condition of each disease. However, it is necessary to analyze DNaseI activity in more number of patients with vasculitis.

W69-3

Comprehensive evaluation of clinical features and therapeutic response by multiple modalities in NPSLE patients

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Conflict of interest: None

[Objectives] It is hard to make the diagnosis and to evaluate of therapeutic efficacy in NPSLE. We investigated contribution of multiple examinations including CNS imaging, EEG, and CSF to clinical assessment of each subgroup of ACR-defined NPSLE syndromes. [Methods] We retrospectively analyzed clinical features and the findings of CNS examinations in 39 patients with NPSLE. [Results] The diagnosis of NPSLE was made within a year from SLE onset in about a half of the patients including 9 complicated with APS. The patients were categorized into 3 groups; central nerve symptoms (group N, n=12), psychiatric symptoms (group P, n=13), combined (group N+P, n=14). MRI revealed focal hyperintensities of the white matter (WM) in all groups as the most common finding and diffuse hyperintensities of WM in 50% of group N. Atrophy of cerebral parenchyma was frequently found in group P. SPECT showed cerebral hypoperfusion, particularly in the frontal and parietal lobes in all patients. Of 15 patients having Follow-up SPECT studies, restored perfusion was associated with clinical amelioration responding the therapy in 8 patients. EEG abnormality was more prevalent in group P and N+P than group N. Compre-

hensive evaluation by multiple modalities is essential for clinical assessment of NPSLE.

W69-4

Clinico-radiological features of chronic interstitial pneumonia with systemic lupus erythematosus

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Conflict of interest: None

[Objectives] We examined the clinical and radiological features of chronic interstitial pneumonia (CIP) with systemic lupus erythematosus (SLE). [Methods] Subjects included 13 SLE-CIP patients (10 women, mean age 54 years). [Results] Three patients had systemic sclerosis (SSc), 1 had dermatomyositis (DM), 5 had Sjögren syndrome, 2 had mixed connective tissue disease, and 1 had rheumatoid arthritis associated with SLE (some patients had multiple conditions). Raynaud's phenomenon was observed in 77%, arthritis in 69%, and renal involvement in 23%. Autoantibodies, including speckled type of antinuclear antibody was observed in 85% of patients, anti-RNP antibody was found in 69%, and 3 were positive for anti-CCP antibody. High-resolution computed tomography (HRCT) of the chest showed a reticular shadow and ground-glass opacity on the dorsal side of both lower lungs in all patients. Linear opacity, traction bronchiectasis, and honeycomb-like cysts were observed in 77%, 46%, and 38% of patients, respectively. Lung cysts were observed in 2 patients who had positive anti-SS-A antibodies. The characteristics of SLE-CIP were elderly age and presence of other collagen diseases. HRCT of the chest had features of pulmonary lesions of collagen diseases associated with SLE.

W69-5

Coincidence of tuberous sclerosis and systemic lupus erythematosus

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Conflict of interest: None

<Introduction> Tuberous sclerosis is a rare autosomal dominant hereditary disease. Two causative genes, TSC1(hamartin) and TSC2(tuberin) have been identified. As a mutation in one of these genes can result in failure of suppression of mTOR signaling, treatment with rapamycin is thought to be effective for treating some tumors. On the other hand, mTOR signaling has been demonstrated to be increased in SLE T cells and rapamycin can be an effective treatment for SLE. However, there has not been a report of coincidence of these two diseases. <Case> A 22-year-old woman with tuberous sclerosis was visitted to our medical center, because of proteinuria. Bilateral renal angiomyolipoma, angiofibroma, facial shagreen patch, deformity of aorta, and infantile spasms was consistent with TSC. A diagnosis of SLE was made, because of positive results of autoantibodies against nucleus, ds-DNA, SSA, and SSB; lymphopenia; and proteinuria (6 g/day). After intiation of 40 mg of predonisolone resulted in ameliolation of proteinuria (1.5 g/day). <Discussion> This patient is the first case of coincidence of tuberous sclerosis and systemic lupus erythematosus. To investigate the involvement of mTOR signaling for lupus pathogenesis, both elucidation of genetic abnormality and the use of rapamysin are feasible.

W70-1

Clinical significance of anti-aminoacyl tRNA synthetase antibodies in our hospital patients with various autoimmune diseases.

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Conflict of interest: None

[Objectives] Anti-Jo-1 antibody is especially found in patients with polymyositis (PM) and dermatomyositis (DM). It is known that the target antigen of Jo-1 is histidyl-tRNA synthetase. Recently, several autoantibodies to other aminoacyl-tRNA synthetases (ARS) are detected. We evaluated clinical significance of anti-ARS antibodies in patient with various autoimmune diseases. [Methods] Serum samples from 77 patients were used in this study, including PM, DM, systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), Sjögren's syndrome (SjS), and systemic sclerosis (SSc). The immuno reactivitiy of serum for ARS was studied by commercially available Myositis antigens Profile 3 kit (Euroimmune Lübeck, Deutschland). Then, clinical manifestations were determined. [Results] Anti-ARS antibody was especially found in sera from interstitial lung disease (ILD) associated with PM/DM. Moreover, this autoantibody was also detected in sera with RA patients who had ILD. In PM/DM patients, who were negative for anti-Jo-1 antibody but showed a positive ANA with a cytoplasmic staining pattern, other anti-ARS antobodies were often positive. It is suggested that the ILD patients associated with PM/DM who had autoantibodies against ARS required high dose of steroid and immunosupressive agents.

W70-2

Aquaporin-4 antibodies as a surrogate marker of neuromyelitis optica with SLE/SS

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Conflict of interest: None

[Objectives] To assess the association between serum aquaporin-4 (AQP4) autoantibodies and neuromyelitis optica spectrum disorders (NMOSDs) associated with systemic autoimmune diseases. [Methods] We retrospectively studied 626 hospitalized patients with systemic lupus erythematosus (SLE) or Sjögren's syndrome (SS). We collected serum samples from those patients with suspected NMOSDs (i.e., myelitis or optic neuritis) at the time of onset and thereafter. AQP4 antibodies were measured by a cell-based indirect immunofluorescence assay using AQP4-transfected HEK-293 cells in a semi-quantitative manner. [Results] Sera from 6 patients with suspected NMOSDs and SLE (n = 3) or SS (n = 3) were evaluated. Among these, 2 patient sera samples, i.e., 1 with SLE and 1 with SS, were positive for AQP4 antibodies. There was an inverse relationship between disease amelioration and antibody titer in one NMOSD patient, whereas the antibody titer remained high in the other NMOSD patient, whose clinical manifestations of NMOSDs did not improve despite intensive immunosuppressive treatments. These results indicate that serum AQP4 antibodies are

present in some SLE/SS patients with myelitis/optic neuritis and might be associated with clinical outcomes.

W70-3

Association of anti-U1RNP antibodies with soluble factors in cerebrospinal fluid from neuropsychiatric systemic lupus erythematosus patients

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Conflict of interest: Yes

Objective. To determine an association between anti-RNA binding protein (RBP) antibodies (Abs) in cerebrospinal fluid (CSF) and soluble factors from systemic lupus erythematosus (SLE), mixed connective tissue disease (MCTD), and Sjögren's syndrome (SS) patients with neuropsychiatric (NP) manifestations. Methods. Anti-RBP Abs in sera and CSF were detected by RNA-immunoprecipitation in the enrolled 82 patients. Concentrations of 8 soluble factors in CSF, which had been previously reported to be increased in NPSLE, were determined by multiplex suspension array. Results. In 17 patients with CSF-anti-RBP Abs, headache (29%) and psychosis (24%) were frequently observed. Anti-U1RNP (88%), SS-A/Ro (24%), and Sm (6%) Abs were found in CSF from NPSLE patients. No soluble factors in CSF were more increased from patients with than without serum-anti-RBP Abs. Elevated levels of IFN-α and MCP-1 in CSF, however, were associated with CSF-anti-U1RNP Ab, but not anti-SS-A/Ro Ab positivity. RANTES, MIG, IL-8, IP-10, fractalkine, IL-6 levels in CSF were not different between in CSF anti-RBP Ab-positive and -negative patients. Conclusion. In NPSLE patients, the elevated IFN-α and MCP-1 levels in CSF may be involved in the pathogenesis of anti-U1RNP Ab-associated NPSLE.

W70-4

Long pentraxin PTX3 as a predictive marker for severity in systemic lupus erythematosus

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Conflict of interest: None

[Objectives] Pentraxin 3 (PTX3), the long pentraxin, has been implicated in inflammation and immunity. We previously presented that plasma PTX3 levels were increased in SLE patients with high disease activity, and especially high in neuropsychiatric SLE. We examined whether PTX3 predict disease severity and prognosis in patients with SLE. [Methods] Plasma PTX3 concentrations were measured in 70 patients with SLE and 53 healthy controls by ELISA. [Results] PTX3 levels were significantly higher in patients with SLE than those of controls. Among patients with SLE, PTX3 were correlated with SLEDAI. PTX3 markedly increased in patients with transverse myelitis and psychosis but not in patients with cerebrovascular diseases. SLEDAI values at presentation equal to or greater than 20, as a summary measure of multiple features of active SLE, were known to be a prognostic factor for mortality. Plasma PTX3 levels in patients with SLEDAI□20 were significantly higher in patients with SLEDAI<20. PTX3 was also correlated with maximum dose of prednisolone administered for treatment of active SLE. PTX3 would be a predictive marker for severity in patients with SLE.

W70-5

Increased concentration of serum soluble LAG3 in systemic lupus erythematosus

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Conflict of interest: None

[Objectives] In systemic lupus erythematosus (SLE), type I interferon and plasmacytoid DC (pDC) are supposed to play important roles. However, there are few evidences for pDCs activation in SLE. Murine pDCs are reported to produce soluble LAG3 (sLAG3) upon activation and pDCs are responsible for most of sLAG3 in mice serum. [Methods] We enrolled 60 SLE patients who met ACR criteria. Disease activity was rated using a SLE disease activity index (SLEDAI). sLAG3 concentrations were measured by a quantitative sandwich enzyme immunoassay. Type I IFN signature expression in peripheral blood mononuclear cells (PBMCs) was measured by qRT-PCR. [Results] The ratio of sLAG3 concentration in SLE to control was 36.2+/-21.5, and RA to control was 1.33+/-0.77. In addition, sLAG3 concentrations showed a significant correlation with SLEDAI and association with hematological and renal disorders. Moreover, sLAG3 exhibited significant association with type I IFN signature, such as Mx-1, in PBMCs. These results suggested that sLAG3 in sera of SLE patient may reflect the activation of pDCs and could be a specific and novel marker for SLE.

W70-6

Elevated serum levels of progranulin in patients with SLE

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Conflict of interest: None

[Objectives] Recently, it has been reported that progranulin (PGRN) is a soluble cofactor for TLR9 signaling. The aim of this study was to investigate associations between PGRN and clinical and serologic parameters of SLE, and its role in SLE. [Methods] Serum levels of PGRN were measured by ELISA in patients with active SLE(n=46), inactive SLE(n=23), RA(n=22) and healthy controls(n=32). We also measured the levels of IL-6 secreted by peripheral blood mononuclear cells(PBMCs) from healthy donors in the presence or absence of anti-PGRN under the stimulation with 20% SLE patient's serum for 24-hour. [Results] Serum levels of PGRN were significantly higher in SLE patients than those in RA patients and healthy controls. They were significantly correlated with rash, alopecia, serositis, arthritis, and cytopenia. They were also significantly correlated with SLEDAI and the serum levels of anti-ds DNA antibodies, CH50, C3, and C4. Moreover, they were significantly decreased following treatment. The neutralization of PGRN in the patient's serum significantly decreased the IL-6 levels secreted by PBMCs. [Conclusion] These findings indicate that PGRN is associated with SLE global activity and may have a role in the pathogenesis and exacerbation via increased cytokine pro-

duction.

W71-1

Corticosteroid sensitive IgG4-related pleuritis without sclerosing lesions; a new clinical entity?

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Conflict of interest: None

Objective: IgG4-related diseases are characterized by elevation of serum IgG4 and sclerosing lesions. We often experience pleuritis with hyper-IgG4 globlinemia. Clinical features of this type of pleuritis are unknown. To clarify clinical features of this type of pleuritis, we examined serum IgG4 levels and clinical features of pleuritis patients with elevation of serum IgG4 levels. **Methods:** Medical records were reviewed retrospectively. Serum IgG4 levels were examined in 352 patients with various inflammatory diseases. Patients with pleurtis received thoracoscopy (TS). Samples of pleural biopsy were stained with anti-IgG4 antibody. **Results:** In 352 cases, 90 patients showed elevation of serum IgG4 cases more than 100mg/dl. Pleuritis was found in 11 out of 90 (12%) patients with hyper-IgG4 globlinemia. None of pleuritis patients with elevated IgG4 levels had sclerosing lesions. TS was performed in 11 patient and IgG4 cell infiltration was found in 4 out of 6 biopsy samples. All of 3 patients received corticosteroid improved pleuritis. **Conclusion:** Our study suggests existence of corticosteroid sensitive IgG4-related pleuritis without sclerosing lesions, which might be a new clinical entity.

W71-2

Analysis of IgG4 class switch-related molecules in IgG4-related disease

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Conflict of interest: None

<Objective> IgG4-related disease (IgG4-RD) is a new disease entity characterized by high serum IgG4 levels, IgG4-positive plasmacytic infiltration and fibrosis in various organs. The purpose of this study was to determine the mechanism of up-regulation of IgG4 class switch recombination in IgG4-RD. <Methods> We extracted RNA from PBMC of patients with IgG4-RD (n=4), Sjögren's syndrome (SS) (n=5), and healthy control (n=5), as well as labial salivary glands (LSG) of patients with IgG4-RD (n=11), SS (n=13), and healthy control (n=3). The mRNA expression levels of IgG4-specific class switch-related molecules, such as Th2 cytokines (IL-4 and IL-13), Treg cytokines (IL-10 and TGFβ), transcriptional factors (GATA3 and Foxp3) were examined by quantitative PCR. IgG4-non-specific class switch related molecules, such as CD40, CD154, BAFF, APRIL, IRF4, and AID were also examined. <Results> The expression levels of Treg cytokines (IL-10 and TGFβ) and AID were significantly higher in LSG of IgG4-RD than SS and the control ($P<0.05$). In contrast, that of CD40 was significantly lower in PBMC of IgG4-RD than SS and control ($P<0.05$). <Conclusion> Overexpression of IL-10, TGFβ, and AID in LSG might play important roles in the pathogenesis of IgG4-RD.

W71-3

Clinicopathological characteristics and their changes associated with corticosteroid therapy in IgG4-related kidney disease

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Conflict of interest: None

[Objectives] To clarify the clinicopathological characteristics and their changes associated with corticosteroid therapy in IgG4-related kidney disease (IgG4-RKD). [Methods] We evaluated clinical data, imaging studies, and histological and immunohistochemical findings before and after corticosteroid therapy in 11 patients with kidney involvement among 33 IgG4-related patients. [Results] Elevated serum creatinine levels and abnormal radiological findings rapidly improved after corticosteroid therapy, but renal insufficiency and focal cortical atrophy persisted in some cases. Histologically, dense lymphoplasmacytic infiltration, interstitial fibrosis, and IgG4+ plasma cell and Foxp3+ cell infiltration were characteristic before therapy. After therapy, the area with cell infiltration decreased and regional fibrosis became evident in the renal interstitium. The number of IgG4+ plasma cells and Foxp3+ cells significantly diminished even in the early stage of therapy, while low to moderate numbers of CD4+ T cells and CD8+ T cells still infiltrated where inflammation persisted in the later stage. Persistent renal insufficiency associated with atrophy and fibrosis is not so rare in IgG4-RKD. Relation between clinical course and behavior of infiltrating cells should be further investigated.

W71-4

IL-6 blocking therapy by tocilizumab in patients with multicentric Castleman's disease results in a significant decrease in serum IgG4/IgG ratios

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Conflict of interest: None

[Objectives] An increase in serum IgG4 levels in patients with multicentric Castleman's disease (MCD) is frequently observed. Blocking IL-6 with tocilizumab (TCZ) ameliorates not only systemic inflammatory symptoms but also abnormal laboratories including hyper-γ-globulinemia. The purpose of this study is to analyze differences in clinical features between MCD patients with high serum IgG4 and those with normal serum IgG4 as well as changes in serum IgG subclass levels of MCD patients by TCZ treatment. [Methods] Serum levels of total IgG and four IgG subclasses of 18 MCD patients were measured. Eleven were treated with TCZ, and serum IgG subclass levels were compared before and after the treatment. [Results] Serum IgG4 levels at baseline were elevated in 12 of 18 MCD patients (542.2±387.7 mg/dl, n=12). Clinical features between MCD patients with high serum IgG4 and those with normal serum IgG4 were not distinct. While the mean absolute number of each IgG subclass was significantly decreased after TCZ treatment, the mean ratio of only IgG4 to total IgG was significantly decreased (7.4% vs. 5.5%, $p<0.05$). The production of total and four subclasses of IgG depends on IL-6. A decrease in the IgG4/IgG ratios after TCZ treatment implies that IL-6 may be involved in the class switch to IgG4.

W71-5

Relapse of IgG4-related disease after corticosteroid therapy

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Conflict of interest: None

[Objective] To examine relapse of IgG4-related disease [Methods] We retrospectively examined relapse in 18 patients with IgG4-related disease who had been treated with prednisolone at Nagaoka Red Cross Hospital between 1996 and 2010. [Results] The mean follow-up period after treatment was 5.1 years (range 1 - 15 years). The main targets of treatment in these cases included autoimmune pancreatitis in 5 patients, tubulointerstitial nephritis in 5, lung lesions in 3, Mikulicz's disease in 2, orbital tumor in 1, pelvic tumor in 1 and retroperitoneal fibrosis in 1. The initial dose of prednisolone was 15-60 mg/day (mean 34.7 mg). All 18 patients responded to prednisolone therapy, and prednisolone was successfully withdrawn without relapse in the 1 patient with retroperitoneal fibrosis. Among the other 17 patients who were maintained with prednisolone (mean maintenance dose 5.0 mg/day), 4 relapses occurred: lymph-node swelling in one patient with tubulointerstitial nephritis and one with orbital tumor, and swelling of the salivary and lacrimal glands in 2 patients with Mikulicz's disease. [Conclusion] Our findings suggest that relapse may easily occur in lymphoplasma cell-rich organs in patients with IgG4-related disease.

W71-6

Corticosteroid maintenance therapy in IgG4-related disease

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Conflict of interest: None

[Objectives] To evaluate the incidence of newly developed lesions, recurrent lesions in the original organs and allergy-related symptoms in patients (Pts) with IgG4-related disease (IgG4-RD) during corticosteroid (prednisolone: PSL) maintenance therapy (mTx). [Methods] Patients with IgG4-RD (n=24) who were treated with PSL for more than 12 months were studied. Newly developed lesions, recurrent lesions in the original organs or allergy-related symptoms that developed during the mTx were noted. [Results] Ten Pts had neither recurrence nor allergy-related symptoms during mTx (average follow-up: 28.4 months, prednisolone dose: 3-7mg). Four Pts had recurrent lacrimal or salivary gland lesions, 2 recurrent or newly developed skin lesions, 1 recurrent kidney lesion, and 1 exacerbated lung lesion with fatal outcome. One Pt underwent vascular surgery because of worsened inflammatory abdominal aneurysm. Five Pts had recurrence of allergy-related symptoms. Only 3 Pts (skin, kidney, and lung) needed increased doses of PSL. [Conclusions] These data suggest that frequent recurrent symptoms in Pts with IgG4-RD under PSL mTx are reswelling of lacrimal or salivary glands or allergy-related symptoms, while PSL mTx seems to be effective in preventing severe recurrence.

W72-1

Analysis of the cases with IgG4-related disease presented with steroid-resistant

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Conflict of interest: None

[Objectives & methods] Steroid therapy is shortly effective for remission in IgG4-related disease (IgG4-RD), but most cases suffer from relapse. So we analyzed efficacy of rituximab (RTX) for IgG4-RD. [Results] Patient 1. A 41-year-old female suffered from Mikulicz's disease (MD) with lymphoma, and breast involvements. She was treated with chemotherapy. She consulted to us for swelling of submandibular glands (SG) 10 years later. SG specimen showed IgG4+plasmacytes infiltration without IgH-rearrangement. We made no treatment for it, but soon prescribed with RTX for new lymph node (LN) involvements. RTX led to remission, but SG lesion appeared after a year. Patient 2. A 57-year-old man was investigated for systemic lymphadenopathy. Abdominal MRI revealed mass lesion in liver. He was diagnosed as multicentric Castleman's disease by LN and liver biopsies. He was treated with RTX, but intrahepatic lesion developed with elevated level of serum IgG4 after 6 years. He was rediagnosed as IgG4-related cholangitis. Patient 3. A 60-year-old woman had MD and autoimmune pancreatitis. She experienced twice relapse for 3 years. RTX could reduce steroid without relapse for 6 months. [Conclusions] RTX is effective for clinical remission of IgG4-RD, but it is necessary for maintenance therapy.

W72-2

Clinical features of IgG4-related respiratory disease - a multicenter retrospective study -

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Conflict of interest: None

Aims: The aim of this study is to clarify the clinical characteristics of IgG4-related respiratory lesions. **Methods:** A multicenter retrospective study was performed through the Japanese Government Research groups. We collected data for 74 cases with respiratory lesions, and analyzed 60 cases. **Results:** Sixty-five patients (male44: female 16) were identified. The mean age was 64 years old. Thirty -one patients (35%) had a history of allergy, and 10 patients (17%) had only respiratory tract lesions. Mean serum IgG and IgG4 were 3459mg/dL, 1119mg/dl, respectively. Chest CT presented hilomediastinal lymphadenopathy, thickening of the bronchial wall and bronchovascular bundles, diffuse or local pul-

monary infiltration and various other findings. **Conclusion:** The cases with only respiratory lesions are difficult to diagnose as IgG4-related disease.

W72-3

The current situation of diagnostic approach for IgG4-related systemic disease at 6 institutes in Kagawa Prefecture

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Conflict of interest: None

[Objectives] Though elevated serum IgG4 {>135mg/dl} (esI4) are useful to diagnose IgG4-related systemic disease (IgG4-RSD), only esI4 may lead false-positive for IgG4-RSD diagnosis. We investigated the problems in IgG4-RSD diagnosis, including the significance of fluorodeoxyglucose-positron emission tomography (FDG-PET) findings. [Methods] We investigated the patient profiles examined serum IgG4 (sI4) retrospectively based on data sheet from 6 institutes in Kagawa Pref. for 2 years 3 months until November 2011. The reason of IgG4 analysis, the titer of sI4, major manifestations, and which imaging conducted were examined in each patient respectively. [Results] sI4 was examined in 178 cases. There were 39 esI4 cases and 23 IgG4-RSD cases. FDG-PET was performed in 10 of these cases. In IgG4-RSD patients with several involved organ involvement, FDG uptake into their lesions were relatively mild, while sI4 levels were remarkably elevated. However, in non- IgG4-RSD patients, sI4 level was not so much increased. Additionally, FDG uptake were not detected significantly. The analysis of FDG uptake and the titer of sI4 might be useful for making differential diagnosis IgG4-RSD from other diseases.

W72-4

Clinicopathological analysis of IgG4-related skin disease

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Conflict of interest: None

[Objectives] IgG4-related skin disease (IgG4-RSD) is not widely known. This prompted us to analyze its clinical and pathological features. [Methods] Five patients with IgG4-related disease (IgG4-RD) exhibiting skin lesions (SLs) were studied. We evaluated the onset of the eruptions, their regions and types, pathological features, affected organs and immunochemical tests. [Results] SLs appeared before the diagnosis of IgG4-RD in 3 Pts. SLs in IgG4-RD were erythematous nodule, erythematous papule and prurigo predominantly in the head and neck area. In all Pts, sialadenitis and/or dacryoadenitis were observed. The average serum levels of IgG and IgG4 were 2029.6±391.1 and 665.6±410.0 mg/dl, respectively. Infiltrations of IgG4-positive plasma cells and germinal center formations were observed in dermis in dermis and subcutaneous tissue. Three of the Pts exhibited mild fibrosis. The average count of IgG4-positive cells was 71.0/hpf (23.0-128.6). [Conclusions] SLs in IgG4-RD were most frequent in the head and neck area, and erythematous eruptions were dominant. A wide variation in the numbers of infiltrating IgG4-positive cells was seen. Because the eruptions developed before the diagnosis of IgG4-RD in 3 of the Pts, IgG4-RSD may exist in Pts whose skin disease was not correctly diagnosed.

W72-5

Serum IgG4 level and IgG4+ cell ratio in histopathology for diagnosis of IgG4-related disease.

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Conflict of interest: None

[Objectives and Methods] We assessed serological data of 132 cases of IgG4-related disease (IgG4-RD) and 48 of others, and histopathological findings of 36 of IgG4-RD and 21 others to evaluate which cut-off levels is more reliable for diagnosis of IgG4-RD. [Results] Sensitivity and specificity of serum IgG4 >135mg/dl and IgG4/IgG >8% are 97.0%/79.6% and 95.5%/87.5%, respectively. Sensitivities and specificities of cut-off level 40% or 50% in tissue are 94.4%/85.0%, and 94.4%/95.0%, respectively. However, numbers of IgG4+cells in the fibrotic lesion tend to be small, therefore some cases don't fill the cut-off of 50%. These results suggest that serum IgG4 >135mg/dl are reliable and IgG4/IgG >8% can assist to diagnose in some case. And cut-off level 40% in tissue is reliable for the criteria.

W72-6

Evaluation of IgG4+ cells in immunohistochemistry in IgG4 related diseases

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Conflict of interest: None

[Background] Quantitation of IgG4 producing cell by immunohistochemistry have been difficult because of technical limitations. [Objectives] To clarify technical problems in calculating quantity of IgG4 producing cells. [Methods] Percentages of IgG4 producing cells were compared in different immunostainings in 12 patients with non-IgG4 related diseases (IgG4RD) and 3 with IgG4RD. [Results] 1; The ratio of IgG4/IgG in IgG4RD showed more than 50%, but one showed >100% and non-IgG4RD showed 0-75%. 2;IgG4/IgG1+2+3+4 revealed no overlap between IgG4RD and non-IgGRD. 3;Staining with IgG2+3+4 could be done simultaneously. Conclusion) It was suggested that IgG subclass staining in immunohistochemistry was effective in evaluating IgG4 producing cells.

W73-1

Role of apolipoprotein B100 and oxidized low-density lipoprotein in anti-beta2 glycoprotein I induced tissue factor expression on monocytes

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Conflict of interest: None

Purpose: To explore plasma molecule involvement in the tissue factor (TF) expression induced by β2GPI dependent anticardiolipin antibody (aCL/β2GPI) on monocytes. Method: To identify β2GPI binding proteins, FLAG-tagged human β2GPI was constructed. Human serum sample with FLAG-β2GPI was incubated and applied for affinity chromatography with anti-FLAG antibody. The purified fractions were subjected to SDS-PAGE and were analysed by an online-nano LC-MS/MS. Obtained MS/MS data were searched against nrNCBI database using MASCOT algorithm. Result: Apolipoprotein B100 (APOB) was the only identified molecule as a candidate plasma protein. Since there was no significant binding between β2GPI and APOB in ELISA, oxidized LDL(Ox-LDL), containing APOB as well as ox-Lig1 (a known ligand of β2GPI) in its molecule, was considered as a β2GPI-binding molecule in plasma. The presence of Ox-LDL and WBCAL-1, a monoclonal aCL/β2GPI antibody, markedly increased TF mRNA expression on RAW264.7, a mouse monocyte cell line. Conclusion: Ox-LDL was detected as a major β2GPI binding plasma molecule by proteomics analysis. The presence of Ox-LDL up-regulated aCL/β2GPI induced TF expression on monocytes, suggesting the involvement of Ox-LDL in the pathophysiology of thrombosis in patients with APS.

W73-2

The clinical features of only positive for anticardiolipin antibodies or anti-β2-glycoprotein I antibodies

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Conflict of interest: None

[Objectives] The classification criteria for definite antiphospholipid syndrome (APS) includes anticardiolipin antibodies (aCL) and anti-β2-glycoprotein I antibodies (anti-β2GPI). However, these assays theoretically recognize the same antibody. The aim of this study was to investigate the significance to test both assays. [Methods] This study comprised 257 sera from patients who visited our autoimmune disease clinic including 40 with primary APS, 38 with APS complicated with SLE, and 179 with SLE in the absence of APS. EliA™Cardiolipin and EliA™β2-Glycoprotein (Phadia, Germany) were used to detect aCL IgG/M, anti-β2GPI IgG/M, respectively. Cut off value was defined using 99% tile of healthy subjects. [Results] Of 257 patients, 56 (21%) had either aCL or anti-β2GPI (44 patients had aCL alone and 12 anti-β2GPI alone). APS manifestations (past history of thrombosis or pregnant morbidity) were significantly more prevalent in the patients with anti-β2GPI alone than those with aCL alone (8/12 (67%) vs. 12/44 (27%), OR 5.3, 95%CI 1.35-21.0). [Conclusion] APS manifestations are prevalent in patients having either aCL or anti-β2GPI, although anti-β2GPI was more specific to APS manifestations than aCL. Concurrent detection of aCL and anti-β2GPI may improve the diagnostic yield of APS.

W73-3

Prophylaxis of recurrent arterial thrombosis in patients with antiphospholipid syndrome

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Conflict of interest: None

[Background] The optimal treatment for recurrent arterial thrombosis in patients with antiphospholipid syndrome (APS) is unclear. [Objective] To clarify the efficacy of prophylaxis for recurrent arterial thrombosis in patients with APS. [Patients and Methods] This study comprised 82 patients with APS with arterial thrombosis (female 67, age 44±16). We retrospectively assessed the efficacy of warfarin monotherapy (Group1: G1), antiplatelet monotherapy (Group2: G2), combination therapy of warfarin and antiplatelet agent (Group3: G3), and dual antiplatelet therapy (Group4: G4) in the secondary prevention of arterial thrombosis in patients with APS. [Results] The mean follow up period was 8.5 years (2-22). Thrombotic events recurred in 25(30%), (G1:G2:G3:G4 3:12:10:0). Thirteen (16%), (G1:G2:G3:G4 1:4:4:4) patients died and a total of 7 (9%), (G1:G2:G3:G4 2:1:4:0) had serious bleeding events. In Kaplan-Meier analysis, treatment with Group IV was more effective than other treatment groups (Log-rank p=0.01). There was no difference in the bleeding event and mortality between each group. [Conclusion] Dual antiplatelet therapy may be more appropriate therapy than others for prevention of recurrent arterial thrombosis in patients with APS.

W73-4

Risk factors for Mixed Connective Tissue Disease in a Japanese Population: a Case Conrol Study

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Conflict of interest: None

[Objectives] A case control study was conducted to investigate risk factors for the development of mixed connective tissue disease (MCTD) in a Japanese Population [Methods] Cases were MCTD patients while controls were so called healthy subjects. Unconditional logistic regression analysis was used to compute the Odds ratios (ORs) and their 95% confidence intervals, with adjustments of age and sex. P<0.05 was considered as statistically significant. [Results] Walking (30 min / day or more) (OR=2.6) and medical history of collagen diseases (OR=35.7) increased the risk of MCTD. In contrast, medical histories of allergy (OR=0.35) and atopic dermatitis (OR=0.33) showed a nonsignificant decreased risk of MCTD. Neither smoking nor drinking showed any meaningful relation to the risk of MCTD. This work was partly supported by Health and Labour Sciences Research Grants, Research on Intractable Diseases from the Ministry of Health, Labour, and Welfare, Japan.

W73-5

Clinical characteristics of aseptic meningitis in mixed connective tissue disease.

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Conflict of interest: None

Objective: To assess the clinical characteristics of aseptic meningitis associated with mixed connective tissue disease (MCTD). Methods: 5 patients with MCTD were evaluated to clinical characteristics and treatment. Results: All of patients were women and their mean age was 29.6 years old (range 19-54). Two patients received oral prednisolone, and 1 patient received cyclosporine A and azathioprine, and 2 patients had been followed without medication. Headache and high fever were the most frequent clinical symptoms and observed in 4 patients. One patient might be caused by Non-Steroidal Anti-Inflammatory Drug. IgG index was 0.7 (0.61-0.83), and IL-6 were increased with 3647 pg/ml (1080-6950 pg/ml) in cerebrospinal fluid by 3 patients. Three patients were treated for aseptic meningitis with methylprednisolone pulse therapy, followed by oral prednisolone with favorable response. The mean time of the improvement was 7 days. The recurrences of meningitis were found 2 patients. Conclusion: Aseptic meningitis in MCTD is an important complication, and we reported 5 cases of aseptic meningitis in MCTD with the review of the previous literature.

W73-6

Anti-U1RNP Ab and inflammatory cytokines induce the splice variant of *Tie-2* in human pulmonary artery smooth muscle cells

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Conflict of interest: None

[Objectives] We previously found that the angiogenic factor Angiopoietin-1 (*Ang-1*) splice variant (*Ang-1*/ins) was significantly induced in the patients with MCTD. We also found that *Ang-1*/ins was induced with the introduction of anti-U1RNP Ab cultivated with TNFα and IL6 in human pulmonary artery smooth cells (HPASMC). This suggests that anti-U1RNP Ab interferes the splicing of many genes including *Ang-1*, because U1RNP is the general splicing factor. A tyrosine kinase receptor Tie-2 which is the receptor of Ang-1 has also some splice variants. Here we examined the splicing interference for *Tie-2* with anti-U1RNP Ab and inflammatory cytokines in HPASMC. [Methods] We introduced anti-U1RNP Ab into HPASMC by using protein delivery reagent (PULSin) and stimulated with TNFα and IL6. After 24 hours, we analyzed the sequence of RT-PCR product of *Tie-2*. [Results] Anti-U1RNP Ab and inflammatory cytokines induced the splice variant of *Tie-2* lacking exon 7 in HPASMC. [Conclution] Our result showed that anti-U1RNP Ab and inflammatory cytokines also interfere the splicing of *Tie-2* as in the case with *Ang-1*.

W74-1

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 clinical efficacy of ABT in Japanese is still unknown. [Methods] Ninety-four RA patients treated with ABT for longer than 24 weeks were included, from the 153 patients with ABT therapy in the Tsurumai Biologic Communication (TBC), which is the multicenter registry for RA patients taking biologics. We retrospectively reviewed the clinical data. [Results] Mean age was 63.5 years and mean disease duration was 10.5 years. Fifty-seven patients (63%) were taking methotrexate. Thirty-seven patients were biologics naïve and forty-two patients had previous biologics history. Mean DAS28ESR before abatacept therapy was 5.23, mean CDAI was 24.5, and SDAI was 26.8. Drug survival rate was 81.9% at 24 weeks. Patient global assessment, swollen/tender joint counts, and serum CRP were significantly decreased at 4 weeks, while ESR decreased at 12 weeks. Taking methotrexate brought no change on response to abatacept. The biologics naïve patients showed better responsiveness to ABT therapy compared to the patients with previous biologics. ABT showed good clinical efficacy and safety in Japanese RA patients.

W74-2

Clinical Efficacy of Abatacept in Japanese Rheumatoid Arthritis Patients in the TBC registry

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Conflict of interest: None

[Objectives] Abatacept is a new biologic drug and has been available for rheumatoid arthritis (RA) patients since 2010 in Ja-

pan. We need the clinical data in Japanese patients to improve our way of ABT therapy. In this study, we studied the effect of disease duration on clinical efficacy of ABT therapy. [Methods] Thirty-six patients who were biologics naïve and taking ABT therapy for longer than 24 weeks were included, from the 143 patients with ABT therapy in the Tsurumai Biologics Communication Registry (TBCR) We retrospectively reviewed the clinical data. [Results] Fifteen patients with less than 2 years of disease duration (early RA) and 21 patients with over 2 years (established) were studied separately. The mean age was 61/66 years (early/established, respectively) and the MTX usage rate was 67/71.4%. The mean CDAI score was 20.7/23.3 at baseline and 9.68/10.62 at 24 weeks. ACR20 response rate was 40/60% and ACR50 response rate was 20/26.6% at 24 weeks. Drug survival rate was 80/90.5% at 24 weeks. [Discussions] ABT therapy showed good clinical efficacy in not only early RA group but also established RA group. This study suggested that ABT would be considered as the first line in the strategy of biologics treatment in Japanese RA patients.

W74-3

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: Yes

[Objectives] To analyze the patients characteristics of rheumatoid arthritis(RA) patients who are treated with abatacrept(ABT) with rapid effectiveness. [Methods] A multicenter registry databese(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=14) and patients below 50% are called slow effectiveness group (SG, n=14). Patients characteristics were compared between two groups. [Results] Mean DAS28-CRP were 4.59(0w), 2.89(4w), 2.50(12w), 2.25(24w) in RG and 4.20(0w), 3.92(4w), 3.05(12w), 2.57(24w) in SG. There was a significant difference between two groups at only 4w. The rate of bio naive was 85.7% in RG and 35.7% in SG (p=0.018). Serum IgG value at initiation of ABT was 1672mg/dl in RG and 1332mg/dl in SG (p=0.035). There was a tendency of difference in MTX usage (78.6% in RG, 35.7% inSG) and RA duration (8.8 y in RG, 12.6y in SG). Previous biologics may affects immunologucal condition in patients with RA and that may result in the differences in effectiveness pattern of ABT.

W74-4

Results of a Multicenter Trial og Abatecept in Rheumatoid Arthritis

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Conflict of interest: None

[Objective] To assess the results of a multicenter, 24-week trial of abatacept (ABT) in rheumatoid arthritis (RA). [Method] The efficacy of ABT was evaluated using LOCF analysis of the SDAI in 42 RA patients who received ABT for at least 24 weeks out of 96 patients who were treated with ABT at institutions participating in The Academy of Clinical Rheumatoid Arthritis Gunma Institute (ACAGI). [Results] The mean SDAI decreased from 23.0 at baseline to 10.1 at 24 weeks of treatment in patients treated concomitantly with MTX (n=24). The mean SDAI decreased from 27.7 to 12.4 in patients who did not use MTX (n=18). When analyzed by previous use of biologics, the mean SDAI decreased from 22.8 to 8.1 in biologic-naive patients (n=10) with 2 (20%) and 5 (50%) respectively classified into remission and low disease activity. The SDAI also decreased from 25.7 to 12.1 in those who switched to ABT (n=32) in this trial, with 3 (9.4%) and 17 (53.1%) respectively classified into remission and low disease activity. The persistence rate at 24 weeks was 90.5%. [Conclusion] ABT shows excellent efficacy, and patients showed good adherence to the drug, which seems to be a reliable treatment option for RA.

W74-5

Multicenter prospective study of clinical usefulness of abatacept in patients with rheumatoid arthritis

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Conflict of interest: None

[Objective] To study clinical usefulness of abatacept in patients with rheumatoid arthritis (RA), a multicenter prospective study was performed in eleven institutions belonging to Shizuoka Rheumatism Network. [Methods] 35 cases that completed the study for 6 months were subjected. The mean age was 58.8 year-old (range 32~79), male:female=5:30, mean disease duration was 8.7 years (3m~31y). 26 were on methotrexate (MTX), 9 were not. Mean MTX dosage was 8.8 mg/week. 12 were Bio-Naive, and 23 were Bio-Switched. [Results] In all cases, mean DAS28-ESR were 5.46/4.21/4.17 (0 month/3 months/6 months), SDAI were 25.9/14.5/12.9. In Bio-Naive, DAS28-ESR were 4.76/2.73/2.84, and SDAI were 23.4/7.9/8.6. In Bio-Switched, DAS28-ESR were 5.59/4.80/4.69, and SDAI were 26.1/17.9/15.2. Remission rate by DAS28-ESR at 6 months were 14.7% (all cases), 45.5% (Bio-Naive), 0% (Bio-Switched). Remission rate by SDAI were 11.8% (all cases), 27.3% (Bio-Naive), 4.5% (Bio-Switched). One patient developed bacterial pneumonia, and the other developed liver dysfunction. Abatacept was discontinued in these two cases, and they were fully recovered. [Conclusions] These findings suggest that abatacept is useful and more effective in Bio-Naive patients compared to Bio-Switched patients in RA.

W74-6

Efficacy of abatacept treatment in RA patients: comparison between groups classified by their background

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Conflict of interest: None

Objective: To examine clinical efficacy of abatacept (ABT) by various background. **Methods**: We assessed clinical response (DAS28-ESR, CDAI and mHAQ) until week 32 in 30 RA patients treated with ABT. Patients were divided into the following subsets: concomitant MTX treatment (with vs. without); Stage (I II vs. III IV); disease activity at baseline (DAS28 <5.1 vs. ≧5.1); previous biologics (naive vs. switch). **Results**: In the MTX (+) group and the high disease activity group, DAS28 and CDAI were significantly improved all over until 32 weeks, and the rate of good and moderate response (LUNDEX score) was better in the MTX (-) group and the low disease activity group. The Stage I II group showed better improvement of DAS28, CDAI and DAS response than the Stage III IV group. On the examination of previous biologics, both groups showed good clinical response. The mHAQ score worsened in the MTX (-) group, the Stage III IV group and the low disease activity group. **Conclusion**: In our study, ABT treatment was useful for patients with high disease activity as well as with concomitant MTX and non-progressive disease stage. The patients with high disease activity had significantly higher serum levels of IgG, IgA and γ-globulin, suggesting that ABT exert a greater effect on RA patients with hyperglobulinemia.

W75-1

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-ESR, SDAI, as well as survival rate, and safety at 24 weeks in 94 RA patients. 59 patients were in combined group, 35 patients were in not combined group. Average dose of MTX were 7.5mg/week in combined group. The ratio consecutive rate after 24 weeks period was 84.7% in combined group, 77.1% in not combined group. Average of DAS28 improved 5.24±1.23 to 4.21±1.38 in combined group, 5.15±1.54 to 4.11±1.30 in not combined group after 24 weeks later. Average of SDAI improved 24.1±13.7 to 14.6±12.2 in combined group, 26.9±14.7 to 15.5±11.4 in not combined group. There was no difference in effectiveness of concomitant MTX with each analysis. DAS-28 and SDAI began to improve after 4 weeks later and continue efficacy at 24 weeks. 10 patients (17%) in combined group and 10 patients (29%) in not combined group achieved low disease activity after 24 weeks later. In combined group, dose of MTX was no influence with efficacy of ABT. Adverse events occurred in 14 cases in combined group, 3 cases in not combined group.

W75-2

Concomitant DMARDs with Abatacept (ABT): Tacrolimus (TAC) and Methotrexate (MTX)

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Conflict of interest: None

[Objective] The efficacy and safety of ABT in combination therapy with TAC, MTX, and other DMARDs (or ABT alone) for patients with rheumatoid arthritis (RA) were compared in a multicenter study at sites affiliated with Tsurumai Biologics Communication (TBC). [Method] The disease activity, adherence, and reason for discontinuation were analyzed in 94 patients who had been administered ABT for 6 months in the TBC. These 94 patients consisted of 11 treated with TAC/ABT group (TG), 62 with MTX/ABT group (MG), and 23 with other DMARDs or ABT alone group (OG). [Results] The SDAI scores showed decreases in the TG, MG, and OG from 31.2, 27.0, and 25.1 at baseline to 15.8, 19.4, and 21.3, respectively, at Week 4. The rates of decrease were 49.4%, 28.1%, and 15.1%, respectively, showing a larger decrease in the TG. The 6-month adherence for the 3 groups was respectively 81.8%, 85.5%, and 73.9%, showing no large difference between the TG and MG. Two patients discontinued ABT in the TG, but no discontinuations due to adverse events have been reported. [Conclusion] The findings of this study indicate that the combination of ABT and TAC, both of which exert effects by inhibiting T-cell activity, is comparable in efficacy and safety to the combination of MTX and ABT.

W75-3

Study on the efficacy of combination therapy, abatacept and methotrexate

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Conflict of interest: None

OBJECTIVE: To study the efficacy of combining abatcept(ABT) with methotrexate (MTX). MATERIALS AND METHODS: Sixteen of twenty-three rheumatoid arthritis (RA) patients treated with ABT in our department were deemed eligible for efficacy evaluation after ≧ 12 weeks of treatment (mean treatment period, 33 weeks). Classified into ABT-MTX combination (n=7) and ABT-only treatment groups (n=9), patients were compared on the basis of the European League Against Rheumatism DAS28-CRP and shift in serum MMP-3 levels. RESULTS: In the combination treatment group, 2 patients had good response, 3 patients had moderate response, and 2 patients had no response. In the ABT-on-

ly treatment group, 6 patients had good response, 2 patients had moderate response, and 1 patient had no response. No significant intergroup differences were seen (p=0.31). Mean serum MMP-3 improved by 23% (43.6 ng/ml) in the combination treatment group and by 39% (111.7 ng/ml) in the ABT-only treatment group, with no significant intergroup difference seen (p=0.13). CONCLUSIONS: This study failed to demonstrate any superiority of ABT-MTX combination therapy. ABT by itself is a promising and important drug for the treatment of RA.

W75-4

Different between BIO switch and duration for RA patients treated with tocilizumab (TCZ) and abatacept (ABT) on remission rates

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Conflict of interest: None

(Purpose) RA treatment evaluations depend on background and biologics used. Analyses were conducted pertaining to how many times TCZ/ABT patients switched, disease duration, and remission rates. (Method) We selected RA patients who'd been administered TCZ/ABT for >1yr. (TCZ 68, ABT 40). We conducted analyses on remission with patient duration of >2yr. or <2yr. Rates for those using only 1 biologic and those using 2 or more were analyzed. Rates for each clinical end-point were assessed for 1yr. after initiation of treatment with DAS28, CDAI, SDAI and Boolean. (Result) Using TCZ, compared to rates of stable patients, early stage patients achieved higher rates, which continued to rise 12mo. after initiation. The rates were DAS>CDAI=SDAI>Boolean. With Boolean, almost none achieved remission. Also LDA continued to rise 6mo. after initiation. For rates between BIO-switch and BIO naïve patients, BIO naïve patients treated with TCZ or ABT, rates were higher and continued to rise at 12mo. after initiation. With TCZ rates were: DAS>CDAI=SDAI>Boolean, for ABT: DAS=CDAI=SDAI>Boolean. Almost none who'd switched achieved remission using Boolean.(Conclusion) For TCZ or ABT, >6mo. is necessary to decide if switching medications is applicable as TCZ and/or ABT are slow-acting biologics.

W75-5

Clinical outcomes of patients after switching to Abatacept from TBC data. -TNF inhibitor vs Anti IL-6R Antibody-

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Conflict of interest: None

【Objective】To examine the efficacy and drug survival rates of abatacept (ABT) in the rheumatoid arthritis (RA) patients with previous biologics histories.【Methods】Ninety-four RA patients treated with ABT for longer than 24 weeks were included, from the 153 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 : Group A (Bio-naïve), Group B (Switching from TNF inhibitor) and Group C (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, and 24weeks. Furthermore, we compared EULAR response criteria and continuation rates.【Results】EULAR response criteria at 24 weeks showed apparent difference between group B and C. Group B showed 46.5% of response rate, while 23.1% in group C (good 0%, moderate 23.1%). Group C showed no significant improvement in CDAI and SDAI at 24 weeks. ABT survival rates at 24 weeks were greater than 80% in group B and group A, while 69.2% in group C.【Conclusion】ABT showed appropriate efficacy in the patients with switching from anti-TNF. However, the patients from anti-IL-6R showed only inappropriate response to ABT therapy.

W75-6

Efficacy of abatacept in the patients with inadequate response to TNF-α inhibitors, registered in Tsurumai Biologics Communication Registry (TBCR)

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Conflict of interest: None

[Purpose:] To investigate the efficacy of abatacept (ABT) for the treatment of rheumatoid arthritis in the patients with inadequate response (IR) to TNF-α inhibitors. [Patients and Methods:] 153 cases treated with ABT were registered in TBCR. In these cases, we analyzed the patients with 24 weeks and more of observation period from initiation of ABT. The efficacy of ABT by each previous anti-TNFα therapy (IFX, ADA, ETN) was compared. [Results:] In 32 cases, the reason for switch of previous anti-TNFα therapies was IR. IFX or ADA was used in 13 cases and ETN in 19 cases. Discontinuation of ABT caused by IR was significant high rate (p=0.03), 32 % (6 /19 cases) in switch from ETN group but no cases in IFX or ADA group. In ABT-continuation group, significant clinical response was found based on SDAI and CDAI but patient global assessment was not improved. [Discussion and Conclusion:] One of reasons for IR of anti-TNF α antibodies is inadequate dosage against disease activity. The results of clinical trials in Japan showed that dosage of ABT and ETN is adequate compared to those in Europe and US. ABT could replace the inadequate dosage of anti-TNF-α antibodies. It could take long time to achieve good clinical response after switch from TNF-α inhibitor.

W76-1

Study of the background factor which controlled the effectiveness of TCZ therapy for RA patient

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Conflict of interest: None

[Objectives] We examined the background factor which controlled the effectiveness of TCZ therapy for RA patient. [Methods] TCZ therapy was introduced to 106 RA patients(age 58.1+/-13.1y. o., F:M=82:24) in our hospital from May, 2008 to April, 2011. We studied the background factor (age, duration of disease, Stage, Class, DAS28, tender joint count(TJC), swollen joint count(SJC), overall patient evaluation(pVAS), dosage of MTX and PSL, history of biological agent(Bio.) use) before TCZ therapy between non-remission and remission group at 24 weeks. [Results] The remission rate of non-Bio.used or Bio.used group at 24 weeks were 58.3%(14/24) vs 31.6%(30/82) in DAS evaluation, and 8.3%(2/22) vs 13.4%(11/82) in Boolean's definition. Continuation rate of TCZ therapy was 91.5%, and there was no difference between both group. In the examination of the background factor which contributed to achievement of DAS remission at 24 weeks, low age, Class 1,2, no history of Bio use, low score of DAS28, TJC and low pVAS were statistically significant. [Conclusion] TCZ therapy showed a high continuation rate with or without history of Bio. use. It was thought that the introduction of the TCZ therapy at a stage of Class1-2 without history of Bio. use was desirable for the achievement of remission.

W76-2

Efficacy and safety of tocilizumab (TCZ) in patients with rheumatoid arthritis (RA) stratified according to the previous use of biologics (pre-bio) and the concomitant use of methotrexate (con-MTX)

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Conflict of interest: None

[Aim] To elucidate efficacy and safety of TCZ in patients with RA stratified according to pre-bio and con-MTX. **[Methods]** We examined clinical background of RA patients treated with TCZ in our hospital from July, 2008 to May, 2011 and prospectively evaluated its efficacy and safety. **[Results]** Of 101 patients (12 males, 89 females), 28 had pre-bio and con-MTX (**Group A**), 20 had pre-bio and no con-MTX (**Group B**), 26 had no pre-bio but con-MTX (**Group C**), and 27 had none of pre-bio or con-MTX (**Group D**). Overall average age at the commencement of TCZ was 56.2±13.2, DAS28-ESR 5.03±1.36, and HAQ-DI 1.11±0.74, proportion of concomitant prednisolone 46%, duration of TCZ administration 49.3±35.2 weeks, where there was no significant difference among these 4 groups. In 67 patients administered TCZ for 24 weeks, the proportions of patients achieving remission at week 24 in Group A, B, C and D were 61.1%, 54.5%, 66.7% and 60.0%, respectively, with no significant difference among the groups. Seven ceased TCZ by week 24: 3 (2 inadequate responses (IR), 1 adverse event (AE)) in Group A, 3 (1 IR, 2 AE) in Group B, and 1 (IR) in Group C. **[Conclusion]** TCZ is efficacious regardless of use of pre-bio or con-MTX, and safe regardless of the use of con-MTX but safer in biologics-naive cases.

W76-3

Marked improvement can be expected with tocilizumab regardless of MTX use or prior biologicals: Retro-analysis of 80 patients in 6 Juntendo-facilities

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Conflict of interest: None

[Objectives] The efficacy of TNFα inhibitors differs according to MTX use or prior biologicals (BIOs). We examined the characteristics of tolcilizumab (TCZ), an anti-IL-6 receptor antibody. [Methods] TCZ was started at 6 Juntendo-facilities from April 2008 to August 2010, and 80 RA patients with at least 6 months of follow-up were retro-analyzed. [Results] Average age was 57.8 (35.8% 65 or older), with RA duration 9.81 years, pretreatment DAS28-ESR 5.5, prior BIO 69.0% and MTX use 72.0%. After 6 months DAS28-ESR fell from 5.63 to 2.89 with clinical remission rate of 47.5% and retention rate of 86.2%. In comparison between 2 groups by prior BIO, MTX and age (under 65 and 65 or over), the good response rate was about 60% in any group. TCZ was discontinued in 11 patients (13.8%) due to inadequate response in 3, patient choice in 1 and infection in 1 case (1 cellulitis). [Conclusion] High efficacy can be expected with TCZ regardless of MTX use or prior BIO.

W76-4

The influence of disease duration on clinical effectiveness of Tocilizumab in RA patients-Examination from multi-institution research registry (TBC registry)-

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Conflict of interest: None

[Objectives] To investigate the relationship between the clinical effectiveness and the disease duration in RA patients treated with Tocilizumab(TCZ). [Methods] Among 2072 patients of TBC registry, 122 patients treated with TCZ and whose clinical data could be followed for a period of 12 months were divided into 5 groups by the disease duration (group A: less than 1 year, group B: from 1 to 2 years, group C: from 2 to 5 years, group D: from 5 to 10 years, and group E: more than 10 years) and evaluated TJC, SJC, GH, CRP, ESR and MMP-3 at baseline, 6 months and 12 months after the treatment, respectively. [Results] CRP and ESR

were rapidly normalized by 6 months regardless of disease duration. The proportion with TJC≦1 and Patients GH≦10mm was lower with long disease duration groups (group D and group E). SJC was reduced to less than one joint among more than 50 % patients by 12 months in all groups, and there was no correlation between the proportion with SJC≦1 at 12 months and disease duration. In group A, MMP-3 fell into normal range among 68.2% patients at six months, and 81.8% at 12 months. There was a correlation between the rate of normalizing MMP-3 and disease duration. Earlier introduction of TCZ therapy is important to maximize the effectiveness of TCZ therapy.

W76-5

Effectiveness and Safety of Tocilizumab (TCZ) for the rheumatoid patients— 52 weeks follow up study —

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Conflict of interest: None

[Purpose]: The authors evaluated the efficacy of Tocilizumab (TCZ) at 52 weeks after medication. [Materials and Methods]: Fifty one patients treated with TCZ were analyzed. They were 37 females and 14 males. Their age was 62.2±10.2 years old and the duration of rheumatoid arthritis 7.2±7.0 years. Fifteen patients (29.0%) have been treated with previous biological agents, 31 patients (62.7%) were treated with MTX (5.5±1.9 mg) and 30 patients (58.8%) with PSL (5.2±2.8 mg). For all patients, DAS28 ESR, Eular response and mHAQ were discussed at 52 weeks after medication. [Results]: DAS 28 ESR improved from 5.28 to 2.83 (remission rate 60%), good Eular response 60%, moderate 32.5%, and no response 7.5%. On the other hand, TJC≦1:66.7%, STC≦1:35.4%, and mHAQ<0.5 were 54.9%. Nine patients discontinued. They were 1 due to side effect and another 1 due to no- effectiveness, 7 due to unknown causes. So, continuation of 52 weeks of TCZ was 40 patients (78.4%). PSL could be reduced in 22 of 30 patients and 2 could be discontinued. [Conclusion]: TCZ medication of 52 weeks for rheumatoid patients demonstrated high remission rate (60%) and high continuation rate (86.3%).

W76-6

Efficacy of tocilizumab therapy in patients with rheumatoid arthritis of Nagasaki prefecture, Japan

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Conflict of interest: None

Objectives; We evaluated the efficacy of TCZ in RA patients during 3 years in the PMS in Nagasaki. *Methods;*152 RA patients, who received TCZ during 3 years, were enrolled. 99 patients have passed longer than 1 year after the introduction of TCZ. Clinical response was evaluated by DAS 28, CDAI, Boolean approach and HAQ, respectively. *Results;* The mean of age and disease durations were 58 y.o. and 11 years at baseline, respectively. The patients had high disease activity at baseline (mean of DAS28:5.5, that of CDAI:25.5). 59.6% patients had received TNF inhibitors before TCZ. Continuation rate of TCZ, DAS28 remission rate and CDAI remission rate during the 3 years was 73.7%, 46.2% and 22.5%, respectively. Among the 99 patients being treated with TCZ longer than 1 year, the rate of remission at 1 year was high in patients with short disease duration (<2 ys; DAS28 62%, CDAI 31%) or no previous history of TNF inhibitors (DAS28 61 vs 41%, CDAI 20 vs 9%, Boolean approach 20 vs 9%). Low HAQ at baseline was the only variable to be associated with HAQ remission at 1 year defined by logistic regression analyses (OR: 0.03, p=0.01). *Conclusion;* The present study showed an excellent therapeutic efficacy as well as the characterisitic of patients being achieved in remission by TCZ in RA patients.

W77-1

Prevention of COX-2 selective inhibitor related upper gastrointestinal ulcer by concomitant therapy with anti-ulcer agent: randomized control study

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Conflict of interest: None

[Objectives] Substitution of NSAIDs with a COX 2 inhibitor reduces the risk of gastrointestinal (GI) events. We aimed to confirm the hypothesis that combined treatment with celecoxib and rebamipide would be more effective than celecoxib alone for prevention of upper GI ulcer. [Methods] This prospective, randomized, open-label blinded end point study was conducted. Sixty-five patients with rheumatoid arthritis, osteoarthritis, and low back pain enrolled to this study. Endoscopic examinations were conducted before starting the study and after 3 months. Patients were randomized to two groups: mono-therapy group (celecoxib) and combination-therapy group (celecoxib and rebamipide). The primary endpoint was to evaluate the prevalence ratio of GI events by endoscopic findings between the mono-therapy group and combination-therapy group. [Results] The incidence of upper GI ulcer was 5 of 34 (15%) in the mono-therapy group and 0/31 (0%) in the combination-therapy group (p=0.03). The prevalence of gastrointestinal events was 6/34 (18%) in the mono-therapy group and 0/31(0%) in the combination group (p=0.01), and our hypothesis was verified.

W77-2

Efficacy of opioid treatment for patients with rheumatoid arthritis

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Conflict of interest: None

Objective: we investigated the clinical efficacy of opioid analgesics in rheumatoid arthritis (RA) patients with chronic pain

which were not adequately controlled by NSAIDs and/or steroid. Methods: 10 RA patients (female, n=7; male, n=3) with an average age of 68 years (range 55-80 years) were administered opioid analgesics in our hospital. The mean disease duration was 14 years. Codeine phosphate hydrate was administered to 3 patients, tramadol/acetaminophen combination tablets to 5, transdermal fentanyl patches to 2. 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 69.9 mm to 49.6 mm. The mean HAQ-DI score improved from 1.89 to 1.53. Adverse events were constipation, drowsiness, nausea and general malaise. Conclusion: Opioid treatment was highly effective for RA patients with chronic pain. Opioids are valuable treatment option for RA patients with uncontrollable pain by DMARDs or biologics.

W77-3

Effect of anti-rheumatic drugs by using regional assessment: a nationwide study based on the *NinJa* database

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Conflict of interest: Yes

Objective: To examine whether anti-rheumatic drugs have the equal effect on every joint. **Methods:** Data were extracted from *Ninja* database only if a patient was administered the same drug from 2008 to 2010. Single drug user was selected in case of MTX, SASP, SH groups (bucillamine and D-penicillame), TAC (tacrolimus). Total Joint indices (TJI) were calculated as described previously (1). **Results:** Disease duration did not differ among patients with different drugs. Age of onset in patients with MTX/anti-TNF/ETN was significantly younger than that in patients with SASP/SH groups/TAC. Number of progressed stage increased in the following order: SASP/SH groups, MTX/TAC, and anti-TNF/ETN/TCZ. TAC had the highest rate of steroid user (69%). Regions where TJI decreased significantly in 3 years were as follows: upper/large, upper/small, and lower/small for MTX, none for SASP, lower/small for SH groups, upper/large and lower/large for TAC, lower/large for anti-TNF, upper/large and upper/small for ETN, and upper/large for TCZ. **Conclusion:** Effective regions may be different among anti-rheumatic drugs. **Reference:** 1. Nishiyama S, et al. Proposing a method of regional assessment and a novel outcome measure in rheumatoid arthritis. Rheumatol Int. DOI 10.1007/s00296-011-2058-9, 2011

W77-4

Clinical outcomes and anti-rheumatic drugs: long-term observational study

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Conflict of interest: None

[Objectives] We aimed to evaluate the changes of clinical outcomes and the use of anti-rheumatic drugs in patients with rheumatoid arthritis (RA) by using our database that established in 2005. [Methods] Patients with RA who visited our center between 2005 and 2011 and who accepted to participate in this study were included. Number of accumulated total subjects was 2,301. Every clinical data was statistically evaluated using SPSS. Bonferroni correction was used for multiple comparisons. [Results] Mean ages became higher in the recent 7 years, however, mean HAQ was improved (2005: 1.2 vs. 2011:0.8, $p < 0.01$). Tendencies of improvement in DAS28(CRP) and DAS28(ESR) were observed. Patients treated with MTX (2005: 46.3 %, 2011: 64.1 %) and whose dose of MTX equal to or more than 8 mg/week (2005: 22.1 %, 2011: 44.6 %) were increased in these 7 years. Patients treated with biologics were also increased (2005: 11.8 %, 2011: 26.4 %). [Conclusion] Clinical outcomes were improved in these 7 years, which may be explained by aggressive use of anti-rheumatic drug.

W77-5

Non-biological DMARDs Treatment for New Onset Rheumatoid Arthritis Patients and Change of Serum Cytokine Level

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Conflict of interest: None

[Objective] To evaluate the kinetics of serum cytokines of rheumatoid arthritis (RA) patients whom non-biological DMARDs were initiated. [Patients] 46 RA patients in prospective cohort of newly diagnosed RA of our hospital (SAKURA) and treated with non-biological DMARDs. Median duration of RA was 4 months, and 77% was stage I [Method] Serum level of TNFα and IL-6 was measured before the treatment and one year after. When the biological DMARDs were initiated within a year, serum cytokines were measured just before the biologics. [Result] Significant relationship between IL-6 and DAS28 or HAQ-DI at the time of the diagnosis was observed ($p<0.001$, $p=0.026$, respectively), but estimated yearly progression of TSS was significantly correlated with only TNFα ($p=0.046$). DAS28 was decreased from 4.3 to 2.3 ($p<0.01$), and serum level of IL-6 was lowered from 5.9 pg/ml to 1.2 pg/ml ($p<0.01$). But serum TNFα didn't significantly changed from 1.50 pg/ml to 1.15 pg/ml ($p=0.716$). [Discussion] Widely used disease activity assessment was more strongly correlated with serum level of IL-6 than that of TNFα. Meanwhile, it was suggested that there was more strong correlation between TNFα and joint destruction and that the effect of the DMARDs, such as MTX, was achieved through the IL-6 blockade

W78-1

A 12-month randomized controlled trial for combination of bucillamine+salazosulfapyridine vs each drug alone in early RA

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Conflict of interest: None

[Objectives] [Methods] Eighty patients with active early RA of < 5 years' duration from 12 sites in Kanagawa were randomized to receive bucillamine 200mg/day alone (Group B), salazosulfapyridine 1000mg/day alone (Group S), or BUC plus SASP (Group C) in a 12-month multicenter open label study. The primary end point

was the proportion of patients in low disease activity (LDA). [Results] The percentages of LDA and DAS28-defined remission at year 1 in Group B, S, and C were 52.2%, 42.9% and 59.1%, respectively, and 34.8%, 33.3%, and 45.5%, respectively. The percentages of adverse reactions and stopped cases in Group B, S and C were 50%, 8.3% and 46.4%, and 32%, 4.2% and 25%, respectively. Serious adverse events were not recorded. Combination of BUC + SASP was well tolerated and showed higher proportion of patients achieving LDA in early RA patients. Monotherapy with each drug also showed good clinical response. The annual progression of bone destruction each treatment group are now on evaluating with kellgren scoring system.

W78-2

The change of renal function in 3 years in Japanese RA patients with chronic kidney disease.

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Conflict of interest: None

[Objectives] To clarify the problems in the treatment for RA patients with chronic kidney disease (CKD). [Methods] Estimated GFR (eGFR) was calculated in 141 RA patients (male:30, female:111), who visited our outpatient clinic from Jan. 11th, 2005 until Sept. 30th, 2010. 62 patients (male:16, female:46), whose serum creatinine levels at two time points with 3-year interval were available, were chosen to subtract 3-year-previous eGFRs from recent eGFRs (Δ3yr-eGFR). The difference of the Δ3yr-eGFR in each drug for RA treatment was statistically analysed. [Results] Δ3yr-eGFR was 9.24±14.3 mL/min./1.73m^2 in total 62 patients. Δ3yr-eGFR was not statistically different between MTX(+) group (19 patients) and MTX(-) group (43 patients),(11.1±9.63 vs 8.42±16.0, P=0.184, Mann-Whitney), and Biologics (infliximab, adalimumab, etanercept), prednisolone, salazosulfapyridine similarly did not make significant difference of Δ3yr-eGFR. Meanwhile, NSAIDs(+) group (13 patients) and taclorimus (TAC)(+) group (7 patients) had significantly larger Δ3yr-eGFR than NSAIDs(-) group (49 patients) or TAC(-) group (55 patients) (NSAIDs:18.9±15.2 vs 6.67±13.1, P=0.0095, TAC:25.9±11.7, 7.13±13.3, P=0.0016, Mann-Whitney).

W78-3

A study on tolerability of MTX therapy in MTX naïve early RA patients

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Conflict of interest: None

[Objectives] Treat to Target (T2T) for RA therapy recommended drug therapy should be adjusted at least every 3 months until the desired treatment target has been reached. And, maximum dose of MTX was accepted to 16mg/w in Japan at March 2011. In this study, we investigated the the tolerability of MTX therapy in MTX naïve early RA patients. [Methods] 45 MTX naïve RA patients within 1 year after disease onset were started MTX therapy at 6 mg/w. 2 mg/w of MTX were increased every two weeks until DAS28 remission and the maximum dose of MTX was 16 mg/w. 5 months after, we investigated the tolerability. [Results] MTX dose at 5 months was 1 case of 4mg, 12cases of 6mg, 12 cases of 8mg, 1 case of 10mg, 4 cases of 12mg and 12 cases of 16mg. 3 cases were discontinued by GI symptom. 6 cases reduced the MTX dose because by the elevation of serum ALT level.

W78-4

Dose escalation of methotrexate (MTX)in rheumatoid arthritis (RA) patients.

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Conflict of interest: Yes

Objective: To evaluate the efficacy and safety after dose escalation of MTX (the use up to 16 mg/w was approved in February 2011 for RA patients in Japan). **Method**: We retrospectively studied 32 RA patients (male/female: 6/26, mean age: 55.1 (30–73) years, mean disease period: 8.6 (1–54) years, Steinbrocker's stage: I, 7; II, 13; III, 3; IV, 9 patients, Steinbrocker's class: I, 11; II, 16; III, 5 patients). **Results**: The mean MTX dose and observation period after dose escalation were 10.4 (9–16) mg/w and 4.2 (1–8) months, respectively. Significant improvements of ESR (32.2 ± 24.5 to 23.9 ± 21.6 mm/h), MMP-3 (167.0 ± 174.5 to 123.9 ± 124.5 ng/mL), DAS28-ESR (4.1 to 3.5), and SDAI (16.6 to 12.0) were noted. The EULAR response after dose escalation of MTX in 26 patients with a poor response to DMARDs including MTX, 3 patients with a poor response to biologics (adalimumab: 2, infliximab: 1), and 2 patients with a decreased effect of biologics (infliximab: 1, etanercept 1) showed a moderate or more response in 11 of 26, a moderate response in all of them, and a moderate response in one of them, respectively. There were no serious adverse effects. **Conclusion**: Dose escalation of MTX was effective in patients with a poor response to DMARDs or biologics and a decreased effect of biologics.

W78-5

Efficacy and safety of methotrexate at a dose of at least 10 mg/week for rheumatoid arthritis patients in a community hospital

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Conflict of interest: None

Objective: To investigate the efficacy and safety of methotrexate (MTX) at a dose of at least 10 mg/week for rheumatoid arthritis (RA) patients in a community hospital. *Methods:* MTX was initially administered at 8 mg/week to 56 patients, and then increased to at least 10 mg/week from March 2011 to July 2011. Fourteen patients (25%) were also treated with biological agents. Disease activity was measured by DAS28-ESR at the baseline, 3 months, and 6 months. Adverse events and abnormal laboratory data (particularly alanine aminotransferase levels and white blood cell count) were investigated at 3 and 6 months. *Results:* MTX was continued for 40 patients at a mean dose of 10.3 mg/week for 3 months (10 mg/week in 34, and 12 mg/week in 6). Biological agents were newly introduced in 3 patients and switched in 1 patient. In the other 36 patients, the mean observed DAS28-ESR values were 3.9 and 3.1 at the baseline and 3 months, respectively. Good or moderate responses were achieved in 21 patients (60%), and DAS28-ESR remission was newly achieved in 8. There were no serious adverse events at 3 and 6 months. *Conclusion:* MTX dose escalation between 10 and 12 mg/week is effective and safe for RA patients.

W78-6

Long-term analysis of the combination therapy of tacrolimus and methotrexate in patients with rheumatoid arthritis

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Conflict of interest: None

[Objectives] We have previously reported that efficacy of low-dose tacrolimus added to methotrexate (MTX) in patients with RA. The aim of the current study is to assess the continuation rate, safety and clinical utility of this therapy for the long-term use. [Methods] The clinical course of 31 RA patients who started tacrolimus in addition to MTX before August 2007 was analyzed retrospectively. [Results] Tacrolimus was started at ≤1.5 mg/day in 28 patients, 3 mg/day in 3 patients. At 48 months, tacrolimus was continued at ≤2 mg/day in 18 patients and 3 mg/day in 2 patients, but was discontinued in 11 cases. The continuation rates at 6, 12, 24 and 48 months were 84, 77, 71 and 65% respectively. The prednisolone dose was reduced from 3.53 mg/day to 1.28 mg/day after 48 months. No significant difference was observed in clinical background or laboratory data in patients (n=20) who continued the combination therapy for 48 months compared with those in patients (n=8) who discontinued it due to inadequate response. [Conclusion] The addition of tacrolimus at low-dose to MTX for the treatment of patients with RA was well tolerated for the long-term use and associated with a good clinical response.

W79-1

Efficacy of single-dose mizoribine therapy in combination with methotrexate for patients with rheumatoid arthritis who show an insufficient respose to methotrexate: a prospective study

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Conflict of interest: None

[Objectve] The purpose of this study is to evaluate prospectively the efficacy and safety about single-dose daily mizoribine (MZR) therapy in combination with methotrexate (MTX) for elderly patients with rheumatoid arthritis (RA) who show an insufficient respose to MTX. [Methods] This study enrolled 11 elderly patients with RA: 3male, 8female; 76 years-old; mean disease duration 14.7year; mean dose of MTX 5.5mg weekly dose. At baseline, 7 patients were in moderate disease activity (MDA) and 4 patients ware in high disease activity (HDA). DAS28-ESR, MMP-3, maximum drug concentration (Cmax) of MZR, continuation rate and adverse events were evaluated. [Result] The mean follow-up duration was 5.5 months. At last observation, four patients were in low disease activity (LDA), three patients were in MDA and four patients were in HAD. The effective group (n=4) belonging within LDA indicated mean Cmax of MZR was 2.47 (2.01-3.22) and the noneffictive group (n=7) indicated that was 0.87 (0.82-1.36). Comparing DAS28-ESR between both groups, these indicated a significant difference at 12 weeks and last observation. MMP-3 in the effective group was also significantly lower at last observation period. The continuation rate of MZR was 27%. Adverse event was only a stomatitis.

W79-2

The efficacy of the simultaneous combination therapy of mizoribine and methotrexate in elderly rheumatoid arthritis patients with insufficient response to methotrexate

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Conflict of interest: None

[Objective] We examined the efficacy of the simultaneous combination therapy of mizoribine (MZR) with methotrexate (MTX) for 24 weeks in elderly patients (aged ≧ 65) who had active rheumatoid arthritis (RA) despite MTX therapy. [Methods] Nineteen RA patients (mean age 74.1 years) who had moderate or high disease activity (DAS28 > 3.2) after treatment with MTX (6-8 mg/week) were enrolled. MZR was administrated simultaneously with MTX with initial dose of 300 mg/week. The dose of MZR was permitted to increase to 450 mg/week if the disease was active 12 weeks after inducing MZR. [Results] At the time of 24 weeks, 89.5 % of the patients continued MZR, and their DAS28 score improved from 5.0 ± 0.8 to 4.3 ± 1.3 (P = 0.026). Good or moderate European League against Rheumatism (EULAR) response was achieved in 35.3 % of patients. Significant improvement was seen in tender joint count and DAS28 score even 4 weeks after starting MZR. Adverse events were observed in 3 patients (15.8 %) but no serious side effect by MZR was observed. [Conclusion] This preliminary study suggests that the additional MZR combined therapy with MTX is well tolerated and can be beneficial in elderly RA patients with insufficient responses to MTX, and can be considered before starting biologics.

W79-3

Prospective Study on the Influence of Renal Function to the Efficacy of Mizoribine in Rheumatoid Arthritis

Tomomi Tsutsumi[1], Masato Moriguchi[1], Tadashi Sakurai[1], Kazutoshi Aoki[2], Takanori Azuma[3], Koichi Amano[4], Ayumi Okuyama[4], Motohide Kaneko[14], Mitsuhiro Kawagoe[13], Issei Kida[11], Yoshiaki Kuga[12], Shigeto Kobayashi[11], Kimihiro Suzuki[5], Kentaro Chino[2], Kyoichi Nakajima[6], Yuichi Handa[7], Tatsuo Hirose[8], Tsuyoshi Matsuzaki[9], Hide Yoshida[10], Chihiro Terai[1]
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Conflict of interest: None

【Objective】 According to the JCR guideline for RA, mizoribine (MZR) is classified as recommendation B drug. MZR is excreted through kidney and is sometimes very effective in patients with impaired renal function. We investigated the efficacy of MZR according to patient's renal function and its different docing method. 【Methods】 In multicenter trial, we prospectively examined 99 patients who started MZR medication and followed for 24 weeks. Disease activity was evaluated by DAS28 and renal function was evaluated by serum creatinine (sCr), eGFR and cystatin C. 【Result】 Among 99 RA patients (mean age 66.1 years, disease duration 8.4 years, male 19), 6 patients showed increased sCr, on the other hand, 24 had elevated cystatin C, indicating cystatin C more sensitive marker for impaired renal function among RA. Cystatin C was significantly higher in the patients with good response by EULAR criteria using DAS28-CRP than those with no response. MZR was more effective when administered once a day than by divided med-

ication.【Conclusion】Cystatin C seems to indicate more accurate renal function of RA patients with possible muscle atrophy than sCr. MZR is more effective for RA patients with higher cystatin C level or taking higher single dose of MZR.

W79-4

Leflunomide or Methotrexate? Comparison of Clinical Efficacy and Safety in Low Socio-economic Rheumatoid Arthritis Patients

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Conflict of interest: None

Objectives: To compare the efficacy of methotrexate and leflunomide for the treatment of rheumatoid arthritis. **Methods:** A double-blind randomized clinical trial was carried out at the Department of Medicine, Jinnah Medical College Hospital, Korangi, Karachi. Sample size was 240 patients and duration of the study was one year. Materials used in this clinical trial were drugs and preformed clinical assessment scales. Clinical assessments of RA activity were obtained. Data was expressed as mean±S.D. P value of <0.05 calculated by paired t-test was considered significant. **Results:** A total of 368 subjects were enrolled in this study. Of these, 128 subjects were withdrawn in the screening phase. Of the 240 subjects randomized and treated, 129 received leflunomide and 111 received methotrexate. The difference between baseline and end-point measurements of all primary clinical efficacy endpoints was significantly greater in methotrexate than in leflunomide-treated subjects. In both treatment groups, the most common reason for withdrawal during the treatment was adverse events. It was concluded that methotrexate, which is ten times cheaper drug than leflunomide, is a drug of choice especially for the patients who belong to lower socioeconomic group.

W79-5

The clinical features of 63 Japanese patients with rheumatoid arthritis administered Leflunomide

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Conflict of interest: None

Background:Leflunomide(LEF) is recommended for the treatment of patients with rheumatoid arthritis(RA) by EULAR and ACR. However its use in Japan seems to be limited. **Purpose**:To study clinical features of RA patients administered LEF at our center. **Patients and methods**:Data on 63 RA patients who fulfilled 2010 ACR/EULAR RA classification criteria were included. Those who received LEF at our center between April 2004 and October 2011 were studied. **Results**:Among 63 patients, 50(79%) were female. The mean age was 59.9 years(range 23-83).7 patients had concomitant CKD, 14 had respiratory diseases, 2 had gastrointestinal diseases, 8 had diabetes mellitus. No patient had concomitant interstitial pneumonia. The number of patients received LEF as the first DMARD was 4. All patients had concomitant CKD. 19 patients received LEF as second DMARD, 15 switched from MTX, 4 from SASP. The reasons for switch from MTX were side effects of MTX in 13, and inefficacy in 2. Persistence of LEF at 6 months and 12 months were 54% and 41.3%, respectively. The reasons for discontinuation were side effects in 19, and inefficacy in 5. **Conclusion**:RA patients with CKD received LEF as the first DMARD. For patients with CKD and those who are intolerant to MTX, LEF might be a useful alternative.

W79-6

Effective usage of Salazosulfapyridine (SASP) based on *NAT2* genotyping -Personalized Medicine in Rheumatoid Arthritis (RA)-

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Conflict of interest: Yes

[Objectives] SASP is commonly used for RA patients with relatively good prognosis or with difficulty in usage of methotrexate. Efficacy and safty during SASP treatment are known to relate the *N-acetyltransferase 2 (NAT2)* genotypes. Utility of SASP treatment on such patients was retrospectively and prospectively studied. [Methods] Relationship between *NAT2* genotypes and efficacy/adverse reactions (AR) was retrospectively investigated for 94 patients based on physician's reports and medical information. Prospective study was conducted from Jan 2010, and 32 patients were registered until now. Genotyping was done using i-densy (ARKRAY Inc.). [Results] 1) Retrospective studies: No relation was found between efficacy and genotypes in retrospective studies, but hepatic, hematologic, and dermatologic AR except gastrointestinal AR were significantly frequent in patients with SA genotype. 2) Prospective studies: Thirteen patients (4 FA, 8 IA, 1 SA) have come to end of the 1 year observation period. Mean changes in DAS28 (CRP) at 6^{th} month and 12^{th} month from the before using (ΔDAS28) was significantly greater in IA genotypes than FA genotypes. [Conclusion] Genotyping of *NAT2* was shown to predict efficacy and safty of SASP and may contribute to establish personalized medicine of RA.

W80-1

Cost-effectiveness analysis of DMARDs and biologics therapy (annual report from NinJa 2010)-The beginning of improvement?-

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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 2004-2010 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 380,000 yen / patient in 2010. That was increasing year by year. But the increasing rate of that decreased in 2010. ([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 at the level in 2004. [Conclusion] The increasing rate of the cost decreased just in 2010. On the other hand, the disease activity is steadily continuing to improve. Accordingly the improvement of cost-effectiveness might have begun in 2010.

W80-2

Database of Rheumatoid Arthritis for Clinical Research Cooperation with Electronic Medical Chart

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Conflict of interest: None

[Objectives] As information technology (IT) advanced, and electronic medical charts spread, various medical data came to be accumulated. We develop a medical support system for rheumatoid arthritis (RA) cooperation with electronic medical chart to use these data for a clinical study. [Methods] We developed a medical support system for RA to input medical data necessary for evaluation and treatment of RA. As a main function, ①Touch-panel method to input (patient oneself inputs) such as mHAQ and VAS ②Chart to input (doctor inputs) swollen joints and tender joints (up to 71 joints) and automatic calculation of DAS28ESR, DAS28CRP, SDAI, CDAI and mHAQ. ③List of record for medication and laboratory data. [Results] In cooperation with the electronic records of medication, laboratory data, operation, we can glance all through the medical data easily by inputting minimum data such as swollen and tender joints, VAS, and mHAQ. Our system is a useful medical support tool. Furthermore, It would be high-precision database for clinical study. We would be able to develop high quality clinical research easily using our system.

W80-3

The Treatment of Rheumatoid Arthritis in Nagano Prefecture

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Conflict of interest: None

[Objectives] To investigate the treatment of rheumatoid arthritis(RA) in Nagano prefecture. [Methods] The Network Of Rheumatic Disease In Shinshu (NORDIS) was established in 2007 under the principle that every patient with RA should be treated with the best possible therapy in all areas of Nagano prefecture. Annual questionnaire has been performed since 2006. The contents of questionnaire were about number of patients who were treated with biologics and the problem of RA therapy. [Results] Thirty two doctors used biologics in 2006 and 44 doctors used them in 2011. Thirty percent of the doctors who had not used biologics answered that they would like to use biologics in cooperation with rheumatologist in 2006, and 54.5% in 2008. Fifty two percent of doctors answered that they had not performed the evalutation with DAS28. [Conclusions] In order to improve the RA therapy in Nagano, it is necessary to spread the new strategy of RA treatment widely.

W80-4

Joint destruction in rheumatoid arthritis patients diagnosed using the 2010 ACR/EULAR classification criteria

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Conflict of interest: None

【Objectives】To investigate joint destruction in rheumatoid arthritis (RA) patients diagnosed using the 2010 ACR/EULAR classification criteria compared to the 1987 ACR criteria.【Methods】RA patients with a diagnosis and treatment time greater than 1 year were divided into two groups. Group A (n=18): RA patients fulfilling only 2010 criteria and, Group B (n=30): RA patients fulfilling 2010 and 1987 criteria. Modified total Sharp score (mTSS) was obtained at the first visit, and at the 1 year point following initiation of therapy.【Results】In Group A, the mTSS at the first visit and at the 1 year point after therapy was significantly lower compared to Group B scores. Patients received medical therapy earlier in Group A compared to Group B; therefore, we initially considered that early therapy using the 2010 criteria resulted in decreased joint destruction. However, there was little difference in the overall ΔmTSS between Groups A and B. Most patients in Group A were not prescribed methotrexate due to their low disease activity, and we assume this explains why the progression of joint destruction in Group A did not vary overall from Group B despite early therapy.

W80-5

Learning from the patients who have experienced the Great East Japan Earthquake

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Conflict of interest: None

[Objectives]The coast of Iwate was devastated by the Great East Japan Earthquake on March 11, 2011. Our clinic's 125 RA outpatients (otpts) from neighboring coast; 50 had complete/half home destruction or lost household jobs. Half year passed from eq; we assessed its effect on pts' inflammation marker levels & laboratory test results by pre/post eq; 40 otpts divided to 2 groups of disaster victim or non & questionnaire survey on physically/mentally (p/m) stress also done. **[Methods]** Group A 17 pts non eq disaster victim; Group B 23 pts entitled Disaster Victim Certificate. **[Results]** No difference in pre/post eq laboratory test results. In groups A & B, 50% & 65% experienced insomnia; 48% & 87% felt anxiety for future; 35% & 78% felt stressed in current everyday life; 21% & 60% experienced flashbacks, respectively. Group B was markedly p/m stressed. Some pts complained depression; some were traumatized against water disasters like typhoon. Pts on biologicals were said to be able to participate social activities w/out sharp pain owing to treatment. Comparison of 2 groups showed significant difference of p/m stress; controlling RA helps overcome large-scale disaster induced stress. We were able to create a pt education booklet based on findings aiming to improve medical examination.

W80-6

Educational rheumatology lectures for non-specialized medical staffs.

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Conflict of interest: None

We reported from questionnaire data that primary care physicians were less aware of complications of rheumatoid arthritis and adverse events of rheumatic DMARDs than specialized rheumatologists. In order to educate rheumatology to non-specialized medi-

cal staffs, we conducted educational lectures in non-rheumatology hospitals.

W81-1

Clinical characteristics, long-term survival and causes of death in 177 Japanese patients with systemic sclerosis; a retrospective analysis in a single institute.

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Conflict of interest: None

[Objectives] To investigate clinical characteristics, long-term survival and causes of death in systemic sclerosis (SSc). [Methods] SSc patients who visited to our hospital from 2006 through 2011 were retrospectively analyzed. [Results] A total of 177 patients, consisted of 50 diffuse cutaneous SSc (dcSSc) and 127 limited cutaneous SSc (lcSSc), were included. Mean follow-up period (SD) was 89 (74) months. Survival by Kaplan-Meier method showed that patients with 60 or older (P<0.0001), interstitial lung disease (ILD) (P<0.05 by Gehan-Breslow) and dcSSc (P<0.05) had significantly lower survival compared to those without them. Frequency of ILD was higher in dcSSc (86%) than in lcSSc (37.8%) (P<0.0001). DcSSc patients developed borderline or manifest pulmonary hypertension (PH) more frequently than lcSSc patients (17.0% vs. 7.3% at 5-year, P<0.05). Only 2 dcSSc patients developed renal crisis. Thirteen patients died. Death in 6 patients was associated with pulmonary arterial hypertension (2), PH form ILD (2) and progressive ILD (2) and another 3 with cardiac failure. Notably, 3 dcSSc patients died form chronic intestinal pseudo-obstruction (CIPO). **[Conclusion]** Cardiopulmonary complications and CIPO were the most important cause of death in SSc in our patient population.

W81-2

Association of *UBE2L3* polymorphisms with systemic sclerosis

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Conflict of interest: None

[Objectives] *UBE2L3* encodes a ubiquitin-conjugating enzyme, and was found to be associated with systemic lupus erythematosus (SLE) and rheumatoid arthritis (RA). In this study, we examined whether *UBE2L3* is associated with systemic sclerosis (SSc). [Methods] A case-control association study was performed in 391 Japanese patients and 1010 healthy controls. [Results] Although significant association was not detected in the whole SSc group, rs2298428T allele was significantly associated with diffuse cutaneous systemic sclerosis (dcSSc) (*P*=0.010, odds ratio [OR] 1.74, 95% confidence interval [CI] 1.14-2.64, recessive model), presence of interstitial lung disease (ILD) (*P*=0.040, OR 1.59, 95%CI 1.59-2.47, recessive model), and anti-topoisomerase I antibody (ATA) (*P*=0.017, OR 1.40, 95%CI 1.06-1.85, allele model) when compared with healthy controls. Significant association of rs131654T allele was also detected in dcSSc (*P*=0.007, OR 1.58, 95%CI 1.13-2.20, recessive model) and presence of ATA (*P*=0.004, OR 1.79, 95%CI 1.20-2.68). These SNPs were in linkage disequilibrium (*D'*=0.94, *r2*=0.44), and the association was not attributable to either one of the SNPs. These results suggested that *UBE2L3* is a shared susceptibility gene to SLE, RA and dcSSc.

W81-3

Pathological comparison of hypertensive and normotensive scleroderma renal crisis (SRC) by renal biopsy

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Conflict of interest: None

Objective. To assess clinicopathological differences between hypertensive and normotensive SRC by renal biopsy. Methods. We evaluated 4 patients with SRC, excluding ANCA positive cases, between 2007 and 2011, three female and one male, mean age 60.3 years. Two cases were normotensive. Mean duration from onset of systemic sclerosis to SRC was 24 months. Three cases had taken steroid at the diagnosis of SRC. Anti RNA polymerase I/III was positive in 3 cases. All patients were treated with ACE inhibitors, 2 normotensive cases with plasma exchange, 2 with temporary dialysis and 1 with permanent dialysis. Renal biopsy was performed in all patients when the platelet count became normal. Results. One of two normotensive patients had clinically hypertensive SRC because he had heart failure and could not raise blood pressure. Another normotensive patient showed severe hemolytic anemia, thrombocytopenia and relatively low plasma renin activity. Renal biopsy of this patient showed glomerular lesions such as thrombi, which were compatible with thrombotic microangiopathy (TMA). Endothelial cell injury was shown in smaller arteries than in the other 3 hypertensive cases. Conclusion. In normotensive SRC, endothelial cell injury in relatively small arteries may cause TMA.

W81-4

HLA-DRB5* 01:05 is a Risk Factor for Systemic Sclerosis with Interstitial Lung Disease

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Conflict of interest: None

[Objectives] Interstitial lung disease (ILD) is a serious complication of systemic sclerosis (SSc). We aimed to elucidate markers associated with ILD in patients with SSc. [Methods] RNA samples prepared from PBMCs were divided into 4 sets of RNA pools according to the presence or the absence of ILD and to the treatment,

and then were subjected to microarray analysis. Genomic DNA samples were collected from 147 healthy controls and 70 SSc patients who received HRCT for the evaluation of ILD. Genotyping was done using sequence specific primers method. Obtained results were re-evaluated using 2nd cohort that comprised 83 healthy controls and 79 SSc patients. [Results] Microarray analysis revealed that *HLA-DRB5* was the only gene commonly up-regulated more than 3 times in patients with ILD compared to those without. The frequencies of *DRB5* genome-carriers were more frequent in SSc patients with ILD than in those without ILD or healthy controls, in both cohorts. Detailed genotyping of *DRB5* gene revealed that *DRB5*01:05* allele was significantly more frequent in SSc patients with ILD than in those without (OR:8.07, 95% C.I. 3.06 – 21.28). This association was confirmed in the 2nd cohort. [Conclusion] *HLA-DRB5*01:05* allele is a risk factor for the development of ILD in patients with SSc.

W81-5

Use of line blot assay as a screening test for autoantibodies in sera of patients with systemic sclerosis (SSc)

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Conflict of interest: None

Objective Measurement of auto-antibody is informative for diagnosis of SSc. Line blot assay provides a qualitative in vitro assay for detecting human IgG class auto-antibodies for 13 different antigens simultaneously. The aim of our study is to evaluate availability of line blot assay for SSc in clinical setting, and assessing sensitivity comparing with conventional assay. **Methods** Serum samples from SSc patients in our hospital were investigated. IgG class autoantibodies for 13 different antigens were analyzed using line blot assay. Anti-Scl70 antibody and anti-centromere antibody was also measured using conventional ELISA assay. **Results** All patients in whom anti-Scl70 antibody positivity by ELISA assay also showed positivity by line blot assay. 95% of patients in whom anti-centromere antibody positivity by ELISA assay showed positivity by line blot assay On the other hand, 22.7% and 11% of patients showed anti-Scl70 antibody and anti-centromere antibody positivity by line blot assay respectively in whom showing negativity by ELISA assay. **Conclusion** Sensitivity is much higher in line blot assay than conventional ELISA assay. Line blot assay provides more beneficial information in terms of multiple parameter measurement, and useful for evaluating the characteristic of SSc.

W81-6

The analysis of CD161$^+$ VΔ1$^+$ $\gamma\Delta$T cells in interstitial pneumonitis patients with connective tissue disease

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Conflict of interest: None

[Purpose] Interstitial pneumonia (IP) is one of the critical complications in patients with several connective tissue diseases. However, the exact mechanism of IP remains elusive. The purpose of this study is to clarify the role of CD161$^+$ VΔ1$^+$ $\gamma\Delta$T cells in the generation of IP. **[Methods]** 1) Peripheral blood mononuclear cells (PBMCs) were isolated from healthy controls (HC, n=20) and patients with rheumatoid arthritis (RA, n=16), polymyositis/dermatomyositis (PM/DM, n=14), and systemic sclerosis (SSc, n=31). Cells were analyzed by flow cytometry. 2) We examined the frequency of CD161$^+$ VΔ1$^+$ $\gamma\Delta$T cells in PBMCs from patients with IP. 3) We examined the correlation between serum KL-6 values and the frequency of CD161$^+$ VΔ1$^+$ $\gamma\Delta$T cells in patients with IP. **[Results]** 1) In SSc patients, the frequency of CD161$^+$ VΔ1$^+$ $\gamma\Delta$T cells was significantly higher than that of HC ($p<0.05$), whereas RA and PM/DM were not. 2) In SSc patients, the frequency of CD161$^+$ VΔ1$^+$ $\gamma\Delta$T cells from IP-negative subjects was significantly increased than that of IP-positive ($p<0.05$), whereas RA and PM/DM were not. 3) IP-positive SSc patients had negative correlation between KL-6 values and CD161$^+$ VΔ1$^+$ $\gamma\Delta$T cells ($p<0.05$). **[Conclusion]** CD161$^+$ VΔ1$^+$ $\gamma\Delta$T cells might play a regulatory role in the generation of IP in patients with SSc.

W82-1

Decreased plasma ghrelinlevels in patients with systemic sclerosis

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Conflict of interest: None

[Objectives] The aim of the present study was to investigate the levels of plasma ghrelin in patients with systemic sclerosis (SSc) and to determine the association between ghrelin levels and disease phenotypes. We also explored the effects of ghrelin on collagen production in skin fibroblasts derived from patients with SSc. [Methods] 47 patients with SSc and 19 healthy controls (HC) were enrolled in this study. Plasma acylated ghrelin and desacylated ghrelin were determined by ELISA. Skin fibroblasts derived from 6 patients with SSc were cultured with various concentrations of ghrelin. [Results] Plasma acylated ghrelin levels were significantly lower in patients with SSc (median 13.7 fmol/l (3.65-26.6)) compared with HC (median 21.8 fmol/l (11.4-39.1); $p < 0.0001$). Plasma desacylated ghrelin levels were significantly lower in patients with SSc than those with HC ($p < 0.0001$). In particular, the levels of acylated ghrelin in patients with interstitial lung disease (ILD) were lower than those in patients without ILD ($p = 0.02$). In the experiments in vitro, procollagen type I C peptide production was suppressed by optimal concentrations of ghrelin ($p < 0.05$). In conclusion, our results suggest that ghrelin may exert an anti-fibrotic effect in skin fibrosis.

W82-2

Measurement of serum Fibroblast Growth Factor (FGF)19 in patients with scleroderma bowel involvements

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Conflict of interest: None

[Objectives] Fibroblast growth factor (FGF)19 is one of the metabolic hormone which regulate bile acid synthesis and lipid metabolism. To evaluate the role of serum FGF19 in patients with scleroderma bowel involvements we measured the level of FGF19 in sera of patients with SSc. [Methods] We measured FGF19, FGF21, and FGF23 by ELISA in the sera of 37 patients with SSc, and normal subject. Between clinical finding, 13C-fatty acid absorption breath test and level of FGF19 were analyzed in patients with SSc. [Results] Level of serum FGF19 of patients with SSc were significantly lower than normal subjects(SSc: 140.9±92.6pg/ml, Normal: 211.3±78.9pg/ml, P=0.002). Serum level of FGF19 were correlated with 8 hours ^{13}C cumulative recovery ratio in ^{13}C-fatty acid absorption breath test and clinical severity scleroderma

bowel involvement(GI) grading scale in SSc. GI grading 3, 67.47±24.9pg/ml, Grade4, 14.8±23.0pg/ml. FGF19 were measured before and after therapy in a patient with severe GI involvements of SSc. FGF19 increased the basic level in fast condition but also induction level by prokinetic drug and antibiotics. [Conclusion] Measurement of serum FCF19 level is a useful clinical parameter for diagnosis and monitoring in Scleroderma bowel involvements. [

W82-3

Assessment of peripheral blood flow with systemic sclerosis (SSc) using thermography and laser doppler flowmeter

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Conflict of interest: None

[Objectives] To incestigate usefulness of digital peripheral blood flow evaluation system. [Methods] We evaluated digital peripheral blood flow of SSc patients (N=20) and healthy controls (N=5) before and after the cold stress, using thermography and laser doppler flowmeter. Using thermography, skin temperature of finger was measured before and after the cold stress. And the skin temperature recovery rate was calculated. Using laser doppler flowmeter, we measured blood flow of finger before, durin and after the cold stress. And decreased rate of blood flow and velocity of blood flow recovery were calculated. [Results] The mean skin temperature recovery rate of SSc patients and controls at 5 minuted and 10 minutes after cold stress were 0.55 and 0.96 (p=0.04), and 0.52 and 0.96 (p=0.03), respectively. The dicreased rate of blood flow and velocity of blood flow recovery of SSc and control were 0.67 and 1.44 (p=0.08), 0.5 and 0.96 (p=0.09), respectively. [Conclusion] Using these evaluation systems, we could detect the delay of peripheral blood flow recovery. These results suggest thermography and laser doppler flowmeter to be promissing tools for peripheral blood flow assessment for SSc patients.

W82-4

Hemodynamic Characteristics in pulmonary Arterial Hypertension Associated with Systemic Sclerosis

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Conflict of interest: None

[Objectives] To reveal the characteristics of hemodynamics in pulmonary arterial hypertension (PAH) associated with systemic sclerosis (SSc), we performed a retrospective study. **[Methods]** We analyzed 156 right heart catheter data obtained from 65 patients with PAH associated with connective tissue diseases, including 30 patients with SSc, 16 patients with systemic lupus erythematosus, and 13 patients with mixed connective tissue disease, who were followed between January 1980 until October 2011 in our hospital. We compared mean pulmonary artery pressure (PAP), cardiac output (CO), and pulmonary capillary wedge pressure (PCWP) between SSc patients (SSc group) and non-SSc patients (non-SSc group). **[Results]** There were no significant difference in mean PAP (SSc group vs. non-SSc group: 36.1±11.9 mmHg vs. 37.9±12.2 mmHg, p=0.340) and CO (SSc group vs. non-SSc group: 4.54±1.34 L/min vs. 4.81±1.42 L/min, p=0.246) between SSc and non-SSc group. In contrast, PCWP in SSc group was significantly higher than that in non-SSc group (SSc group vs. non-SSc group: 7.77±4.00 mmHg vs. 6.38±2.71 mmHg, p=0.246). In conclusion, these results demonstrated that left ventricular diastolic dysfunction due to heart involvement of SSc may also play a role in pathophysiology of PAH associated with SSc.

W82-5

The states of systemic sclerosis patients administered Toshilizumab for three years.

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Conflict of interest: Yes

[Objectives] Systemic sclerosis (SSc) is an autoimmune disease characterized by fibrosis of the skin and internal organs. Although the etiology remains uncertain, many reports have suggested IL-6 is involved in the pathological condition of SSc. We have reported cases who were administered anti-IL-6 receptor antibody tocilizumab (TCZ) for six months [Rheumatology 2010,49]. To know the effect of TCZ on SSc for longer period, we administered TCZ for three years. [Methods] Three diffuse cutaneous SSc patients (male 1, female 2) have received TCZ with their informed consent and under the permission of ethical committee of Osaka University Hospital. One of three patients showed lung fibrosis. Two patients continued telmisartan because they had developed renal crisis before started. All patients continued predonisolone. The administration dose of TCZ was 8mg/kg, and the interval was 4 weeks. An examiner monitored skin hardness with modified Rodnan skin score manner. [Results] The skin score were decreased as following respectively; from 23 to 0, from 26 to 10, from 27 to 4. TCZ is worth investigating the effect on SSc. Because, occasionally, skin involvement can improve by itself, we are conducting parallel-group trial between conventional therapy and TCZ added group.

W82-6

Long-term efficacy of autologous hematopoietic stem cell transplantation for severe systemic sclerosis

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Conflict of interest: None

[Objectives] Recent phase II study has revealed that autologous hematopoietic stem cell transplantation (auto-HSCT) is more effective on severe systemic sclerosis (SSc) than conventional intravenous cyclophosphamide pulse therapy. However, there is paucity of the study showing the long-term efficacy of auto-HSCT. The aim of this study is to investigate the long-term efficacy of auto-HSCT on severe SSc. [Methods] Nineteen patients with SSc received auto-HSCT with (n=11) or without (n=8) CD34+ selection. [Results] Skin sclerosis and interstitial pneumonia were improved after auto-HSCT and the effect was sustained for 7 years. The serum levels of anti-Scl-70 and KL-6 was significantly decreased for 7 years after auto-HSCT. There was no treatment-related mortality. Five and seven years after auto-HSCT, the overall survival was 95 and 81%, and the progression-free survival was 69 and 58%, respectively. CD34+ selected auto-HSCT was more effective on skin

sclerosis and more strongly associated with viral infection than unmanipulated auto-HSCT. The delayed and Th1-skewed reconstitution of CD4+ T cells was observed after both CD34+ selected and unmanipulated auto-HSCT. [Conclusion] Auto-HSCT was effective in the treatment of SSc and the effect was sustained for 7 years.

W83-1

Fas-FasL dependent induction of autoantibody suppressive Egr2 expressing $CD4^+CD25^-LAG3^+$ regulatory T cell

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Conflict of interest: None

Systemic lupus erythematosus (SLE) is an autoimmune disease characterized by autoantibody production. It was recently shown that T-cell-specific Egr-2-deficient mice develop lupus-like autoimmune disease. Egr2 is a zinc finger transcription factor required for T cell anergy induction. We have previously reported the novel Foxp3-independent $CD4^+CD25^-$ regulatory T cells (Tregs) that characteristically express both LAG3 and Egr2, and forced expression of Egr2 in naïve $CD4^+$ T cells can convert them into $CD4^+CD25^-LAG3^+$ Treg ($LAG3^+$ Treg) phenotype. Here, we demonstrated the role of $LAG3^+$ Tregs in lupus pathogenesis. Adoptive transfer of $LAG3^+$ Tregs from control MRL/+ mice significantly suppressed the progression of nephritis and autoantibody production in MRL/*lpr* lupus prone mice. In contrast, $CD4^+CD25^+$ Tregs from MRL/+ mice exhibited no significant therapeutic effect. Interestingly, Fas-FasL costimulating signaling was required for the induction of Egr2 in $LAG3^+$ Tregs. Moreover, $LAG3^+$ Tregs coexpressed Egr2 and PD-L1, and failed to suppress antibody production by $PD1^{-/-}$ B cell. These findings elucidate that the Fas-FasL costimulation induced Egr2 expressing $LAG3^+$ Tregs play a crucial role in preventing the excessive B cell responses via PD-1-PD-L1 interaction.

W83-2

A novel autoantibody against EphB2 in a patient with systemic lupus erythematosus who manifested severe encephalitis

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Conflict of interest: None

[Objectives] It is generally accepted that autoantibodies against integral membrane proteins are usually pathogenic. We constructed a retroviral vector system to identify autoantigens expressed on the cell surface. Anti-endothelial cell antibodies (AECA) are thought to be critical for vasculitides in collagen diseases. In this study, we detected high AECA activity in a patient with central nervous system (CNS) lupus and tried to identify the target autoantigen. [Methods] 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] An AECA-positive clone was isolated using serum IgG from a lupus patient who manifested severe encephalitis without anti-ds DNA antibody. The clone was identical to cDNA of ephrin type-B receptor 2 (EphB2). HUVEC expressed EphB2 and the prototype AECA IgG bound specifically to EphB2-transfected cells. EphB2 has roles in the endothelium, and also control N-methyl-Daspartate (NMDA) receptor function in nervous system. Furthermore, EphB2 is related to some neurological diseases. Identification of EphB2 in this patient might suggest that AECA play roles not only in endothelial dysfunction but also in target organ damage.

W83-3

Antiribosomal P protein antibodies enhance the production of IL-17 in human activated T cells

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Conflict of interest: None

[Objectives] Autoantibodies to ribosomal P proteins (anti-P) are detected in 30-40% of patients with SLE. We have recently disclosed that anti-P react with activated human peripheral blood monocytes. It was recently shown that anti-P enhance their production of TNF-α and IL-6 and induce Th1 responses by up-regulating their production of IL-12. It has been known that the expression of the ribosomal P epitope is induced on T cells after activation. However, the effects of anti-P on the function of activated T cells remain unclear. The current study was undertaken to explore the effects of anti-P on the production of IL-17 and IFN-γ in activated T cells. [Methods] IgG anti-P were affinity-purified from sera of anti-P positive lupus patients. Purified T cells from healthy donors were cultured in wells in the presence of immobilized anti-CD3 (UCHT1) with anti-P or control IgG for 5 days. The concentrations of IL-17 and IFN-γ in the culture supernatants were measured using ELISA. [Results] Anti-P significantly enhanced the production of IL-17 in activated T cells, whereas anti-P did not influence their production of IFN-γ. These results indicate that anti-P play an important role in the pathogenesis of SLE through their direct effect on IL-17 production of activated T cells.

W83-4

The autoantibodies to citrullinated-glucose-6-phospate isomerase (GPI) in patients with RA

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Conflict of interest: None

[Objectives] To identify anti-citrullinated GPI peptide antibodies (Abs) in patients with RA. [Methods] 1) To map the antibody response, 9 peptides bearing arginine in human GPI protein were selected and their cyclic-citrullinated peptides (CCG-1-9) were constructed. Samples were obtained from patients with RA (n=208), SLE (n=101), SS (n=101) and healthy control (HC) (n=174). The levels of Abs against CCGs were measured by ELISA. As controls, their non-citrullinated GPI peptides were used as well. 2) Anti-citrullinated enolase peptide-1 (CEP-1) and anti-CCP Abs were also screened and compared with anti-CCG Abs. 3) GPI proteins were citrullinated by PADI and their Abs were detected by Western blot analysis. [Results] 1) Anti-CCG-2 Abs was most specifically identified in patients with RA (the positivity and specificity of was 25.5%, 99.7%, respectively). None-citrullinated form of GPI-peptides did not react to RA serum. 2) The positivity of anti-CEP-1 and CCP were 44.2%, 86.2%, respectively. Anti-CCG-2 was clearly correlated with anti-CEP-1 and CCP Abs. 3) The serum reaction to cit-GPI protein is under investigation. We identified anti-CCG-2 Abs specifically in patients with RA, suggesting that anti-CCG-2 Abs might be a new diagnostic marker for RA.

W83-5

Anti Carbonic Anhydrase III antibody in vasculitis syndrome

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Conflict of interest: None

[Objectives] To find useful markers other than anti-neutrophil cytoplasmic antibodies (ANCA) in the diagnosis of vasculitis syndrome [Methods] Sera from patients with vasculitis were screened for antibodies to lysate of mouse blood vessel by Western blotting. The protein spot corresponding to the band by 2-DE Western blotting was identified using MALDI-TOF/TOF MS. [Results] We observed one dominant band corresponding to a protein with a molecular weight of 30 kDa by 1-DE Western blotting. Nest, we detected the 30 kDa protein spot corresponding to the band by 2-DE Western blotting, and identified using MALDI-TOF/TOF MS as Carbonic Anhydrase III (CAIII). Using Western blotting with recombinant CAIII, we detected anti CAIII antibody at high frequency in sera from microscopic polyangitis (9 of 10) as well as Wegener granulomatosis (6 of 7). On the other hand, blot reactivity was scarcely observed in sera from aortitis syndrome (2 of 12). Our results suggest that anti CA III antibody could be a useful marker for vasculitis syndrome.

W84-1

Involvement of IL-6 on steroid-resistance

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Conflict of interest: None

[Objectives] Steroids are commonly used for the treatment of chronic inflammatory diseases. They are very effective, but, a high dose of steroid induces many side-effects. Therefore, rapid reduction of dose of steroid is very important once disease activity becomes low. Patients with chronic inflammatory disease sometimes show the resistance to steroid therapy. In addition, elevated levels of IL-6 are found in these patients. In this study, we examined whether IL-6 plays a role in steroid-resistance. **[Methods]** PMA-treated THP-1 cells (THP-1 macrophages) were cultured with IL-6 for 24 h. After medium replacement, cells were cultured with LPS in the presence of dexamethasone (DEX) for another 3 h. After culture, CCL20 mRNA expression was examined. Moreover, the effect of IL-6 on the localization of glucocorticoid receptor (GR) by DEX was examined. **[Results]** CCL20 mRNA induction by LPS was clearly suppressed by DEX, but IL-6 pretreatment attenuated the inhibitory effect of DEX. Furthermore, IL-6 pretreatment decreased GR expression and inhibited GR nuclear translocation. These effects of IL-6 were partially restored by the treatment with MEK/ERK inhibitor, PD98059. In conclusion, IL-6 might participate in steroid-resistance by reducing GR expression and nuclear translocation of GR.

W84-2

Agonist for cannabinoid receptor 2 (CB_2) ameliorates murine collagen-induced arthritis

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Conflict of interest: None

[Objectives] Cannabinoids (CBs) are chemical compounds included in marijuana. Its receptor CB_1 is predominantly expressed in the brain, whereas the cells of immune system express CB_2. Therefore, CB_2-specific agonist should affect on immune cells but not on central nervous system. Endogenous CB is one of the lipid mediators, which exhibit immunosuppressive properties. In this study, we investigated therapeutic effect of CB on arthritis. [Methods] Expression of CB_2 in the rheumatoid arthritis (RA) synovium was analyzed by immunohistochemistry. Effect of JWH133, CB_2-specific agonist, on murine collagen-induced arthritis (CIA) was evaluated. Osteoclastogenesis from peripheral blood monocyte with RANKL+M-CSF was analyzed by TRAP staining. IL-6 production was measured by ELISA. [Results] CB_2 was highly expressed in the RA synovium compared to osteoarthritis, which was expressed on macrophage, T cells, B cells and fibroblast-like synoviocytes (FLS). JWH133 reduced arthritis score, inflammatory cell infiltration and bone destruction on CIA mice. JWH133 also inhibited osteoclast formation from monocyte and IL-6 production by FLS *in vitro*. [Conclusion] Present study suggests that CB_2-specific agonist could be new therapy for RA by inhibiting osteoclast differentiation and cytokine production.

W84-3

Autotaxin and lysophosphatidic acid receptors: potential target molecules in new therapies for rheumatoid arthritis

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Conflict of interest: None

[Introduction] Lysophosphatidic acid (LPA), a bioactive lipid, is generated by autotaxin (ATX). Last year in JCR meeting, we showed ATX and $LPA_{1\text{-}4}$, receptors for LPA, were highly expressed in rheumatoid arthritis (RA) synovium, LPA induced cell proliferation and cytokines production in RA fibroblast-like synoviocyte, and BrP-LPA (a dual inhibitor for ATX and pan-LPA receptors) inhibited murine collagen-induced arthritis (CIA). In this study, we analyzed the effects of LPA on osteoclastogenesis and inflammatory cell migration. [Methods] Peripheral blood monocytes were incubated with RANKL+M-CSF, and osteoclast formation was analyzed by TRAP staining. Migrated fluorescence labeled-$CD11b^+$ splenocytes, which were transferred into CIA, into the synovium were counted. Effect of ATX inhibitor or LPA_1 antagonist on CIA was also analyzed. [Results] LPA enhanced the osteoclast formation in lipid-free condition. BrP-LPA inhibited the osteoclastogenesis. BrP-LPA also inhibited the $CD11b^+$ cell migration into the synovium. Both ATX inhibitor and LPA_1 antagonist reduced arthritis score, bone destruction, histological changes, and IL-17 production from collagen-stimulated splenocytes. [Conclusion] Collectively, our results indicate ATX and LPA_1 are promising target molecules for new RA therapy.

W84-4

Interaction between CCL25 and CCR9 might play important roles in the pathogenesis of rheumatoid arthritis

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Conflict of interest: None

[Objectives] To explore pathogenic roles of CCL25 on rheumatoid arthritis (RA), we analyzed expression of CCL25 and its receptor, CCR9, in the RA synovium, stimulatory effects of CCL25, and the effect of CCR9 blockade on collagen-induce arthritis (CIA). [Methods] Expression of CCL25 and CCR9 was examined by immunohistochemistry. Cytokine production was measured by ELISA. Osteoclastogenesis was determined by TRAP staining of peripheral blood monocyte incubated with RANKL+M-CSF. CIA mice were treated with CCR9 antagonist (ChemoCentryx, Inc.), and arthritis scores were evaluated. [Results] CCL25 and CCR9 were highly expressed in the RA synovium compared to osteoarthritis. CCL25 was expressed on macrophages, and CCR9 was expressed on macrophages, dendritic cells, fibroblast-like synoviocytes (FLS), and T cells in the synovium. Stimulation with CCL25 increased IL-6 and MMP-3 production from FLS and IL-6 from peripheral blood monocytes. CCL25 also enhanced osteoclast formation from the monocytes. CCR9 antagonist inhibited the arthritis in CIA. These results suggested that CCL25 and CCR9 interaction might play important roles for cell infiltration into the RA synovium, inflammatory mediator production, and osteoclast formation. Blockade of CCL25 and CCR9 could be a new therapy for RA.

W84-5

Mechanism of ectopic calcification of adipose-derived mesenchymal stem cells mediated by inflammatory cytokines

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Conflict of interest: None

[Purpose] Ectopic calcification in autoimmune diseases is considered as calcium deposits, but its mechanism remains unclear. We estiamted the role of inflammatory cytokines in differentiation of human adipose-tissue derived stem cell (ADSC) to osteoblast-like cells. [Method], ADSC was cultured in osteoblast induction medium in the presence of Inflammatory cytokines (IL-6/sIL-6R, TNFα, IL-1β) for 8 days. Calcification was evaluated by arizarin red staining and RUNX2 expression was done by Real-time PCR analysis. [Results] Addition of cytokines to ADSC increased calcifications and the expression of RUNX2 in a dose-dependent manner at day 8. Among the cytokines, strongest calcification was observed with IL-6/sIL-6R, although IL-6 alone did not show any effect. TNFα and IL-1β increased WNT5A expression and IL-6/sIL-6R increased ROR2 expression on day 1. However, expression level of β-catenin, indispensable for canonical pathway of Wnt-signaling did not change. [Conclusion] Our results indicate that inflammatory cytokines like IL-6 act on ADSC and induce differentiation of ADSC to osteoblast-like cells depositing calcium via activation of non-canonical pathway of Wnt-signaling, resulting in ectopic calcification in autoimmune diseases.

W84-6

Analysis of pathological role of cytokines in pulmonary hypertension using Bio-plex ctytokine array

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Conflict of interest: None

Objective: We have reported VEGF is associated with Raynaud's phenomenon in the treatment with bosentan therapy using Bio-Plex cytokine array. We investigated the pathological role of cytokines in pulmonary hypertension (PH) compared between collagen disease group and cardiology group. METHODS: 11 patients in our department (SSc 6, PM2, RA2, SLE1 61.7±8.4 yrs, M/F;1/9), or 14 patients in the cardiology department of National Hospital Organization (IPAH5, CTEPH9, 53.2±19.8 yrs, M/F; 4/10) were examined the clinical parameter or serum cytokine level using Bio-Plex cytokine array (27-plex, 21-plex) Results: mPA (25.5±6.6 vs.52.6±30.3mmHg, p = 0.0002) and PVR (142.0±72.8 vs. 981.5±495.6 dyne * sec * cm-5, p <0.0001) showed significant differences between two groups, but not 6MW and BNP. IL-7, IL-8, Eotaxin, IL-12p40, IL-16, TRAIL, HGF (553.6±485.4vs. 8392.9±11187.8pg/ml, p=0.0209), IFN-α2 showed significant differences between two groups. After adjustment for age and BMI, Borg scale and IFN-α2, PCWP and MCP-1, and PVR and Eotaxin were significantly correlated. Logistic regression analysis using age, HGF and SCGFβ were distinguished with collagen disease, IPAH and CETPH (R0.797, p <0.0001). These results suggest that cytokines play an important role in the pathogenesis of PH.

W85-1

The clinical course and treatment in patients with intestinal Bechet's disease; a single center experience of current 30 cases

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Conflict of interest: None

[Objectives] We examined the clinical characteristics, features of intestinal lesions, treatment in 30 patients with the intestinal Bechet's disease followed at the Teikyo University Hospital currently. [Methods] Sixteen patients were male, 14 were female. The mean age at onset of Bechet's disease was 32.9 years. They developed the intestinal lesions at the mean age 39.4 years. [Results] Eight patients were HLA-B51 positive. 16 were HLA-B51 negative and the rest 6 were not tested. 11 cases showed the complete phenotype of the Bechet's and 18 were incomplete and one was not determined. Five patients involved in vascular, 2 in central nervous system. The most frequent initial symptom was abdominal pain (13 cases). Other initial symptoms were melena/bloody stool (11 cases) and diarrhea (6 cases), dysphagia, gastric distress, losing weight. The intestinal lesions existed in esophagus (1 case) and small intestine (2 cases), from small intestine to ileo-cecal area (2 cases), ileo-cecal area (11 cases), from ileo-cecal area to ascending colon (2 cases), transverse colon (1 case), rectum (1 case). Nineteen patients were treated and well-controlled by steroid, 5-ASA or colchicine. 7 cases were treated with MTX, 1 case with cyclosporine. Infliximab was administrated in 4 cases.

W85-2

Clinical features of Vasculo- Behçet's disease in Japan: Behcet's Disease Research Committee, MHLW

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Conflict of interest: None

[Objectives] Vascular lesion is one of most serious manifestations in Behçet's disease (BD), whereas some regional differences have been shown in the clinical features. This study characterizes clinical features of vasculo-BD in Japan. [Methods] We retrospectively reviewed clinical data of 57 patients (mean 55 y.o. male 69%) with vasculo-BD in 8 institutions. [Results] Fifty three of 57 patients were enrolled. Ocular lesions were found in 45 % including 10 patients with complete type. The vein system was most frequently affected (64%), followed by the arterial and pulmonary systems. Corticosteroids and immunosuppressant were used in 74% and 37%, respectively, whereas 7 patients (13%) had surgical operation without local recurrence. Infliximab was administered into 3 patients, resulting in improvement of vascular lesions. Two patients have died: one died from postoperative aortic pseudoaneurysm and the other died of sepsis. Anticoagulants and/or anti-platelets were given to 83% of the patients, though EURLAR recommendation (2008) which refers to avoid usage of these agents in vasculo-BD. Although minor gastrointestinal bleeding and subcutaneous hemorrhage were noted in 6 patients, no major bleeding event including fatal pulmonary hemorrhage was found in this study.

W85-3

Imputation identifies *CCR1* and *STAT4* as novel Behçet's disease susceptibility loci.

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Conflict of interest: None

[Objectives] A previous genome-wide association study with 300K SNPs in Turkish Behçet's disease (BD) identified two MHC class I loci, *IL10*, and the *IL23R-IL12RB2* locus. We have now used imputation to discover additional BD susceptibility loci. [Methods] Imputation was conducted using MACH v1.0.15 providing 800K SNPs for analysis in the 1215 BD cases and 1278 healthy controls. Two independent replication sets were genotyped for the most significant SNPs and functional studies were undertaken. [Results] An imputed SNP rs7616215 located 3' of the chemokine receptor-1 (*CCR1*), exceeded genome-wide significance ($p=1.9\times10^{-8}$). This finding was replicated in additional Turkish and Japanese BD samples (a meta-analysis of 2641 cases and 2593 controls, OR 0.72, 95% CI 0.66–0.79, $p=5.19\times10^{-13}$). The protective C allele was associated with increased *CCR1* mRNA expression and increased monocyte chemotaxis. In addition, meta-analysis showed association at rs7574070 in *STAT4* (OR 1.27, 95% CI 1,17-1.37, $p=8.58\times10^{-10}$). The risk allele A was associated with increased *STAT4* expression. Our data suggest that increased CCR1 expression and chemotaxis, which may be associated with efficient microbial pathogen clearance, protect against BD and that increased expression of STAT4 is a risk factor.

W85-4

Both Th17 and Th1/Th17 subsets are involved in the pathogenesis of BD

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Conflict of interest: None

[Objectives] Behçet's disease (BD) is one of inflammatory diseases and infiltration of immune cells including lymphocytes is a characteristic of the lesions of BD. We have shown that Th17 are involved in the pathogenesis. To further understand the role of Th17, we examined the behavior of subsets of Th17 in circulation of BD. [Methods] 13 patients with BD (6 active and 7 inactive) and 4 healthy controls were included. Proportion of subsets of Th17 in CD4+ cells (Th17 subset: CCR6+CCR4+, Th1/Th17 subset: CCR6+CXCR3+, other Th17 subsets: CCR2+CCR5-) was examined by flow cytometry. Levels of chemokines matched with receptors on subsets of Th17 (CCL20 for CCR6, RANTES for CCR4 and CCR5, CXCL9 for CXCR3, and MCP-1 for CCR2) were examined by ELISA. [Results] Proportion of Th17 and Th1/Th17 subsets was significantly decreased in active disease phase compared with those in inactive phase. However, behavior of the CCR2+CCR5- subset was not associated with disease activity. Plasma CCL20 levels were significantly higher in BD compared with healthy controls, however, no increase of other chemokines was observed. [Conclusions] These results suggest that both Th17 and Th1/Th17 subsets are migrated to the lesion via CCR6-CCL20 axis and associated with the pathogenesis of BD.

W85-5

Study on the safety and efficacy of Infliximab (IFX), an anti-TNF-α antibody, in patients with refractory intestinal-Behçet's disease (BD).

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Conflict of interest: None

[Objectives] Intestinal BD is one of the intractable category of BD and some patients are refractory to conventional therapy. We evaluate the efficacy of IFX in 18 patients with intestinal-BD. [Methods] The patients who were refractory to conventional therapy, or difficult to continue intensive treatment because of adverse effect and could not taper CS were administered IFX. The primary endpoint is the healing rate of ulceration at 1 year, secondary endpoints is the ameliorating effect based on the "Disease Activity Index for Intestinal Behçet's disease" (DAIBD), and the dose of corticosteroid tapered at 1 year. [Results] The mean age was 42.6, male 4 cases, female 12 cases. 3 patients is HLA-B51 positive. And 9 patients have repeated relapse, 6 patients had a history of perforation or surgical treatment. We used MTX to all of the patients. Retention rate at 1 year treatment of IFX was 88.9 % Healing rate of ulceration is 66.7 %. DAIBD is significantly decreased from 73.9 to 27.2 at 1 year. 56.3 % of the patients reached Quiescent. The dose of CS is reduced from 12.7 to 2.7 mg. The serum

TNF levels at the introduction of IFX and disease activity showed a positive correlation. It was suggested IFX is theoretically useful and effective option for refractory intestinal-BD.

W85-6

Treatment with Infliximab is Effective and Safe in BD Patients with Uveitis.

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Conflict of interest: None

[Objectives] This study determined what factors are associated with ocular attacks during the IFX therapy. [Methods] We retrospectively examined clinical courses of 19 BD patients who received IFX due to uveitis. In the original regimen, IFX (5mg/kg) was given at 0, 2, 6 week, and thereafter every 8 weeks, but the intervals were shortened after major ocular attacks occurred. [Results] Mean duration was 5.7 years from the disease onset to initiation of infliximab therapy. Before the infiliximab therapy, 16 patients had received colchicines and 7 patients had cyclosporine A. Duration of IFX was 29.9 months IFX therapy was discontinued in two patients by infusion reaction. The infusions were suspended one or two week in 2 patients because of infection including infectious mononucleosis by cytomegalovirus. Visual acuity were improved in 18 eyes, unchanged in 7 eyes, and deteriorated in 5 eyes. After ocular attacks, the infusion interval was shortened from 5 to 7 weeks in 7 patients. Ocular attacks were significantly suppressed, resulting in improvement of visual acuity. However, the attacks were accumulated in the last 2 weeks of infusion interval. It is hard to predict responsiveness to IFX therapy based on the pre-therapeutic clinical features.

W86-1

Treatment with Biologic Agents Improves the Prognosis of Patients with Rheumatoid Arthritis and Amyloidosis

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Conflict of interest: None

[Objectives] Our purpose was to examine the safety of therapy with biologic agents in RA patients with reactive AA amyloidosis, together with prognosis and hemodialysis (HD)-free survival, in comparison without such therapy. [Methods] One hundred thirty-three patients with an established diagnosis of reactive AA amyloidosis participated. Patients who had been started on HD were selected for inclusion only after the presence of amyloid had been demonstrated. Fifty-three patients were treated with biologic agents (biologic group) and 80 were not (non-biologic group). [Results] Survival rate was significantly higher in the biologic group than in the non-biologic group (p=0.001). Annual mortality rate due to amyloidosis was 13.2% in the non-biologic group and 4.6% in the biologic group. Nine patients in the biologics group and 33 in the non-biologic group were started on HD. HD-free survival was significantly higher in the biologic group (p=0.00004). The annual HD initiation rate was 14.3% in the non-biologic group and 6.7% in the biologic group. [Conclusion] Our study demonstrates that patients with amyloidosis have a higher mortality rate, but that the use of biologic agents reduces mortality among them. Additionally, the use of biologics improves the HD-free survival rate.

W86-2

Study on the efficacy of biologics in patients with rheumatoid arthritis complicated with secondary AA amyloidosis (A comparison between an anti-IL-6 receptor antibody and TNF blockers)

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Conflict of interest: None

[Objectives] To evaluate the usefulness of biologics on RA complicated with AA amyloidosis and compare the efficacy of an anti-IL-6 receptor antibody with that of TNF inhibitors. **[Methods]** Tocilizumab(TCZ), etanercept(ETN) and infliximab(IFX) were each administered to 7, 4 and one patients. After the treatment two years or more, the clinical and histopathological data were compared between TCZ group (4 cases) and ETN group (3 cases). **[Results]** In 4 cases each treatment were discontinued or switched, because of secondary failure, infections and anxiety disorder. Subsequently one patient died of renal failure and another patient is having decreased renal function rapidly. Between TCZ group and ETN group there was no difference in the administration period as well as the disease duration of RA and amyloidosis. In TCZ group, the concentrations of serum amyloid A became normal in all cases and the AA amyloid protein content of the gastric mucosal biopsy specimens was decreased in 2 cases. In the amyloid staining with BF-227, hematoxylin-eosin and anti-AA antibody three cases of TCZ group showed clear improvement, but none of ETN group was improved, thereby suggesting that TCZ might be superior to remove the AA amyloid deposition from the tissue.

W86-3

Comparison of clinical usefulness between anti-interleukin-6 receptor therapy and anti-tumor necrosis factor treatment in AA amyloidosis complicating rheumatic diseases

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Conflict of interest: None

[Objectives] To compare the efficacy and safety of tocilizumab (TCZ) with that of anti-TNF agents (TNF). **[Methods]** We compared 2 therapy groups (TCZ: 22 patients; TNF: 32 patients) over a 5-year period. We evaluated (1) treatment retention rates (Kaplan-Meier method) and safety profiles, (2) changes in SAA levels, (3) changes in eGFR, (4) changes in occurrence of proteinuria, and (5) episodes of severe GI events. **[Results]** 1. Treatment retention rates at 1 and 5 years were 90.4% and 90.4% (TCZ) and 69.0% and 34.3% (TNF), respectively (logrank test: p=0.0154). Reasons for withdrawal were adverse events (2 in TCZ and 4 in TNF), primary lack of efficacy (2 in TNF), and secondary loss of efficacy (8 in TNF). 2. Median SAA levels fell from 219.2 to 4.95 μg/dL (TCZ) and from 143.6 to 38.1 μg/dL (TNF) (p<0.0001). 3. Median eGFR changed from 41.6 to 50.7 mL/min/1.73 m^2 (TCZ) and from 76.3 to 67.4 mL/min/1.73 m^2 (TNF) (p=0.0062). 4. Proteinuria was resolved at last observation in 9 of 13 cases in TCZ and in 1 of 3 in TNF. 5. Severe GI events were observed in 1 of 22 (TCZ) and 3 of 32 (TNF) during the treatment period. **[Conclusion]** TCZ was confirmed to be superior to TNF in the treatment of AA amyloidosis complicating rheumatic diseases.

W86-4

The clinical feature of AA amyloidosis complicating rheumatoid arthritis (RA) and the efficacy of biological treatment against it

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Conflict of interest: None

[Objectives] To clarify the clinical feature of the patients who diagnosed as AA amyloidosis in our hospital. [Methods] We retrospectively analyzed the clinical feature at the time of diagnosis and progress of the 40 patients up to 2011. [Results] The demographics of the 40 patients are that 36 female patients(90%), mean age 63.8±10.3 y.o. and disease duration of RA 16.7±10.9 years. The mean DAS28-ESR was 4.78±1.54. MTX was used in 12(30%), with mean dosage of 6.0±1.75mg/w. The clinical symptoms associated with AA amyloidosis such as diarrhea, proteinuria were observed in the majority of them. All patients were diagnosed by gastrointestinal (GI) biopsy except 2 patients by renal biopsy. Biological agents have been introduced in 30 patients (75%) and they showed significant improvement. Among 21 patients who have undertaken re-biopsy of GI after biological treatment, amyloid A deposit disappeared pathologically in 14 of them (67%). Four patients have died during the observation by the end of 2011. In addition to the general characteristics of patients with AA amyloidosis, the rate of administration of MTX has been relatively in low and the dosage was tended to be low in these patients. Our data indicates possibility of better clinical prognosis of AA amyloidosis with biological treatment.

W86-5

Treatment with abatacept for patients with AA amyloidosis secondary to rheumatoid arthritis (RA): efficacy and safety

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Conflict of interest: None

Objective: To elucidate the efficacy and safety of abatacept for patients with AA amyloidosis secondary to RA. **Methods**: Abatacept was treated for two patients, who were biopsy-confirmed AA amyloidosis. We monitored CRP, SAA, DAS28, the levels of IL-6 and TNFα, and relative rate of lymphocyte subsets in the disease course. **Results**: Few adverse effects emerged. The patients were SAA1.3 allele genotype, which is a poor prognostic factor of AA amyloidosis in Japanese RA patients, long-standing RA disease duration more than 20 years, and refractory to various DMARDs including methotrexate and etanercept. Besides patients' visual analogue scale in an early improvement, DAS28, inflammatory parameters, proteinuria, and digestive symptoms alleviated according to the treatment with abatacept. IL-6 lowered to control levels, but not TNFα. The relative values of CD4+CD25+Foxp3+Treg, CD4+T, and ratio in CD4/8 lessened to control levels. **Conclusion**: Abatacept showed efficacy on both RA disease activity and AA amyloidosis with ameliorating some surrogate markers and clinical symptoms. The changes among the levels of proinflammatory cytokines and the percentage of lymphocyte subsets suggested a complicated pathological states, both cell to cell cross-talk and cell with cytokine interaction in RA.

W87-1

Clinical, Structural, and Functional Assessments of Tocilizumab (TCZ) in the Clinical Setting

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Conflict of interest: None

[Objective] To assess the efficacy of TCZ in the clinical setting, investigate patient characteristics conducive to remission, and identify patients for whom TCZ is optimally suited. [Method] The subjects were 115 patients receiving TCZ 8 mg/kg q4w in our department. DAS28-ESR and CDAI were assessed at TCZ treatment initiation and at 52 weeks using LOCF. Efficacy was also assessed using a definition of remission based on the Boolean method. [Results] The mean age was 58.8 years and the mean duration of illness 12.5 years. The proportion concomitantly receiving MTX was 51.3%, and 55.8% had used TNF inhibitors in the past. After one year, the DAS28 scores had fallen from 5.8 to 3.0, and the CDAI scores had fallen from 27.0 to 11.3. The proportion with CDAI ≤ 2.8 was 14.2%, and the proportion achieving Boolean remission was 12.4%. Examination of the individual components of the Boolean remission criteria suggested the importance of VAS for achieving Boolean remission. A multivariate logistic regression analysis identified age and HAQ at treatment initiation as factors affecting DAS28 and CDAI remission at one year. [Conclusion] Our results suggest that it is important to initiate TCZ therapy in the early stages of the disease, before the progression of functional disorders.

W87-2

ACR/EULAR provisional definition of remission in patients using tocilizumab in clinical practice

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Conflict of interest: None

[Objectives] The concept of the definition of remission was proposed at the ACR/EULAR scientific meeting in 2010. However, this definition is based on a survey of past clinical trial data on MTX and TNF inhibitors. We attempted to evaluate the predictive validity of the new remission criteria from tocilizumab (TCZ) data obtained in clinical practice. [Methods] The subjects for the analysis were 61 patients in whom degree of progression of joint destruction and physical function could be evaluated among 155 patients administered TCZ 8 mg/kg Q4W in our department. DAS28-ESR, CDAI, HAQ and TSS were examined by the LOCF method at the start and after 24 weeks and 52 weeks of TCZ treatment. A good outcome for rheumatoid arthritis (RA) in this study was defined as $\Delta TSS \leq 0$ in X-ray imaging and $\Delta HAQ \geq 0.22$ in the HAQ after 1 year of TCZ treatment. The ability of evaluation items to predict a good outcome was validated using the sedimentation rate. [Results] In several remission candidates based on the Boolean method and patients who reached remission based on DAS28, SDAI and CDAI definition, prediction of a good outcome on X-rays was not possible. When a good outcome was defined as patients showing stability on X-rays and the HAQ, the sedimentation rate was the highest for CDAI (LR: 5.6).

W87-3

Comparison of RA patients in tocilizumab (TCZ) who showed only DAS28-ESR remission and both DAS28-ESR and SDAI remission.

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Itabashi Chuo Medical Center

Conflict of interest: None

[Objectives] To compare the patients with TCZ who showed only DAS28-ESR remission and both DAS28-ESR/SDAI remissions. [Methods] We examined patients who met DAS28-ESR remission criteria after 6 months of TCZ therapy. Patients who showed only DAS28-ESR remission were compared with those with both DAS28-ESR/SDAI remissions in age, sex, RA duration, RA stage, anti-CCP antibody, quantitative RF, MMP-3, tender joints, swollen joints, VAS, ESR, CRP, DAS, SDAI, mHAQ, PSL and MTX dose. Statistical analysis was by Fisher's exact test and Wilcoxon rank test. [Results] After 6 months, 31 patients met DAS remission criteria (8 showed DAS only, 23 showed both DAS/SDAI). Statistically significant differences at start were seen in anti-CCP antibody, quantitative RF and DAS (p=0.005, p=0.02, p=0.006, respectively). After multivariate analysis of these three for DAS/SDAI remissions, only anti-CCP antibody remained. Anti-CCP antibody in DAS remission and DAS/SDAI remissions was 8.30±8.65 and 84.3±72.9, and patients with high value of anti-CCP antibody tended to achieve SDAI remission. [Conclusions] Anti-CCP antibody is likely a factor related to DAS/SDAI remissions in TCZ therapy.

W87-4

Medium/long-term efficacy of tocilizumab treatment in RA patients: comparison of efficacy between groups classified by their background and radiographic evaluation

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Conflict of interest: None

Objective: To examine clinical and radiographic response of tocilizumab (TCZ) by various background. **Methods**: We assessed DAS28-ESR and mHAQ until week 104, and evaluated the total Sharp score (TSS) at baseline and at week 52 using LUNDEX method in 69 RA patients treated with TCZ. Patients were divided into the following subsets: concomitant MTX treatment (with vs. without); Stage (I II vs. III IV); disease duration (less than 5 years vs. more than 5 years); previous biologics (naive vs. switch); disease activity at baseline (DAS28 < 5.1 vs. ≧ 5.1). **Results**: In the MTX (+) group, DAS28, mHAQ and DAS response were more improved than in the MTX (-) group. DAS response was better in Stage III IV group, low disease activity group, switch group and short disease duration group than in Stage I II, high disease activity, naive and long disease duration group, respectively. ΔTSS was significantly less in MTX (-) group and short disease duration group than in MTX (+) group and long disease duration group. **Conclusion**: It goes without saying that TCZ treatment is more effective for early RA patients with low disease activity. However, TCZ is useful for patients with advanced disease stage or switchers in our study. Furthermore, TCZ monotherapy has possibility to suppress radiographic progression.

W87-5

Radiographic progression of cervical spine and hand in patients with rheumatoid arthritis receiving Tocilizmab treatment.

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Conflict of interest: None

[Objective] To evaluate radiographic change of cervical spine and hand in patients with RA receiving TCZ treatment. [Methods] We used TCZ for treating 32 RA patients for at least 1 year. Patients were extracted from multicenter study group for the treatment of RA using biolosics database (TBC). For evaluation of cervical lesions, the atlanto-dental interval (ADI), the space available for the spinal cord (SAC), and the Ranawat value were measured by plain lateral radiographs in the flexion position, at initiation and Week 54. [Results] The number who showed progression in at least one of radiographic cervical lesion parameters (ADI, SAC, Ranawat value) for 1 year was 12 (38%). In the non-progressive(ΔTSS≦0, n=10) and progressive patients (ΔTSS≧1, n = 22), the respective changes in cervical lesion parameters in 1 year were as follows: ADI: 0 and 0.50 ± 0.60 mm (p = 0.012); SAC: 0 and −0.36 ± 0.49 mm (p = 0.030); and Ranawat value: 0 and −0.36 ± 0.58 mm (p = 0.048). [Conclusion] TCZ treatment can be used to suppress the progression of RA cervical lesions, as well as hand and foot joints lesions. 1 year after initiation, the cervical lesion did not progress at all for the patients that a hand joint destruction did not progress.

W87-6

Long-term therapeutic results for tocilizumab in our hospital

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Conflict of interest: None

[Objective] Long-term treatment of rheumatoid arthritis (RA) patients with tocilizumab (TCZ) in our hospital was investigated. [Method] TCZ was introduced in July 2008 and we examined 45 patients observed for 24 weeks or longer (40 women, mean age of 55 years, mean disease duration of 8.2 years and mean treatment period of 24.6 months). [Results] All patients took one or more DMARDs (26 patients took biological products). Eight patients underwent monotherapy. Concomitant medication was MTX (8-15 mg/w) in 31 and others in six patients. DAS28(ESR) was 5.6±1.1 at baseline and 3.5±1.3, 2.4±1.4 and 2.0± 0.8 after 24, 52 and 104 weeks of treatment respectively. Remission rates were 57%, 67% and 68% (DAS28(ESR)<2.6); 50%, 53% and 61% (CDAI) ;45%,62% and 64%(SDAI) and 39%, 47% and 52% (Boolean) respectively. Continuation rates were 93%, 93% and 90% respectively. Treatment was discontinued during observation in five patients, adverse events in two, insufficient effects in two and remission in one]. Adverse events were very mild except for pneumonia in two, herpes zoster in two, cellulitis in one and meningitis in one patient. [Discussion] Remission and continuation rates for TCZ tended to be higher than in past trials and long-term treatment appeared to be useful.

W88-1

Familial Mediterranean fever in Japan

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Conflict of interest: None

Objective: Our aim was to determine the prevalence of FMF in Japan and elucidate the clinical and genetic features of Japanese patients. ***Methods:***The primary nationwide survey of FMF was conducted between January and December 2009. ***Results:*** The estimated total number of Japanese FMF "patients" was 292 persons. We evaluated the clinical and genetic profiles of Japanese patients from the data obtained secondary survey. High-grade fever was observed in 95.5%, chest pain in 36.9%, abdominal pain 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. AA amyloidosis was confirmed in 5 patients (3.7%). Of the 126 patients studied, 109 (86.5%) were positive either for one, more mutations and 17 (13.5%) had no mutations detected. Common *MEFV* mutations were E148Q/M694I (19.8%) and M694I/normal (12.7%). The differences in the prevalence of peritonitis and pleuritis were statistically significant between FMF patients with *MEFV* exon 10 mutations and those without exon 10 mutations. ***Conclusion:*** A significant number of patients with FMF exist in Japan, and the delay of colchicine treatment could an issue to be resolved.

W88-2

Prevalence of *MEFV* gene mutations in Japanese patients with unexplained fever

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Conflict of interest: None

Objective: The aim is to determine the frequencies of *MEFV* gene mutations in Japanese patients with unexplained fever or undifferentiated arthritis. ***Methods:*** The study was carried out on 142 patients with unexplained fever or undifferentiated arthritis. The tested individuals were screened for the exons1, 2, 3, and 10 of *MEFV* gene. ***Results:*** Of 142 tested patients, all 16 patients having *MEFV* exon10 mutation (M694I) satisfied typical FMF criteria. Exon 1 of *MEFV* gene mutation (E84K) was found in 12 patients, exon 2 (L110P, E148Q, R202Q, G304R) mutations in 72 (50.7%), and exon 3 (P369S, R408Q) mutations in 15 (10.6%). Among these 75 patients having mutations in exon1, 2, or 3 of *MEFV* genes, 21 patients (28.0%) satisfied typical or incomplete FMF criteria. Among 12 patiens with E84K, Six patients had symptoms and signs fulfilling clinical diagnosis of FMF. The remaining patients presented with signs and symptoms not typical for FMF and had other concomitant diseases. ***Conclusion:*** Japanese patients having mutations in exon1, 2, and 3 of *MEFV* gene could be associated with typical or untypical FMF manifestations. These findings suggest that the *MEFV* gene is associated with more than a single clinical entity as FMF and to be responsible for additional autoinflammatory diseases.

W88-3

Genetic analysis of patients suspected for tumor necrosis factor receptor associated periodic syndrome (TRAPS)

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Conflict of interest: None

A nation-wide surveillance of Japanese patients suspected for TRAPS was conducted in 2010. 76 patients were studied for mutations of the genes, *TNFRSF1A*, *MEFV*, and *MVK*. Six were carrying heterozygous mutations of *TNFRSF1A* gene. *MEFV* gene mutation was observed in 42 patients, while none had any *MVK* gene mutation. No mutations in either of the three genes were detected in 32 patients. Genetic analysis is useful for the diagnosis of such diseases as TRAPS, that is lacking simple blood test for diagnosis.

W88-4

Rapid detection of NLRP3 somatic mosaicism in CINCA syndorme using next-generation sequencing

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Conflict of interest: None

[Objectives] CINCA syndrome, also known as NOMID is characterized by an urticarial rash, neurological manifestations and arthropathy. This dominantly-inherited systemic autoinflammatory disease is provoked by heterozygous germline gain-of-function NLRP3 mutations. However, conventional genetic analyses failed to detect disease-causing mutations in approximately 40% of patients ("mutation-negative" patients). Recently, we have identified high incidence of NLRP3 somatic mosaicism on those patients in the international collaborative study. To detect NLRP3 somatic mosaicism, we used Sanger-sequencing along with subcloning, but this approach requires large investments of time, cost, and labor.

Thus, we developed a routine pipeline to detect even a low-level allele of the NLRP3 gene. [Methods] Genomic DNA was isolated from previously-reported Japanese CINCA/NOMID patients with NLRP3 somatic mosaicism, NLRP3 heterozygous mutations, healthy donors, and newly-identified "mutation-negative" CINCA/NOMID patients. We used the Roche GS-FLX 454 Genome Sequencer. [Results] NLRP3 somatic mosaicism was identified in all previously-reported Japanese CINCA/NOMID patients with NLRP3 somatic mosaicism, and 4 out of the newly-identified 10 "mutation-negative" CINCA/NOMID patients.

W88-5

Elucidation of the pathogenesis in rheumatoid arthritis using the result of analysis in proteasome disability syndrome

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Conflict of interest: None

[Objectives] Nakajo-Nishimura syndrome (NNS) (MIM 256040) is a new autoinflammatory disorder that shows inflammatory and wasting symptoms. We previously reported that a decrease in proteasome activity, which is associated with a novel mutation of the β5i immunoproteasome subunit (G201V), causes definitive human autoinflammatory phenotypes in NNS. This fact suggests that the ubiquitin-proteasome pathway might play an important role for inflammation and provides a new insight into the pathogenesis of other persistent inflammatory diseases including in rheumatoid arthritis. In this study, we examined the role of proteasome in rheumatoid arthritis. [Methods] 1) Genomic DNA samples (50 RA patients and 20 healthy subjects) were analyzed with the SNPs about *PSMB8* gene (exon 1b, 2, 3, 4, 5, 6, UTR). 2) Synovial fibroblasts derived from RA patients or OA (osteoarthritis) patients were assayed for three different peptidase activities (chymotrypsin-like activity, trypsin-like activity and caspase-like activity). [Results] 1) Missense mutation in exon 1b was detected in one RA patient. SNPs in 3'-UTR lesion were detected in 6 RA patients and 2 healthy controls. 2) The three peptidase activities were decreased in RA synovial fibroblasts compared to OA synovial fibroblasts.

W88-6

Inflammatory cytokines and chemokines in an autoinflammatory disorder, Nakajo-Nishimura syndrome.

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Conflict of interest: None

[Objectives] The ubiquitin-proteasome pathway is responsible for selective degradation of short-lived, misfolded and toxic proteins. Nakajo-Nishimura syndrome (NNS) is an autoinflammatory disorder with impaired proteasome function, its newly identified causative mutation and inflammatory symptoms including periodic fever and skin rash. To analyze the expression of inflammatory cytokines and chemokines in the cells of proteasome impairment. [Methods] Skin fibroblasts obtained from NNS patients and healthy controls were cultured in the presence or absence of proteasome inhibitor. Gene expression of inflammatory cytokines and receptors were consecutively analyzed by SYBR Green-based quantitative reverse transcription-PCR. [Results] 26 up-regulated genes and 3 down-regulated genes were identified in cultured cells under the condition of proteasome inhibition as compared with control. Among these candidate genes CXCL-10 was significantly increased by the inhibition of proteasome (4.10-fold, p=0.008). This was compatible with the higher concentration of in sera of patient with NNS. [Conclusion] The ubiquitin-proteasome pathway would play an important rule against inflammation. This may provide a new insight into the pathogenesis of other persistent inflammatory diseases.

W89-1

Clinicopathological analyses in patients with other iatrogenic immunodeficiency-associated lymphoproliferative diseases and rheumatoid arthritis

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Conflict of interest: None

[Objectives] The mechanism of other iatrogenic immunodeficiency-associated lymphoproliferative diseases (OIIA-LPDs) remains poorly understood, especially in rheumatoid arthritis (RA) patients. To address the clinocopathogenesis, we analyzed data at a single institution. [Methods] Data on 23 patients with RA who developed LPD and were treated between 1998 and 2010 were gathered. [Results] Patients were categorized into three groups according to whether they had methotrexate (MTX); MTX-regressive LPDs, MTX-persistent LPDs, or other drugs-mediated LPDs. The overall survival of all patients was 74% at 5 years, and those of the three groups were 100%, 64%, and 60%, respectively. Among the 6 patients who died, 4 had LPDs that were detected late, and thus adequate treatment was not given. In addition, several patients with diffuse large B cell lymphoma with a complex karyotype achieved complete remission (CR). Only one patients among the 17 patients who achieved CR relapsed. OIIA-LPDs-RA appeared to have a better prognosis than other more common types of lymphomas. Regarding RA treatment, various anti-RA drugs were given to the patients after developing LPDs, including MTX, but no recurrent patients were documented (Tokuhira M. et al. publication in Leuk Lymphoma. 2011).

W89-2

7 cases of Epstein-Birr virus-associated lymphoma in rheumatoid arthritis

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Conflict of interest: None

We experienced 7 cases of Epstein-Birr virus-associated lymphoma (EBV-ML) in rheumatoid arthritis (RA) between 2006 and 2011. Patients (Age:36-78 years old. Gender:Female 5 male 2. Duration of RA :5-30 years). All patients were treated with MTX (dose 4-9.5mg/week) and 4 out of 7 patients were treated with anti-TNF therapy. All patients were diagnoses EBV-ML by the pathologies that EBV was stained in the tumor cells. Many types of ML pathologies were showed (3 cases were DLBCL, 2 cases were HD,

1 case was NK/T cell lymphoma, 1 case B cell lymphoma) EBV load were increased in 2 out of 3 cases and EBV antibody titer were increased in 3 out of 5 cases. The outcome was that 4 cases were alive and 3 cases died. But they showed unusual clinical courses that 3 cases were recovered completely just only by stopping MTX and anti-TNF therapy and that all dead cases were died within a month. It is said EBV-ML is caused by the destruction of immune system and the patients have been increasing since the advent of MTX and anti-TNF therapy in RA. We consider it very important in RA treatment to comprehend this rare disease, so we will report the character of our 7 cases.

W89-3

Treatment of rheumatoid arthritis patients with chronic hepatitis B

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Conflict of interest: None

[Objectives and Methods] We focused on the treatment of rheumatoid arthritis (RA) patients with chronic hepatitis B. We selected RA patients with chronic hepatitis B virus (HBV) infection among 384 RA outpatients treated at Osaka Rosai Hospital. Patient characteristics, medication including immunosuppressive agents, time point when HBV infection was detected, reactivation of hepatitis, and outcome were examined. [Results] Seven patients were HBsAg-positive. Disease duration was 8.9 years (1~31) and mean age was 56 years (40~63). Four patients were treated with prednisolone, 7 patients with MTX, and 3 patients with biologic-agent (IFX1, TCZ2). Two patients were detected as HBV infection before undergoing immunosuppressive therapy, 3 patients after immunosuppressive therapy, and 2 patients after reactivation of hepatitis. Hepatitis reactivated patients were resolved with appropriate antiviral therapy. All patients can be treated with immunosuppressive therapy consecutively without reactivation of hepatitis by treating with prophylactic antiviral agent [Conclusion] To check HBV markers is important before immunosuppressive therapy. We could treat chronic hepatitis B infected RA patients without reactivation of hepatitis by using immunosuppressive agent and antiviral agent concomitantly.

W89-4

Comparison of disease activity, health status and satisfuction between RA patients in remission in patient global assessment and those in non-remission at 24 weeks of treatment with biologic agents

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Conflict of interest: None

[Objictives] To compare improvement of disease activity, health status and satisfaction between RA patients with VAS remission and those with VAS non-remission treated with biologic agents. [Methods] Thirty-nine patients were treated with tocilizumab, 17 with infliximab and 11 with etanercept. The patients were divided to 2 groups, VAS remission group (patient VAS score ≦ 10mm) and VAS non-remission group (patient VAS score >10mm), at week 24. Disease activity, health status and satisfuction assessed utilizing AIMS-2 were compared between 2 groups at week 0 and 24. [Results] Baseline characteristics except satisfaction to housework and task did not differ between remission group and non-remission group (houssework 4.3; 5.8, $p<0.05$, task 0.5; 1.3, $p<0.001$, respectively). At week 24, disease activity and physical function, symptom and work of AIMS-2 improved significantly at week 24 in remission group. Satisfuction except social phase also improved in remission group significantly at week 24. [Conclusion] Disease activity, health status and satisfuction except social phase improved significantly in VAS remission group at week 24. Moreover, obtaining satisfuction to work or task before treatment is suggested to play good influences on improvement of PGA.

W89-5

High validity of intevention of expert pharmacologist in the private clinic specialized for rheumatic diseases

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Conflict of interest: None

Objectives: It is inevitable for organization with rheumatic division to have a clinical pharmacologist with knowledge for rheumatology. Besides, establishing pharmaceuticals control and perform the preparation, the Japanese regulation requires a expert pharmacist should be involved in the outpatient facitility for administration of biologics. Not only in preparation of biologics and control, but also to assist doctors to report adverse drug reaction(ADR). In 2003, Pharmaceuticals and Medical devices Agency required every doctors to report ADR promptly, and in 2005, especially for infection related adverse event have to be reported completely. Methods: A pharmacologist independently seeks for the abnormal clinical data, check the on-line medical records, and find out the ADR, and confirm the severity with the doctor, and reported to the makers and Ministry of Health. The reports for makers sometimes require minute descriptions, when the record is filled with a pharmacologist, but not a doctor, less time consuming for the company and routine work for doctors. Results: By doctors, one case of minute description was made in a few month, but now by a phamacologist, 20 cases of minute descriptions are made every month.

W89-6

Determination of the observation period after the infusion of the biologics via intravenous pathway

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Conflict of interest: None

Objectives: It requires intensive observation by nursing staffs, in an independent infusion room for biologics where adverse events, such as infusion reaction(IR) occurred and these should be reported to doctors who is on duty at clinic. Methods: From 2004 to 2011 infliximab (IFX)116 patients 2784 administration, tocilizumab(TCZ) 71patients 1490 administration were preformed. 12 patients of IFX and none of TOZ showed withdrawal of the biologics due to IR. 86 of undesired reaction(UR) was recorded in the midst of injection for IFX and 56 of UR for TCZ. For post infusion obsavation period, 17 of UR, mainly elevated blood pressure were observed in IFX group, but every case occurred within 30min. of the completion. 45 of UR also seen in TCZ group, but for this group, 17 of UR occurred on 60min. In either groups, no UR was found patients with stable condition until 60min. after completion. Ms. Joyce Kortan announced that with no UR on the first 6-month biologics adminstration, patient may go back home immediately

after the infusion. In our clinic, no serious event in TCZ groupbut, 19 denovo UR occurred after 10th injection Conclusion: Every infusion should be closely observed until 30min. for IFX, and 60min. for TCZ, after confirm the condition, give permit patients to go back home.

International Workshop

IW1-1

Gene-environment interaction between HLA-DRB1 shared epitope and smoking increased the risk of ACPA-positive RA but not ACPA-negative RA: results from the Malaysian Epidemiological Investigation of Rheumatoid Arthritis (MyEIRA) case-control study.

Abqariyah Yahya[1,2], Chun-Lai Too[2,3], Leonid Padyukov[3], Per Larsson[3], Lars Klareskog[3], Lars Alfredsson[1], Shahnaz Murad[2], Camilla Bengtsson[1], for MyEIRA study group
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According to many recent studies, interaction between HLA-DRB1 shared epitope (SE) alleles and smoking provides a high risk of anti-citrullinated peptide antibodies (ACPA) -positive rheumatoid arthritis (RA) in Caucasian populations. We studied how the SE alleles and smoking interact in the multi-ethnic Malaysian population, in the development of RA characterised by ACPA. A case-control study was conducted in Peninsular Malaysia between August 2005 and December 2009, with primarily early diagnosed RA cases. Controls were matched according to sex, age and residential area to the cases. High resolution HLA-DRB1 genotyping was performed for shared epitope (SE) alleles and the presence of ACPA were determined for both cases and controls. All cases and controls answered a questionnaire containing lifestyle habits. In total, 1,056 cases and 1,416 matched controls were analysed in this report. The effect of SE alleles and smoking exposure were assessed by conditional logistic regression. Biologic interaction was analysed by quantifying whether the combined effect of risk factors exhibited departure from additivity. A significant interaction between smoking exposure and SE alleles was found for ACPA-positive RA (OR=24.0, 95%CI 10.0-57.4) as compared to never-smokers without SE alleles with an attributable proportion (AP) due to interaction of 0.7 (95%CI 0.5-1.0). There was no significant effect of the combination between SE alleles and smoking in the risk of ACPA-negative RA. These findings may provide a new insight into the interplay between two major risk factors (smoking and SE alleles) along one or more biological pathways, regardless of population origins.
Chun-Lai Too and Abqariyah Yahya contributed equally to this work.

IW1-2

Nkx3.2 promotes primary chondrogenic differentiation by up-regulating Col2a1 transcription

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Conflict of interest: None

[Objectives] The transcription factor Nkx3.2 promotes chondrogenesis by forming a positive regulatory loop with a crucial chondrogenic transcription factor, Sox9. Previous studies have indicated that factors other than Sox9 may promote chondrogenesis, but these factors have not been identified. Here, we test the hypothesis that Nkx3.2 promotes chondrogenesis directly by Sox9-independent mechanisms and indirectly by previously characterized Sox9-dependent mechanisms. [Methods and Results] C3H10T1/2 cells were cultured with bone morphogenetic protein 2 (BMP2) to induce endochondral ossification. Overexpression of

wild-type Nkx3.2 (WT-Nkx3.2) upregulated glycosaminoglycan (GAG) production and expression of type II collagen alpha1 (*Col2a1*) mRNA, and these effects were evident before WT-Nkx 3.2-mediated upregulation of *Sox9*. RNAi-mediated inhibition of *Nkx3.2* abolished GAG production and expression of *Col2a1* mRNA. Dual luciferase reporter assays revealed that WT-Nkx3.2 upregulated *Col2a1* enhancer activity in C3H10T1/2 cells and also in N1511 chondrocytes. ChIP assays revealed that Nkx3.2 bound to the *Col2a1* enhancer element. Thus, Nkx3.2 promoted primary chondrogenesis by two mechanisms: Sox9-independent upregulation of *Col2a1* transcription and upregulation of *Sox9* transcription.

IW1-3

Dynamic *in vivo* imaging of bone-resorptive functions of mature osteoclasts in live bones by using intravital multiphoton microscopy

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Conflict of interest: None

RA is a chronic autoimmune disease characterized by joint synovial inflammation and progressive cartilage/bone destruction. Recently it has been reported that Th17, a $CD4^+$ T cell subset expressing RANKL, increases in the synovium of RA patients and enhances bone destruction. However it remains unclear how the bone-resorptive functions of osteoclasts are controlled *in vivo* and how Th17 cells influence osteoclastic bone resorption. To answer these questions, we have visualized fluorescently-labeled mature osteoclasts in live bones by using intravital multiphoton microscopy, and identified two different populations of live mature osteoclasts, 'static - bone-resorptive (R)' and 'moving - non-resorptive (N)'. We also found that rapid RANKL injection changed the osteoclast status from N to R, suggesting a novel point of action of RANKL in controlling mature osteoclast function. Furthermore, we showed that Th17 could induce rapid N to R transition of mature osteoclasts via direct cell-cell contact, revealing a mechanism by which Th17 has a potent effect on controlling bone resorption *in vivo*. These findings provide new insights into the activities of mature osteoclasts *in situ* and identify novel actions of RANKL expressed by Th17 that may be promising as a new therapeutic target in RA.

IW1-4

Specific Deletion of PPAR-GAMMA in Mouse Cartilage Results in Accelerated Cartilage Degradation and Spontaneous Osteoarthritis During Aging.

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Objectives: Osteoarthritis (OA), is a age-related degenerative and progressive joint disease. PPARγ, a transcription factor is suggested as an attractive therapeutic target to counteract degradative mechanisms associated with OA. Studies suggest that activation of PPARγ by its agonists can reduce the synthesis of various OA catabolic and inflammatory factors and reduce the development of cartilage lesions in animal models of OA. Since these agonists impart several PPARγ-independent effects; therefore, the specific *in vivo* function of PPARγ in cartilage homeostasis and OA disease is still largely unknown. Here, for the first time, we describe the *in vivo* role of PPARγ in OA using cartilage-specific PPARγ knockout (KO) mice. **Methods:** Cartilage-specific PPARγ KO mice were generated using Cre-Lox system. Mouse knee joints were subjected to histomorphometric analyses, and quantified by OARSI scoring criteria. Gene expression analysis of cartilage markers was determined by qPCR. **Results:** Histomorphometric analyses showed that articular cartilage of 14 months old PPARγ KO mice exhibit spontaneous OA-phenotype associated with enhanced cartilage degradation (significantly elevated OARSI scoring), hypocellularity, synovial inflammation, macrophage influx and increased expression of MMP-13, and MMP-generated aggrecan and collagen type II neoepitopes (VDIPEN and C1-2C short). Subsequently, we show that PPARγ-deficient cartilage exhibits decreased expression of aggrecan and type II collagen but increased expression of catabolic factors including hypoxia-inducing factor-2alpha (HIF-2α), syndecan-4 and ADAMTS-5) and inflammatory markers including COX-2 and iNOS, thus enabling the articular cartilage of PPARγ-deficient mice to be more susceptible to degradation during aging. **Conclusion:** PPARγ is a critical regulator of cartilage health and the lack of PPARγ leads to accelerated and spontaneous OA.

IW1-5

The crucial role of TNFα-induced adipose-related protein (TIARP) in autoimmune arthritis

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Conflict of interest: None

Objective We found that TNFα-induced adipose-related protein (TIARP) is dominantly expressed in macrophages (Mφ) and joints of arthritic mice, although the pathogenic mechanisms of arthritis remain unclear. To elucidate the role of TIARP in the development of arthritis, we have generated TIARP-deficient ($TIARP^{-/-}$) mice in C57BL/6 background. **Methods** (1) We investigated several organs in aged (12-month-old) $TIARP^{-/-}$ mice. (2) Peritoneal Mφ were cultured with TNFα, and the production of IL-6 was measured. (3) We examined the susceptibility of $TIARP^{-/-}$ mice to collagen-induced arthritis (CIA). (4) The level of IL-6 and TNFα in the serum on day 60 were measured. (5) We examined the effects of anti-IL-6R mAb (MR16-1) on the development of arthritis in $TIARP^{-/-}$ mice. **Results** (1) Aged $TIARP^{-/-}$ mice spontaneously developed weak synovitis with enthesitis. (2) Mφ from $TIARP^{-/-}$ mice produced high amount of IL-6 by TNFα. (3) The severity of arthritis score in $TIARP^{-/-}$ mice was higher than that in WT mice. (4) The serum IL-6 was significantly increased in $TIARP^{-/-}$ mice. (5) Administration of MR16-1 significantly suppressed the progression of arthritis in $TIARP^{-/-}$ mice. **Conclusion** TIARP should be a negative regulator against autoimmune arthritis via suppression of inflammatory cytokines.

IW1-6

The apoptosis of peripheral Th17 and Regulatory T cells in rheumatoid arthritis

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Objective: Rheumatoid arthritis (RA) is characterized by a Th17/regualatory T (Treg) imbalance. Alterations in the apoptosis have been described in the pathogenesis of RA. The arm is to study whether insufficient apoptosis is contributed to the imbalance of Th17/Treg in RA. **Methods:** There were 21 RA patients and 8 healthy volunteers involved in this study. The percentage of CD4+ IL-17+ T cells and CD4+ Foxp3+ T cells were measured by flow cytometry, and active caspase 3 labeling was used to detect early apoptosis. The differences of the percentage of subtypes of helper T cells and ratio of apoptotic cells between the two sub-populations were compared, and also correlated with the disease activity. **Re-**

sults: For the number of the T cell subtypes, neither Th17 nor Treg cell was significantly different between the RA patients and the healthy controls. The number of Treg cells, but not Th17 cells was correlated to disease activity, RF and ESR. For the apoptosis of the T cell subtypes, Th17 cells were significantly more sensitive than Treg cells, no matter in RA patients or healthy controls. The percentage of apoptotic Th17 cells in RA patients, but not Treg cells, was significantly higher than in the controls. The ratio of apoptotic cells of both Th17 and Treg did not relate to disease activity. For the same patient, the percentage of synovial Th17 cells was higher than the peripheral blood, and the apoptosis rate was lower. After anti-TNF treatment, the percentage of apoptotic Treg cells was lower than that before therapy. **Conclusion:** There were no significant differences of the percentage of peripheral Th17 cells and Treg cells between the RA patients and the controls. Peripheral Th17 cells are more sensitive to apoptosis than Treg cells. The insufficient apoptosis of Th17 cells in synovial fluid and decreased apoptotic rate of Treg cells after treatment may provide new sight in the Th17/Treg imbalance in RA.

IW1-7

CD11b-Ligation on moDC contracts Human Th17 Cell Populations

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Background: Dendritic cells (DC) are important mediators of immunity and tolerance. Manipulating monocyte-derived DC (moDC) to dampen the secretion of inflammatory cytokines and maturation. Thus altering their T-cell stimulating properties. Is an important strategy for the development of suppressive immunotherapy. We were previously able to show that the ligation of CD11b on moDC decreased the secretion of the Th17-skewing inflammatory cytokines IL-1β and IL-6, but maintained or increased the secretion of "immunosuppressive" TGF-β1, the latter being essential to both, Th17 and Treg development. We thus hypothesized that this "tolerogenic" DC-profile would lead to Th17 contraction in peripheral human T cell populations. A strategy possibly of use for the reduction of Th17-mediated pathogenic autoimmune responses. Methods: Healthy donor peripheral blood mononuclear cells (PBMC) were differentiated into moDC in IL-4, GM CSF-supplemented media for 6 days. CD11b on moDC was targeted via a bead-based surrogate system developed in our lab. Irrelevant IgG, αvβ5 and beads without antibodies were used as controls. DC were stimulated with LPS and MDP or PGN or not stimulated, and then co-cultured with enriched CD4+ human T memory cells. Media containing low levels of IL-2 was replaced every 3 days. Cells were harvested on day 12, intracellular cytokine staining was performed for IL-17, INFγ, and IL-4, and cells were analyzed by FACS. Results: LPS/MDP or PGN-stimulated moDC induced significant increases in the frequencies of IL-17 producing cells (up to15%) as detected by ICS. More than 50% of these cells secreted IL-17 and INFγ. Strikingly, CD11b-ligated DC/T cell conditions showed significantly reduced frequencies of Th17-secreting cells when compared to stimulated controls. Conclusions: We have created a successful method of moDC-mediated Th17 cell expansion through the use of MDP/LPS or PGN as adjuvants, and show that this NOD2/TLR4 or TLR2-mediated effect can be shut off through the ligation of CD11b on moDC. This approach is highly promising to be of use for adoptive transfer-based suppressive immunotherapy for Th17-related autoimmune diseases.

IW1-8

Imputation identifies *CCR1* and *STAT4* as novel Behçet's disease susceptibility loci.

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Conflict of interest: None

[Objectives] A previous genome-wide association study with 300K SNPs in Turkish Behçet's disease (BD) identified two MHC class I loci, *IL10*, and the *IL23R-IL12RB2* locus. We have now used imputation to discover additional BD susceptibility loci. [Methods] Imputation was conducted using MACH v1.0.15 providing 800K SNPs for analysis in the 1215 BD cases and 1278 healthy controls. Two independent replication sets were genotyped for the most significant SNPs and functional studies were undertaken. [Results] An imputed SNP rs7616215 located 3' of the chemokine receptor-1 (*CCR1*), exceeded genome-wide significance ($p=1.9\times10^{-8}$). This finding was replicated in additional Turkish and Japanese BD samples (a meta-analysis of 2641 cases and 2593 controls, OR 0.72, 95% CI 0.66–0.79, $p=5.19\times10^{-13}$). The protective C allele was associated with increased *CCR1* mRNA expression and increased monocyte chemotaxis. In addition, meta-analysis showed association at rs7574070 in *STAT4* (OR 1.27, 95% CI 1,17-1.37, $p=8.58x10^{-10}$). The risk allele A was associated with increased *STAT4* expression. Our data suggest that increased CCR1 expression and chemotaxis, which may be associated with efficient microbial pathogen clearance, protect against BD and that increased expression of STAT4 is a risk factor.

IW1-9

Rapid detection of NLRP3 somatic mosaicism in CINCA syndorme using next-generation sequencing

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Conflict of interest: None

[Objectives] CINCA syndrome, also known as NOMID is characterized by an urticarial rash, neurological manifestations and arthropathy. This dominantly-inherited systemic autoinflammatory disease is provoked by heterozygous germline gain-of-function NLRP3 mutations. However, conventional genetic analyses failed to detect disease-causing mutations in approximately 40% of patients ("mutation-negative" patients). Recently, we have identified high incidence of NLRP3 somatic mosaicism on those patients in the international collaborative study. To detect NLRP3 somatic mosaicism, we used Sanger-sequencing along with subcloning, but this approach requires large investments of time, cost, and labor. Thus, we developed a routine pipeline to detect even a low-level allele of the NLRP3 gene. [Methods] Genomic DNA was isolated from previously-reported Japanese CINCA/NOMID patients with NLRP3 somatic mosaicism, NLRP3 heterozygous mutations, healthy donors, and newly-identified "mutation-negative" CINCA/

NOMID patients. We used the Roche GS-FLX 454 Genome Sequencer. [Results] NLRP3 somatic mosaicism was identified in all previously-reported Japanese CINCA/NOMID patients with NLRP3 somatic mosaicism, and 4 out of the newly-identified 10 "mutation-negative" CINCA/NOMID patients.

IW1-10

Dendritic cell-specific depletion of protein-tyrosine phosphatase Shp1 causes autoimmunity

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Conflict of interest: None

[Objectives] Dendritic cells (DCs) promote immune responses to foreign antigens and immune tolerance to self-antigens. Dysregulation of the function of DCs is through to cause abnormal immune responses, which in turn cause autoimmunity. Spontaneous mutations in the protein tyrosine phosphatase *Shp1* gene in mice produce the *motheaten* phenotypes that exhibit multiple inflammatory and autoimmune defects. Previous studies suggest that Shp1 negatively regulates the function of lymphocytes. But, physiological roles of Shp1 in DCs remain to be elucidated. [Methods] To investigate the Shp1 function in DCs *in vivo*, we generated Shp1 conditional knock out (CKO) mice, in which the *Shp1* gene was specifically deleted in DCs. [Results] CKO mice develop splenomegaly associated with an increased number of CD11c+ DCs. Splenic DCs from the mutant mice showed up-regulation of CD86 expression as well as of production of proinflammatory cytokines. The mice manifested an increased number of activated T cells and the serum immunoglobulins were also increased in the mutant mice. Moreover, aged mutant mice developed glomerulonephritis and interstitial pneumonitis together with increased serum concentrations of autoantibodies. Shp1 is thus a key regulator of DC functions that protects against autoimmunity.

IW1-11

Induction of abnormal conformation and impaired degradation of neutrophil extracellular traps (NETs) by propylthiouracil (PTU): Possible implication of disordered NETs in the pathogenesis of MPO-ANCA-associated vasculitis (MPO-AAV)

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Conflict of interest: None

[Objectives] The pathogenesis of small vessel vasculitis is critically associated with ANCAs. NETs composed of chromatin fibers and antimicrobial proteins, such as MPO, play important roles in the innate immune system. Recent studies suggest that NETs may be involved in the pathogenesis of MPO-AAV, and that impaired regulation of NETs may trigger autoimmune response to NETs. PTU, an anti-thyroid drug, is known to have a risk to induce MPO-ANCA production and MPO-AAV. Thus, we hypothesized that PTU can induce impaired regulation of NETs and consequently result in the induction of MPO-ANCA and MPO-AAV. [Methods] NETs were induced by treatment of neutrophils with PMA *in vitro*. We examined whether the addition of PTU can influence the NETs formation induced by PMA and degradation by DNase I, which is regarded as a regulator of NETs. Furthermore, we examined whether the NETs generated by PMA with PTU can induce MPO-ANCA and MPO-AAV *in vivo*. [Results] When NETs were induced by PMA with PTU *in vitro*, abnormal conformation of NETs was observed. Interestingly, the abnormal NETs were hardly digested by DNase I. Moreover, rats immunized with the abnormal NETs induced by PMA with PTU produced MPO-ANCA. We further established a rat model for induction of MPO-ANCA and MPO-AVV using PMA and PTU.

IW1-12

CD4+ T cell dysfunctions through the impaired lipid rafts ameliorate concanavalin A-induced hepatitis in sphingomyelin synthase 1-knockout mice.

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Background: Membrane microdomains consisting of sphingomyelin (SM) and cholesterol appear to be important for signal transduction in T cell activation. The present study was designed to elucidate the role of membrane SM in vivo and in vitro using sphingomyelin synthase 1 (SMS1) knock out ($SMS1^{-/-}$) mice and Concanavalin A-induced hepatitis. ***Methods:*** After establishing $SMS1^{-/-}$ mice, we investigated CD4+ T cell functions including proliferation, cytokine production and signal transduction in vivo. We also examine severity of hepatitis, cytokine production in serum and liver after concanavalin A (Con A) injection at a dose of 20 mg/kg. ***Results:*** CD4+ T cells from $SMS1^{-/-}$ mice show severe deficiency of membrane SM and several profound defects compared with wild-type controls as follows: 1) cellular proliferation and production of IL-2 and IFN-γ by co-cross-linking of CD3 and CD4; 2) tyrosine phosphorylation of LAT and its association with ZAP-70; 3) clustering and colocalization of TCR with lipid rafts. Consistent with these impaired CD4+ T cell functions *in vitro*, $SMS1^{-/-}$ mice showed decreased serum levels of IL-6 and IFN-γ by Con A injection, which renders $SMS1^{-/-}$ mice less sensitive to Con A-induced hepatitis. ***Conclusion:*** These results suggested that membrane SM is critical for full T cell activation both *in vitro* and *in vivo*, which may be mainly through impaired lipid raft function, and strongly involved in T cell-mediated hepatitis.

IW1-13

Tofacitinib induces $CD4^+CD25^-LAG3^+$ regulatory T cells *in vivo* and the expression of Egr2 in $CD4^+$ T cells *in vitro*

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Conflict of interest: None

[Objectives] $CD4^+CD25^-LAG3^+$ T cells ($LAG3^+$ Treg), a novel subset of murine regulatory T cells, express an anergy associated

transcription factor, early growth response gene-2(Egr-2) and strongly suppress autoantibody production. Previous study reported that the frequency of $CD4^+LAG3^+$ T cells was increased in Jak3-deficient mice. Our objective is to examine the effect of a Janus kinase (Jak) inhibitor tofacitinib on the induction of $LAG3^+$ Treg. [Methods] Tofacitinib was continuously administered to young C57BL/6 (B6) and NZB/W F_1 (BWF_1) mice for 4 weeks. Then splenic $LAG3^+$ Treg were analyzed by flow cytometry. We analyzed the expression of Egr-2 in $CD4^+$ T cells cultured with tofacitinib. [Results] Administration of tofacitinib increased splenic $LAG3^+$ Treg in B6 mice. In BWF_1 mice, splenic $LAG3^+$ Treg showed a decrease at baseline, and tofacitinib did not increase them. Tofacitinib induced the expression of Egr-2 in both B6 and BWF_1 $CD4^+$ T cells *in vitro*. BWF_1 $CD4^+$ T cells required higher concentration of tofacitinib for Egr-2 induction than B6 $CD4^+$ T cells. Our findings may indicate a novel mechanism for the therapeutic effect of tofacitinib. Hyporesponsiveness of BWF_1 $CD4^+$ T cells to tofacitinib may be associated with impaired induction of $LAG3^+$ Treg in BWF_1 mice.

IW1-14

Anti-erythropoietin receptor antibodies in systemic lupus erythematosus patients with anemia

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Objective To investigate the existence and significance of circulating autoantibodies to erythropoietin receptor (EPOR) in sera from patients with systemic lupus erythematosus (SLE). **Methods** One hundred sixty-nine consecutive patients with SLE and forty-five normal individuals were involved in this study. In all patients with SLE, the disease activity was evaluated using the European consensus Lupus Activity Measurement scale. Antibodies to EPOR were detected using an enzyme-linked immunosorbent assay (ELISA). **Results** A higher frequency of Antibodies to EPOR were observed in SLE patients than those in the health controls (18.3% vs 2.2%, *P*=0.007). Moreover, anti-EPOR antibodies were detected in 22(31.9%) of 69 SLE patients with anemia, compared with that in 11 (11.0%, P=0.001) of 100 patients without anemia. Furthermore, the patients with antibodies to EPOR exhibited more severe anemia and often presented as microcytic anemia (P=0.001). Finally, anti-EPOR antibodies seemed more likely to occur in patients with rash (P=0.008), lower levels of C3 component of complement (P=0.01), anti-dsDNA antibodies (P=0.000) and higher disease activity scores (p=0.024). **Conclusion** The higher incidence of antibodies to EPOR finding in SLE patients with anemia suggested that anti-EPOR antibodies might play a vital role in SLE patients developing anemia. Thus, there might be a clinical value by detecting anti-EPOR antibodies in SLE patients with anemia.

IW1-15

B7-H4 expression of Renal tubular epithelial cells in the patients with lupus nephritis

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Background: B7-H4 is a newly identified B7 family negative co-stimulate molecule, the expression and function of B7-H4 is still unclear in lupus nephritis (LN). **Objective:** To investigate the expression of B7-H4 in the patients with LN and the function of renal tubular epithelial cells (TECs) -associated B7-H4 on the regulation of T cell activation in vitro. **Methods:** 90 LN patients, 3 acute kidney injury patients and 20 healthy donors were referred. Disease activity was assessed by SLEDAI scores. The expression of B7-H4 on kidney biopsies from patients with LN and acute kidney injury was measured using immunohistochemistry. In vitro, B7-H4 antigen on cultured HK-2 cells with or without stimulated by inflammatory factors was detected by flow cytometry. After co-cultured with HK-2 and purified CD4+T cells labeled with CFSE for 72 hours, T cell proliferation was detected by flow cytometry. The soluble B7-H4 of serum in LN and healthy donors were analyzed using ELISA **Results:** Immunohistological staining revealed that B7-H4 antigen expressed on tubular epithelium, the percentage of B7-H4 positive expression renal tubules from LN patients (45±16)% was lower than acute kidney injury patients (86±11)% (P<0.05). In vitro, the expression of B7-H4 on HK-2 cells was more driven by inflammatory factors, mixed lymphocyte reactions revealed that HK-2-related B7-H4 inhibits proliferation of co-cultured T cells. The soluble B7-H4 in serum of LN patients (61.45±29.38ng/ml) was not significantly lower than healthy controls(70.57±27.24ng/ml), but stronger association with serum creatinine levels with LN (r=0.353, p=0.005), besides The mean concentration of soluble B7-H4 level in high activity group (74.40±31.95 ng/ml) were significantly higher than those in moderate group (51.89±21.79 ng/ml) (p=0.017) **Conclusion:** The expression of B7-H4 molecules probably has effects during the progress of LN, and a clear understanding of its functional roles may further elucidate the pathogenesis of this disease.

IW2-1

Analysis of three-dimensional computed tomogram of the rheumatoid hand with Swanson implant arthroplasty of the metacarpophalangeal joint

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Conflict of interest: None

[Objectives] Using a X-ray, precise imaging of palmoulnar flexion deformity at the MP joint affected by RA is difficult. The objective of this study is to show analysis of the deformity using a 3D-CT. [Methods] Between April 2006 and April 2011, Swanson implant arthroplasty at the 2nd through the 5th MP joints was performed at 179 joints in 46 hands of 40 patients with RA. Using a posteroanterior view of the hand X-ray, Larsen grade and ulnar flexion angle were assessed. Using a 3D-CT, ulnar flexion angle, palmar flexion angle, grade of MP joint dislocation and resected bone length were assessed by Aquarius iN tuition (Tera Recon). [Results] Preoperative ulnar flexion angle in a X-ray was approximately 9 degrees less than that in a 3D-CT. With progression of Larsen grade, palmar flexion angle of the MP joint increased, and with progression of MP joint dislocation, ulnar flexion angle increased. Average length of bone resection at the metacarpal neck was 9.6mm and that at the proximal phalangeal base was 4.5mm. With progression of MP joint dislocation, resected bone length increased. [Conculusions] A 3D-CT is useful to assess alignment at the severely deformed MP joint. It gives information about an appropriate length of bone resection in the preoperative planning.

IW2-2

Altered expression of TPP1 in Fibroblast-like synoviocytes might be involved in the pathogenesis of rheumatoid arthritis

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Objective: To determine whether the altered expression of telomeric proteins TPP1 and POT1 in fibroblast-like synovial cells (FLS) could provide insights into the pathogenesis of rheumatoid arthritis (RA). **Methods:** FLS were isolated from patients with RA, osteoarthritis (OA) and traumatic joint disease, and cultured in vitro. TPP1 and POT1 mRNA level of FLS was measured using real-time quantitative polymerase chain reaction (RT-qPCR) in 42 RA, 23 OA and 13 healthy cases. Immunofluorescence staining and Western blot were used to detect the expression of TPP1 and POT1 protein. **Results:** Expression of TPP1 and POT1 mRNA was significantly reduced in RA cases (P<0.001, respectively), no significant difference was observed between OA and healthy cases (P>0.05, respectively). Confocal microscopy images showed TPP1 and POT1 proteins mainly located in nucleus of FLS. Western blot demonstrated that TPP1 protein level was significantly reduced in RA cases (P<0.001), POT1 protein expression was not statistical significance among RA, OA and healthy cases (P>0.05). Significant negative correlation was observed between level of TPP1 mRNA and titers of anti-CCP antibody (P<0.001), RF (P<0.01). **Conclusions:** Altered expression of TPP1 might contribute to persistent proliferation of FLS in RA patients; further study on functions of telomeric proteins in RA would be needed.

IW2-3

Musculoskeletal ultrasonography assists the diagnostic performance of 2010 rheumatoid arthritis criteria

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Conflict of interest: None

Objectives. To investigate whether musculoskeletal ultrasonography (MSKUS) assists the diagnostic performance of 2010 RA criteria. *Methods.* Sixty-nine early arthritis patients were consecutively enrolled. None of the patients were treated at entry. In MSKUS of bilateral wrist and finger joints including the 1st – 5th MCP joints, 1st IP joint and 2nd -5th PIP joints, the findings obtained by gray scale (GS) and power Doppler (PD) were graded on a semi-quantitative scale from 0 to 3. Plain MRI of both wrist and finger joints was also examined. The diagnosis of RA was defined by the initiation of DMARDs within the first 3 months. Classification of the patients was evaluated at entry using the 2010 RA criteria in conjunction with MSKUS. *Results.* The 2010 RA criteria classified RA at a sensitivity of 59.5 %, a specificity of 87.5 %, and a positive predictive value (PPV) of 84.6 %. The best MSKUS finding for differentiating RA was the presence of PD grade ≧ 2 that was superior to MRI-proven bone edema. We have found that the decision tree algorithm of 2010 RA criteria with PD grade ≧2 reveals the best discriminative ability. *Conclusion.* MSKUS, especially the strong PD signal, is very useful to assist the diagnostic performance of the 2010 RA criteria in the early recognition of RA.

IW2-4

Can low-dose etanercept prevent joint destruction in PRECEPT study?

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Conflict of interest: None

[Objectives] The efficacy of etanercept (ETN) in RA has been demonstrated. To reduce the cost of biologics, low-dose ETN has been administered without evidence. To evaluate the prevention of joint destruction of low-dose ETN. [Methods] This prospective, randomized study was registered with the UMIN Clinical Trials Registry (UMIN000001798). 70 patients were randomly assigned to receive either ETN 50mg/w or 25mg/w for 1 year. The primary end point was the variation of total Sharp score (TSS), and the secondary end points were that of DAS28 and mHAQ. No progression was estimated as ΔTSS ≦ 0.5 and no progression rate was compared between groups. [Results] Patients had mean disease duration of 9.2 years, DAS28 of 5.45, and annual progression of TSS of 26.1 at baseline. There were no significant differences between groups. No progression rate of 25 mg/w group (36.7%) was significantly less than that of 50mg/w group (67.7%) (p = 0.041). ΔTSS of 25mg/w (1.03) was higher than that of 50mg/w group (-0.13). DAS28 and mHAQ were significantly improved, without significant differences between groups. [Discussion] Low-dose ETN was not inferior to standard-dose ETN in clinical effects. However, from the viewpoint of joint destruction suppression, it was inferior to the effect of standard-dose ETN.

IW2-5

Pulmonary comorbidities predispose patients with rheumatoid arthritis to serious adverse events; analyses from the REAL database

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Conflict of interest: None

[Objectives] To investigate association between pulmonary comorbidities (PC) and serious adverse events (SAEs) in rheumatoid arthritis (RA) patients. [Methods] We analyzed types and incidence rates of SAEs in Japanese RA patients with and without PC. Analysis included 359 patients with PC [PC group, 589 patients-years (PY)] and 1385 patients without PC (non-PC group, 2325 PY). [Results] In the PC group, patients were significantly older, percentage of male was higher, and patients had higher disease activity and poorer physical function. The crude incidence rate ratios comparing the PC group with the non-PC group for SAEs and serious infections (SIs) were 2.3 (95% CI 1.9-2.9) and 2.8 (2.0-3.9), respectively. In the PC group, Cox proportional hazards analysis revealed that age by decade (HR:1.5 [95% CI, 1.1-2.1]), Steinbrocker's stage (III or IV) (HR:2.0 [1.1-3.7]), and DAS28 (3)/CRP (HR:1.3 [1.0-1.7]) were significant risk factors for SIs. In the non-PC group, age by decade (HR:1.8 [1.4-2.3]), presence of diabetes (HR:2.0 [1.1-3.6]) and use of oral corticosteroids ≥7.5mg/day (HR:2.0 [1.1-3.5]) were identified as risk factors for SIs. [Conclu-

sion] RA patients with PC are more vulnerable to SAE and SI than those without PC. Risk factors for SIs were different between the two groups.

IW2-6

Hospitalization and risk of hospitalized infection in patients with rheumatoid arthritis based on IORRA cohort

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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 the IORRA survey, hospitalized patients from October 2009 to September 2010 were extracted based on self-report and confirmed by 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 6,168 patients, 5,182.5 person-years observation, 427 hospitalization (8.24/100 p-y) in 363 patients were confirmed. The causes of hospitalization were infection in 81 (1.56/100 p-y) in 78 patients, orthopedic diseases except planned joint surgery in 45 (0.87/100 p-y), digestive diseases in 43 (0.83/100 p-y), malignancy in 42 (0.81/100 p-y) and circulating diseases in 35 (0.68/100 p-y). Patients with hospitalized infection were older and had higher disease activity, worse physical dysfunction, lower serum albumin and frequent use of corticosteroids ($p<0.05$). The risks for hospitalized infection were low serum albumin (OR 2.6, 95%CI 1.2-6.1) and corticosteroid use (OR 2.4, 95%CI 1.4-4.3).

IW2-7

Assessment of the therapeutic effect by Multi-Biomarker Disease Activity (MBDA) in patients with rheumatoid arthritis treated with TNF inhibitors

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Conflict of interest: None

[Objectives] A simple, objective blood-based disease activity (DA) index is expected to be useful for management of rheumatoid arthritis (RA). We analyzed the multi-biomarker DA (MBDA) algorithm in the BeSt study, and here evaluate it in Japanese RA patients (pts). [Methods] A total of 147 pts with TNF inhibitors (TNFi) (IFX 49, ETN 49, ADA 49) were analyzed. 12 biomarkers (VCAM-1, EGF, VEGF-A, IL-6, TNF-RI, YKL-40, MMP-1, MMP-3, leptin, resistin, SAA, CRP) were measured by Meso Scale Discovery (MSD) at 0, 24, and 52 weeks after starting TNFi and input into the Vectra DA algorithm to calculate a single MBDA score between 1-100. Spearman correlation and AUROC were performed. [Results] Baseline characteristics were: age 60 [50-68], DAS28 5.7 [5.0-6.5], and disease duration 60 [18-168] mo (Median [IQR]). MBDA score was correlated to DAS28 (rho = 0.64, 95%CI = 0.54-0.73, $p < 0.001$, and distinguished low disease activity (AUROC = 0.80, 95%CI 0.72-0.87, $p < 0.001$). At 52 weeks, 56% of the pts achieved EULAR good response (GR), and DMBDA score distinguished GR +/- (AUROC = 0.68, 95%CI 0.58-0.76, $p < 0.001$). No differences in the MBDA/DAS28 relationship were found between the three TNFi. [Conclusion] The MBDA score can assess the efficacy of TNFi in Japanese RA pts.

IW2-8

Color Doppler Ultrasound in Suspected Giant Cell Arteritis: Experience from an Outpatient Clinic

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Aim: Color Doppler Ultrasound (CDUS) is a promising method in diagnostics of giant cell arteritis (GCA). Herein we present our experience in the use of CDUS as a diagnostic tool in a series of 51 patients suspected to have GCA. Methods: Fifty one patients (35 females, 16 males) successively referred to our outpatient clinic for diagnostic evaluations, were examined by CDUS in temporal arteries and large vessels (carotids, axillaries). All were new referrals suspected to have GCA. A Siemens Antares ultrasound system with a high frequency probe 7- 14 MHz was used. CDUS was considered positive when the typical sign of halo (arterial wall swelling in transverse view) and/or stenosis-occlusion was observed (temporal arteries). After the CDUS evaluation, unilateral biopsy of the temporal artery was carried out in 34 patients. In every patient the ACR criteria for GCA were assessed at the presentation time. The diagnosis of GCA was reevaluated and confirmed after 3 months for one and 6 months for the rest of the patients. Results: Twenty five patients had a positive CDUS of the temporal arteries. Twenty of these patients were diagnosed with a GCA. 11 patients with GCA had a positive biopsy and positive CDUS while 6 had a negative biopsy with a positive CDUS. Interestingly in 5 of the patients with GCA and positive CDUS the length of biopsy was below 10 mm. In our case series the CDUS hold a sensitivity of 100% a specificity of 83.9%. The positive predictive value (PV) for CDUS was 80% and the negative PV was 100%. The temporal artery biopsy had a sensitivity of 64.7% and a specificity of 100% and the ACR GCA classification criteria 75 % and 93.5 % respectively. Conclusion: Our results show that the CDUS has an excellent NPV and a high PVV. Therefore a negative result should be used to exclude GCA. A length of biopsy bellow 10 mm seems to lose a significant number of GCA patients. Biopsy should be hold for cases that despite a positive CDUS, the clinical suspicion of GCA is low.

IW2-9

Genetic analysis of ABCG2 and SLC2A9 gene polymorphism in Korean population with gout

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Backgroud: Recently, GWAS identified substantial associations between single nucleotide polymorphism(SNPs), rs2231142 of *ABCG2* and rs6449213, rs16890979 of *SLC2A9* and uric acid concentration and gout in various ethnic **Objective:** The aim of this study is to assess the genetic associations of these SNPs and nearby regions with gout in a Korean population. **Methods:** A total of 109 gout patients and 102 gout-free controls were recruited in this study from Chosun University hospital and Daegu Catholic University medical center. Patients were satisfied the American

College of Rheumatology criteria for gout. The rs2231142, rs6449213, rs16890979 and nearby regions were amplified by polymerase chain reaction(PCR) and PCR product was sequenced by ABI 3730XLto perform mutational analysis. **Results:** Compared with controls, there was a higher A/A genotype of rs2231142 in the gout cases(15.2% vs 2.4% by genotype). And the association to gout reached significance(chi-square=29.42, $p < 0.001$, OR=3.31, 95% CI 2.11-5.20). However, there were not significant difference in rs6449213 and rs16890979 genotype between gout cases and controls. On the other hand, new polymorphism was founded in nearby regions of these SNPs. A c.881A>G and c.1002+78G>A, SNP polymorphism in *SLC2A9* were significant difference in genotype frequency between gout cases and controls respectively. The c.881A>G was a higher G/G genotype frequency in the gout cases than controls (20.1% vs 5.8%, chi-square=9.36, $p < 0.001$, OR=1.54, 95% CI 1.03-2.28). The c.1002+78G>A was a higher A/A genotype distribution in the gout than controls(10.1% vs 2.9%, chi-square=5.93, p =0.05, OR=1.64, 95% CI 1.03-2.62). **Conclusion:** We demonstrate association of rs2231142 in *ABCG2* gene with gout in a Korean population. Also, we newly found the association of c.881A>G, c.1002+78G>A in *SLC2A9* gene with gout in a Korean population.**Key word :** Gout, genetic association, rs2231142, c.881A>G, c.1002+78G>A

IW2-10

The relationship between nail disease and distal interphalangeal joint enthesopathy in psoriasis and psoriatic arthritis: an MRI study

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Subclinical enthesitis on imaging is seen in up to 50% psoriasis patients. The nail is closely attached to entheses around the distal interphalangeal (DIP) joint. Nail pain has been reported in psoriatic nail disease. We therefore ask whether nail disease in psoriasis is associated with DIP joint enthesopathy in psoriasis without clinical arthritis. MRI was performed on 60 patients; 27 with psoriasis (16 with nail disease, 11 with normal nails) and 33 with psoriatic arthritis (PsA) (18 with nail disease, 15 with normal nails). Patients receiving biologic therapies were excluded. High resolution MRI was performed using a 3T magnet with a dedicated finger coil and Gadolinium contrast. MRIs were scored by two musculoskeletal radiologists. The median patient age was 41 (45% female). Enthesitis was common in PsA, and was also seen in clinically uninvolved joints. Subclinical enthesitis in PsA was more frequent in joints with adjacent nail disease than with normal nails (73% vs 36%). Extensor tendon enthesitis was seen in 44% PsA patients with nail disease, 13% PsA patients with normal nails and no psoriasis patients. Flexor tendon enthesitis occurred in 33% PsA patients with nail disease, 6% psoriasis patients with nail disease and no PsA or psoriasis patients with normal nails. Osteitis was more frequent in PsA than psoriasis (36% vs 15%), and was generally more severe and extensive in the PsA patients. Enthesitis is common in PsA, and is also seen in clinically uninvolved joints. A subgroup of psoriasis patients have DIP joint enthesitis and osteitis, although changes are less extensive than those seen in PsA. Extensor tendon enthesitis appears to be associated with nail disease in PsA, but not in psoriasis. These findings suggest that a different pathological process may account for the nail disease in psoriasis patients compared to that in PsA.

IW2-11

Association of intrarenal B cell infiltrates with clinical outcome in lupus nephritis: a prospective study of 192 cases

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Introduction: Lupus nephritis (LN) in systemic lupus erythematosus (SLE) remains a major cause of morbidity and end-stage renal disease. Dysfunction of B lymphocytes is thought to be important in the pathogenesis of SLE/LN. Intrarenal B cells have been found in several forms of inflammatory kidney diseases although their role in LN renal is not well-defined. **Methods**: In this study, intrarenal B cells were analyzed in 192 renal biopsies from patients diagnosed with lupus nephritis. We performed standard immunohistochemistry on serial paraffin tissue sections. **Results**: Intrarenal B cells were more likely to be associated with class IV LN and were mainly distributed in the renal interstitium, with very few in the glomerulus. The Systemic Lupus Erythematosus Disease Activity Index (SLEDAI), blood urea nitrogen and serum creatinine levels were all significantly greater in the LN-B cell groups compared with the LN-non-B cell group (all $P<0.05$). LN renal activity and chronicity indices correlated with B cells infiltrates (all $P<0.0001$). Renal biopsies were classified into four distinct categories according to the organizational grade of inflammatory cell infiltrates. Germinal center (GC)-like structures were not identified in any LN biopsies. **Conclusion**: Intrarenal B cell infiltrates were strongly associated with proor clinical outcome in lupus nephritis patients. It is hypothesized that intrarenal B cells enhance immunological responses and exaggerate the local immune response to persisting autoimmune damage in the tubulointerstitium.

IW2-12

Current Daily Glucocorticoid Use, Serum Creatinine Levels and Premenopausal Status Are Associated with Lower 25 (OH) Vitamin D Levels In Thai Patients with Systemic Lupus Erythematosus (SLE)

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Objective: To examine the prevalence of vitamin D deficiency in Thai SLE patients and possible independent factors affecting serum 25 (OH) vitamin D levels and further examine the associations of serum 25 (OH) vitamin D and the disease activity and damage in Thai SLE patients. Method: A cross-sectional study was performed in 101 SLE patients. Blood samples were prospectively collected. The levels of 25 hydroxyvitamin D2 and D3 [25 (OH) vitamin D] were measured by radioimmunoassay. The cut-off for vitamin D deficiency and insufficiency were 30 and 20 ng/ml, respectively. Demographic, clinical and laboratory data were collected and their associations with 25 (OH) vitamin D level were examined by univariate and multivariate linear regression analyses. Result: The level of 25 (OH) vitamin D [mean (SD)] was 27.9 (7.6). Seventeen patients (17%) had vitamin D deficiency, forty-one patients (41%) had vitamin D insufficiency and forty-three patients (42%) had normal vitamin D levels. Two thirds of the patients were taking vitamin D supplements. Current daily prednisolone dose, serum creatinine levels and premenopausal sta-

tus are negatively correlated with vitamin D levels (β= -0.271, p=0.007, β = -0.251, p=0.011 and β= -0.225, p=0.047, respectively). There were no associations between disease activity or damage and 25 (OH) vitamin D levels. Conclusion: Vitamin D deficiency and insufficiency are common in SLE patients despite more than half of them taking vitamin D supplements. Higher serum creatinine level, higher current daily prednisolone dose and premenopausal status are associated with lower serum 25 (OH) vitamin D levels. These patients may require higher doses of vitamin D supplement.

IW2-13

Surgical Adverse Outcomes in Patients with Systemic Lupus Erythematosus - A Population-based Study

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Background: Limited information was available for the postoperative outcomes in patients with systemic lupus erythematosus (SLE). We used nationwide insurance database to investigate postoperative adverse outcome for surgical patients with preoperative SLE. **Methods:** We conducted a population-based study included 5,028 patients with preoperative SLE receiving major surgery from the Taiwan National Health Insurance Research Database within 2004-2007 and compared with 20,112 surgical patients without SLE. Eight major postoperative complications and mortality after complications were evaluated among patients with and without SLE. **Results:** Patients with SLE had significantly higher risk for postoperative complications including acute renal failure, pneumonia, pulmonary embolism and septicemia when compared with surgical patients without SLE. Surgical patients who experienced hospitalization due to SLE were at significant increased risk of acute renal failure (adjusted odds ratio [aOR]=5.44, 95% confidence interval [CI]=3.49-8.48), pneumonia (aOR=2.22, 95% CI=1.63-3.02), pulmonary embolism (aOR=5.15, 95% CI=1.50-17.6), and septicemia (aOR=2.93, 95% CI=2.19-3.92) compared with control group. The ORs for Increased length of stay, intensive care unit stay and elevated medical expenditure associated with preoperative SLE were 2.04 (95% CI=1.80-2.31), 1.83 (95% CI=1.54-2.17), and 2.62 (95% CI=2.31-2.97), respectively. Compared with patients without SLE, surgical patients with preoperative SLE had higher risk of the 30-day postoperative mortality (OR=2.40, 95% CI=1.36-4.21). **Conclusion:** Surgical patients with SLE showed significantly higher postoperative adverse outcome rates with risk of 30-day mortality more than two-fold when compared with patients without SLE. Our findings suggest the urgency revising the protocol of postoperative care for this specific population.

IW2-14

Prognostic factor in SSc and PM/DM associated interstitial lung disease

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Conflict of interest: None

【Objective】We investigated whether or not clinical data analyzed by the non-invasive examination, were prognostic factors for patients with SSc and PM/DM-associated ILD (SSc and PM/DM-ILD), retrospectively.【Methods】The HRCT findings in patients with 64 SSc and 46 PM/DM-ILD were classified to UIP and not-UIP patterns. We investigated the relationship between several clinical data and history and outcome in patients.【Results】Twenty-two (34.4%) in 64 SSc-ILD patients died for 2008.5 (718.5-3401.5) days as median follow-up period. Causes of death were 31.8% by infection, 22.7% by malignancy and acute exacerbation of ILD, 9.1% by deterioration of ILD and 13.6% by another causes in 22 patients. Fourteen (30.4%) in 46 PM/DM-ILD patients died for 2253.5 days as median follow-up period. Causes of death were 50% by acute exacerbation, 14.3% by deteriotation of ILD, infection, malignancy, 7.1% by another causes in 14 patients. Murtivariate analysis showed that independent poor prognostic factor were treatment without immunosuppressive angents (*P*=0.0179) and UIP pattern in HRCT (*P*=0.0149) in patients with SSc-ILD, high age (≧58 years old, *P*=0.0063), low %vital capacity (<70%, *P*=0.0461).

IW2-15

HLA-DRB5* 01:05 is a Risk Factor for Systemic Sclerosis with Interstitial Lung Disease

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Conflict of interest: None

[Objectives] Interstitial lung disease (ILD) is a serious complication of systemic sclerosis (SSc). We aimed to elucidate markers associated with ILD in patients with SSc. [Methods] RNA samples prepared from PBMCs were divided into 4 sets of RNA pools according to the presence or the absence of ILD and to the treatment, and then were subjected to microarray analysis. Genomic DNA samples were collected from 147 healthy controls and 70 SSc patients who received HRCT for the evaluation of ILD. Genotyping was done using sequence specific primers method. Obtained results were re-evaluated using 2nd cohort that comprised 83 healthy controls and 79 SSc patients. [Results] Microarray analysis revealed that *HLA-DRB5* was the only gene commonly up-regulated more than 3 times in patients with ILD compared to those without. The frequencies of *DRB5* genome-carriers were more frequent in SSc patients with ILD than in those without ILD or healthy controls, in both cohorts. Detailed genotyping of *DRB5* gene revealed that *DRB5*01:05* allele was significantly more frequent in SSc patients with ILD than in those without (OR:8.07, 95% C.I. 3.06 – 21.28). This association was confirmed in the 2nd cohort. [Conclusion] *HLA-DRB5*01:05* allele is a risk factor for the development of ILD in patients with SSc.

Annual Course Lecture Luncheon Seminar

ACLLS

Clinical application of methotrexate (MTX) for the treatment of rheumatoid arthritis (RA)

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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. Although the limitation of MTX dose has been a long-standing problem since Rheumatrex was introduced into the Japanese market in 1999, 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. The JCR released the recommendations for the use of MTX in the treatment of RA in September 2010, and the revised edition was published in March 2011. 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, 417 patients who died during MTX therapy by adverse events have been accumulated until February 2011. During the initial 3 years, cytopenia and pneumonitis were major fatal side effects. Although pneumonitis tends toward decreasing, infection and lymphoproliferative disorders are showing a tendency to increase during the recent 3 years. In addition, fulminant hepatitis by the reactivation of hepatitis B virus is also one of the fatal adverse events. The administration of MTX to patients who have contraindications should be avoided and be cautious of patients with precautions. Patient education is the important factor for the early diagnosis and treatment of side effects. The supplementation of folic acid is effective to decrease GI side effects, stomatitis, the elevation of liver enzymes, and possibly part of cytopenia. It is important to understand dosing and administration of folic acid. In this lecture, the practical points for the use of MTX in the points of view of safety consideration would be discussed on the basis of the JCR recommendations.

International Lecture

IL

Early intervention in RA and remission; are they linked?

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Over 90% of patients with rheumatoid arthritis (RA) developed some sort of disability. However, remission is an achievable goal for many rheumatoid arthritis (RA) patients. Early intervention is key to ensuring optimal patient outcomes. By treating early and appropriately joint damage can be prevented and progression of RA can be minimised. Furthermore early intervention can increase the likelihood that a patient can remain in employment, or otherwise lead a full and productive life and remission rates can be maximised. It is essential that patients with a suspected diagnosis of RA are referred specialist care as early as possible to ensure the initiation of appropriate treatment. But what is remission? It is known that patients in clinical remission on DMARDs can progress structurally. The explanation for this could be: 1. That remission criteria are not stringent enough 2. There are separate factors determining inflammation and damage 3. Clinical measures used are insensitive Cohort studies of patients in remission in Leeds have revealed a number of important features of patients in remission have shown the value of imaging as well as immunological changes in predicting outcomes. How patients should be managed will be discussed.

Poster Session

P1-001

Overexpressions of S100A4/A6/A9/A11/A12 in the patients with RA, SLE, and JIA and correlations of their expression levels with the local and systemic inflammatory biomarkers in RA patients

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Conflict of interest: None

[Background] S100 family molecules are calcium-binding proteins. It is reported that S100A4/A8/A12 are increased in patients with RA or some other autoimmune diseases. [Object & Method] The expressions of fifteen S100 genes in peripheral blood cells from RA, SLE, and JIA patients were investigated using microarray. Correlations between differentially expressed S100 gene expression levels and disease activity, erythrocyte sedimentation rate (ESR), matrix metalloproteinase-3 (MMP3) and C-reactive protein (CRP) levels in RA patients were also investigated. [Result] S100A4, S100A6, S100A9, S100A11, and S100A12 are significantly overexpressed in RA, SLE, systemic-onset JIA (sJIA), and polyarticular JIA (polyJIA) patients compared to healthy individuals. S100A5 and S100G were also increased in RA patients. S100A13 and S100A16 were underexpressed in RA, SLE, and sJIA but not in polyJIA patients. The expression levels of S100A6 and S100A9 were found significantly correlated to MMP3 and CRP levels. S100A12 expression was correlated to ESR and CRP. Cytokines including TNF, IL-6, IL-1, TGF beta and S100 proteins themselves were suggested important in the regulatory networks. [Conclusions] S100 family molecules together with cytokines were suggested to be involved in inflammatory reaction.

P1-002

The apoptosis of peripheral Th17 and Regulatory T cells in rheumatoid arthritis

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Conflict of interest: None

[Objectives] The arm of this article is to study whether insufficient apoptosis is contributed to the imbalance of Th17/Treg in RA. [Methods] There were 21 RA patients and 8 healthy volunteers involved. The percentage of $CD4^+$ $IL\text{-}17^+$ T cells and $CD4^+$ $Foxp3^+$ T cells were measured by flow cytometry, and active caspase-3 labeling was used to detect early apoptosis. The differences of the percentage of subtypes of T cells and ratio of apoptotic cells between the two sub-populations were compared, and also correlated with the disease activity. [Results] Neither the number of Th17 nor Treg cell was significantly different between the RA patients and the healthy controls. The number of Treg cells was correlated to disease activity, RF and ESR. For the apoptosis of the T cell subtypes, Th17 cells were significantly more sensitive than Treg cells, no matter in RA patients or healthy controls. The percentage of apoptotic Th17 cells in RA patients was significantly higher than in the controls. The ratio of apoptotic cells of both Th17 and Treg did not relate to disease activity. For the same patient, the percentage of synovial Th17 cells was higher than the peripheral blood, and the apoptosis rate was lower. The percentage of apoptotic Treg cells was lower after anti-TNF treatment.

P1-003

Analysis of IFN-γ-Positive Th17 Subset (Th17-1 Cells) in Rheumatoid Arthritis

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Conflict of interest: None

[Objectives] Recently, IFN-λ-positive Th17 subset (Th17-1) has been identified and attracted attention in its role in JIA. We examined the proportion of Th17-1 cells in RA. [Methods] Fourteen samples of PBMC from normal controls (cont PBMC), 33 samples of PBMC from RA patients (RA PBMC), and 17 samples of synovial fluid mononuclear cells from RA patients (RA SFMC) were examined. Intracellular cytokine assay by flow cytometry was performed. Among CD4+CD45RO+ cells, we defined each subset as follows: Th1 cells, single positive for IFN-λ; Th17 cells, single positive for IL-17; Th17-1 cells, double positive for IFN-λ and IL-17. [Results] In RA PBMC, the proportion of both Th17 cells and Th17-1 cells were decreased compared to cont PBMC, whereas the proportion of Th1 cells was not different (RA PBMC vs. cont PBMC: Th17, 2.2±1.1% vs. 3.0±1.1%, P=0.006; Th17-1, 0.4±0.3% vs. 1.0±0.5%, P=0.0002; Th1, 24±11% vs. 28±5.6%, P=0.0624). In RA SFMC, the proportion of Th17 cells was decreased, while the proportion of Th1 and Th17-1 cells were increased compared to RA PBMC (RA PBMC vs. RA SFMC: Th17, 2.2±1.1% vs. 1.8±1.4%, P=0.0381; Th1, 24±11% vs. 38±14%, P=0.0004; Th17-1, 0.4±0.3% vs. 1.1±0.9%, P=0.0006). [Conclusion] Th17-1 cells may play a dominant role in the local inflammation of RA.

P1-004

Analysis of BAFF and clinical markers of patients with rheumatoid arthritis (RA)

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Conflict of interest: None

[Objectives] B-cell activating factor belonging to TNF family (BAFF) might play a pathogenic role in RA because it has been reported that BAFF level increases in RA serum, and that anti-BAFF mAb ameliorates RA activity. In this study, we analysed the relevance of serum BAFF (sBAFF) level to clinical backgrounds. [Methods] Sixty three RA patients were enrolled. Calculated was the correlation between sBAFF level and clinical backgrounds (age, disease duration, CRP, ESR, IgM-RF, anti-CCP Ab, MMP-3, HAQ, dosage of MTX and/or Prednisolone), disease activity scores (SDAI, CDAI, DAS28ESR4, DAS28CRP4), Total Sharp score, joint narrowing score, and erosion score. Multiple regression analyses, in which sBAFF level, age, disease duration, IgM-RF, and HAQ were used as independent variables, were performed to analyze the significance of sBAFF with respect to disease activity scores as the dependent variable. [Results] sBAFF was inversely correlated with disease duration($p=0.0353$). In multiple regression analysis, adjusted R^2 of each disease activity scores were 0.62,0.60,0.51,0.48, respectively ($p<0.0001$). Significant independent valuables are sBAFF, age, and HAQ(SDAI, DAS28CRP4), sBAFF, age, IgM-RF, and HAQ(CDAI), age and HAQ

(DAS28ESR4). [Conclusion] sBAFF might be relevant to disease activity scores of RA.

P1-005

Examination of phenotype of CD14^{+} monocytes in bone marrow and peripheral blood from Japanese patients with rheumatoid arthritis

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Conflict of interest: None

[Objective] Recently, we have reported monocyte-derived multipotential cells (MOMCs), which can differentiate into bone and cartilage, and found that precursors of MOMCs mainly exist within CD14^{+}CXCR4^{high} monocytes (Mos) in peripheral blood (PB). On the other hand, it has been reported that CD14^{+}CD15^{+} cells, which are associated with joint destruction, abundantly exist in iliac bone marrow (BM) of rheumatoid arthritis (RA). Therefore, we examined the phenotype of CD14^{+} Mos of RA and investigated subpopulations of Mos. [Methods] Expression of CD15, CD31, CD34, CD144, CCR1, CCR2, CCR4, CCR5, CCR6, CXCR4 on CD14^{+} Mos in BM or PB from 7 RA patients and PB from 6 healthy donors (HDs) were examined using flow cytometry. [Results] High expression of CD34 and CCR5 was observed on CD15^{+} Mos compared with CD15^{-} Mos in BM of RA. CD15^{+} Mos in PB of RA also expressed CD34, but not those of HDs. Low expression of CD15 was observed on CXCR4^{high} Mos in PB compared with CXCR4^{low} Mos, while low expression of CXCR4 was observed on CD15^{+} Mos in PB compared with CD15^{-} Mos, indicating that expression of CD15 and CXCR4 on Mos in PB was exclusive each other. [Conclusion] The distinct subpopulations, which are involved in joint destruction and joint repair respectively, possibly exist in Mos of RA.

P1-006

Effects of TNF-α inhibitors on the in vitro IL-6 production of human peripheral blood mononuclear cells

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Conflict of interest: None

[Objectives] We previously showed that TNF-α antagonisits, etanercept (ETN) and infliximab (IFX) suppress IL-17 production of peripheral blood mononuclear cell (PBMC). It has known that the maturation of Th17 requires the action of IL-6. The current study was undertaken to explore the effects of ETN and IFX on the IL-6 production of PBMC and monocytes. [Methods] PBMC or monocytes from healthy donors were activated with staphylococcal enterotoxin B (SEB) and cultured with pharmacologically attainable concentrations of biological agents or control IgG. The concentrations of IL-6 in the culture supernatants were measured using ELISA. [Results] ETN suppressed the IL-6 production of PBMC activated with SEB, whereas IFX had no significant effects on the IL-6 production of PBMC activated with SEB. The magnitude of IL-6 production of monocytes was much smaller than that of PBMC. [Conclusions] The results indicate that ETN, but not IFX, significantly suppress the IL-6 production of PBMC. The lack of significant effect of IFX might be due to the presence of non-responders, which requires further investigation.

P1-007

Changes of β2-microglobulin in Peripheral Blood Following Leukocytapheresis Therapy for Rheumatoid Arthritis

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Conflict of interest: None

[Objectives] The mechanisms of action for the effect of LCAP(leukocytapheresis) have been made to clarify, but there are many points that are not yet apparent so far. A study suggested an elevation in serum IL-10 levels and reductions in the serum levels of TNF-α and IL-15 in RA (rheumatoid arthritis) patients after repeated LCAP. These dynamic changes in some cytokine levels may explain some of the mechanisms of LCAP. Another study showed the recruitment of various stages of WBCs from bone marrow and other organs was important for the effectiveness of LCAP. [Methods] In the previous study, 16 patients with RA underwent five sessions of LCAP. We performed microarray analysis for more than 25000 gene expression patterns in peripheral blood before and after LCAP. As a result, the LCAP session significantly increased 82 genes and reduced 43 genes in all patients. Genes which had reduced after LCAP session included B2M(β2-microglobulin) and ITGB1(integrin β1). These genes play important roles in the immune respons and cell adhesion, so these changes may explain some of the mechanisms of LCAP. [Results] In this present study, we measured the changes of B2M by real-time PCR and ELISA in peripheral blood following LCAP for RA. We report the results.

P1-008

Increase of plasma pentraxin 3 (PTX3) in patients with rheumatoid arthritis (RA) by leukocytapheresis

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Conflict of interest: None

We have reported that plasma PTX3 levels in patients with RA are high in JCR, 2011. Because PTX3 is stored in the granulocytes, we analyzed plasma PTX3 in 7 patients with RA who were treated with leukocytapheresis. Mean plasma level of PTX3 after the leukocytapheresis column (11.2ng/ml) was significantly increased than that before the column (3.5ng/ml). The final plasma level of PTX3 after the treatment of leukocytapheresis was also significantly increased (15.4ng/ml). When the whole blood of patients with RA was incubated with unwoven polyester fiber for leukocytapheresis column, the plasma level of PTX3 increased. In addition, cytoplasmic vacuolation of granulocytes was observed. These data suggested that PTX3 stored in the granulocytes released during the leukocytapheresis, which could be related with the improvement of RA after this therapy.

P1-009

Increase of eosinophils in the synovium before the onset of arthritis in the murine model for rheumatoid arthritis.

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Conflict of interest: None

[Background] To explore the earliest changes before the onset of arthritis in the mouse gp130F759, in which *gp130 with Y759F mutation* is knocked-in, we examined the profile of gene expression in the joint of gp130F759 at 5 months old, when the very subtle restriction of joint flexibility is detectable. The result revealed the increased expression of genes specific for the multiple lineages of hematopoietic cells. [Objective] Recently novel roles for eosinophils in innate and acquired immunity have been recognized. To clarify roles for eosinophils in the onset of arthritis in gp130F759, dynamics of eosinophils in the joint and lymphoid tissues of gp130F759 around 5 months old were examined. [Methods] Expression of eosinophil-specific genes, *eosinophil peroxidase* (*Epx*) and *major basic protein* (MBP) in the joint were analyzed by real-time PCR assay. Frequencies of eosinophils in the synovium and lymphoid organs are analyzed by flowcytometry using monoclonal antibody for siglec F, an eosinophil-specific surface molecule. [Results] Expression of *Epx* and *MBP* were increased in the joint of gp130F759 compared with wild type. Eosinophils are increased predominantly in the synovium but not in the bone marrow and spleen, suggesting a role for eosinophil in the onset of arthritis in gp130F759.

P1-010

Platelet derived microparticles in patients with rheumatoid arthritis treated with biologic agents

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Conflict of interest: None

[Objectives] We analyzed the plasma levels of platelet derived microparticles (PDMPs) in patients with rheumatoid arthritis (RA), who were treated with biologic agents such as infliximab (IFX) and tosilizmab (TCZ). [Methods] Eleven and 9 cases were treated with IFX and TCZ, respectively. The disease activities were not different in these 2 groups. The levels of PDMPs was measured by flow cytometry. [Results] The mean plasma level of PDMPs of these cases before the treartment was 151 $x10^6$/L, which was significantly higher than that of healthy volunteers (22 $x10^6$/L) ($P< 0.0001$). Almost all of the cases treated with IFX and TCZ reached the low disease activity or clinical remission by the criteria using DAS28 and CDAI. In IFX treated group, plasma PDMPs before and 12 weeks after the IFX treatment were same level such as 153 x 10^6/L and 172 x 10^6/L, respectively. Plasma PDMPs was134 x 10^6/L before the TCZ treatment and decreased to 96 x 10^6/L 12 weeks after the treatment; however, the level after the treatment was still higher than that in healthy volunteers. [Conclusion] These data suggested that TCZ affect the production of PDMPs in RA possibly through the inhibition of IL-6.

P1-011

Role of a transcription factor PU.1 in TGF-β signaling-mediated osteoclast differentiation

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Conflict of interest: None

Object. PU.1 is one of the most important transcription factors in osteoclastogenesis that is associated with rheumatoid arthritis. TGF-β signaling accelerates the development of Langerhans cells and regulatory T cells, in which the expression level of PU.1 is increased during terminal differentiation. We examined the involvement of PU.1 in TGF-β-mediated osteoclast differentiation. Methods. Osteoclasts were generated from mouse bone marrow cells by the cultivation with using M-CSF, and RANKL, in the presence or absence of TGF-β. To evaluate the effect of PU.1 in the development of osteoclasts, PU.1 was knocked down using siRNA. Osteoclasts formation was determined by TRAP staining, and the amount of mRNAs of the osteoclast marker genes was measured by quantitative real-time PCR. Results. The number of TRAP-positive multinucleated cells was significantly reduced by knocked down of PU.1. The expression of Acp5, NFATc1, cathepsin K, Itg3, and Oscar was significantly reduced in PU.1 siRNA-introduced cells. The amount of mRNA of the osteoclast marker and PU.1 gene expression was increased with stimulating TGF-β. Conclusion. TGF-β signaling and PU.1 are involved in osteoclastgenesis. We are going to analyze the role of PU.1 in TGF-β-mediated gene expression by using ChIP assay.

P1-012

Association between time-dependent changes in anti-cyclic citrullinated protein antibody and rheumatoid factor levels and disease activity in disease-modifying antirheumatic drug therapy

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Conflict of interest: None

[Objectives] To observe time-dependent changes in anti-CCP antibody(anti-CCP) and RF levels in DMARDs therapy and determine the association of these markers with disease activity. [Methods] Early RA patients(n=19) received SASP or bucillamine (BUC); MTX was administered to patients poor response to this treatment, and its efficacy was examined. We measured anti-CCP and RF levels after 0, 1, 3, 6, 9, 12 months. [Results] The remission rates were 58%. The RF and anti-CCP levels significantly decreased after 3 and 6 months, respectively, of treatment. Some patients showed a marked decrease in RF and anti-CCP levels in a year (RF, 368 to 23; anti-CCP, 1,180 to 290.5). However, the difference between the baseline levels of these markers and levels at 1, 3, and final months did not affect the efficacy. [Discussion] No significant association was observed between the anti-CCP and RF levels and treatment efficacy during the 1-year period. Because these 2 markers may be involved in the pathogenesis of RA, a time-dependent decrease in their levels may have improved the RA. Remission(clinical, structural, functional) are required for RA, but immunological remission of RA should be targeted using these 2 markers. Therefore, treatment with DMARDs such as SASP, BUC, and MTX is essential.

P1-013

The function of Kruppel-like factor 4 in fibroblast-like synovial cell

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Conflict of interest: None

[Objectives] Kruppel-like factor 4(KLF4) is known factor for the iPS generation from fibroblast-like synovial cell (FLS). Both physiological and pathological effects of KLF4 in FLS are not known. In this study, we analyzed the function of KLF4 in FLS. **[Methods]** Synovial tissue was obtained during operation from RA patient with informed consent. The tissues were used for immunohistochemistry and isolating FLS for primary culture. The avidin-biotin-peroxidase complex method was used to detect KLF4 in synovial tissue. The localization of KLF4 was analyzed by immunofluorescent staining. The protein expression levels of KLF4 were examined by western blot. The knock down of KLF4 in FLS was performed by siRNA technology. The production of interleukin-6 (IL-6) in the FLS culture medium was quantified by Enzyme-Linked ImmunoSorbent Assay (ELISA). **[Results]** The protein expression of KLF4 was observed in the lining layer of RA synovial tissue. The nuclear localization of KLF4 was confirmed by immunofluorescent staining and western blot. We knocked down KLF4 by the treatment with siRNA for 72 hours, and measured the concentration of IL-6 in the culture medium and found that IL-6 was increased by the KLF4 knockdown. Our observation suggest the possible roles of KLF4 in regulating FLS function.

P1-014

Expression of IL-17, IFN-γ and TNF-α in RA synovial tissues and the effects of TNF-inhibitors

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Conflict of interest: None

[Objectives] Recently, role of Th17 and IL-17 in joint destruction in RA has been noted; however, expression of IL-17 and other inflammatory cytokines in the synovium, or effects of TNF-inhibitors on their expression is not known. The aim of this study was to investigate expression of IL-17, IFN-γ and TNF-α in RA synovial tissues and the effects of TNF-inhibitors on their expression. [Methods] Synovial tissues from 25 joints in 25 RA patients were used in this study. Of 25 patients, thirteen had been treated with TNF-inhibitors but twelve without biologics. Following RNA extraction, real-time PCR was performed using specific primers for IL-17, IFN-γ and TNF-α. [Results] Expression of IL-17 was low in cases achieving the radiological remission or in cases whose disease activity was decreased by TNF-inhibitors. On the other hand, IL-17 was increased in cases resistant to TNF-inhibitors or in cases with moderate or high disease activity not receiving biologics. Expression of IFN-γ and TNF-α tended to be associated with IL-17. [Discussion] Expression of IL-17 in the RA synovium was attenuated by TNF-inhibitors in the majority of cases. IL-17 expression was increased in the minority of cases resistant to TNF-inhibitors, suggesting the usefulness of targeting IL-17 in such cases.

P1-015

Regulation of osteoclastgenesis by connexin 43 in vitro and in vivo.

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Conflict of interest: None

[Objectives] Connexin 43 (Cx43) was the main protein in gap junction which were specialized connections between cells in a tissue. Cx43 has been implicated in osteoclasts, but it is not clear of the role for Cx43 in osteoclastgenesis of rheumatoid arthritis (RA). The objective of this study is to investigate whether Cx43 gene silencing in mouse RAW264.7 *in vitro* or in rat synovium *in vivo* by RNA interference inhibit osteoclastgenesis. [Methods] Small interfering RNA targeting for Cx43 (si-Cx43) for mouse or rat was used. Non-specific siRNA was used for control. Osteoclast formation from RAW264.7 by treatment of receptor activator of NF-kappaB ligand (RANKL) was examined with treatment of mouse si-Cx43, and the number of giant multinuclear and tartrate resistant acid phosphatase (TRAP) positive cells was counted. The effects of rat si-Cx43 in a rat model of collagen-induced arthritis (CIA) were also evaluated. [Results] The number of giant multinuclear and TRAP positive cells induced by RANKL was significantly smaller in mouse si-Cx43 group than in control group. Furthermore, treatment with rat si-Cx43 significantly reduced the radiographic scores in rat with CIA. Cx43 may have a potential role for osteoclastgenesis in RA.

P1-016

Hypoxia-induced endogenous prostaglandin E2 negatively regulates hypoxia-enhanced aberrant overgrowth of rheumatoid synovial tissue.

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Conflict of interest: None

[Objectives] We previously established an *ex vivo* cellular model using the synovial tissue-derived inflammatory cells, which reproduced aberrant synovial overgrowth and pannus-like tissue development *in vitro*. Using this model, we investigated the regulatory mechanism of synovial cells against hypoxia in rheumatoid arthritis. [Methods] Inflammatory cells that infiltrated synovial tissue from patients with rheumatoid arthritis were collected without enzyme digestion, and designated as synovial tissue-derived inflammatory cells. Under normoxia or periodic hypoxia twice a week, their single-cell suspension was cultured in medium alone to observe an aberrant overgrowth of inflammatory tissue *in vitro*. Cytokines produced in the culture supernatants were measured by enzyme-linked immunosorbent assay (ELISA) kits. [Results] Primary culture of the synovial tissue-derived inflammatory cells under periodic hypoxia resulted in the attenuation of the spontaneous growth of inflammatory tissue *in vitro* compared to the culture under normoxia. When endogenous PGE2 was blocked by indomethacin, the aberrant tissue overgrowth was more enhanced under hypoxia than normoxia. Indomethacin also enhanced the production of the inflammatory mediators under periodic hypoxia compared to normoxia.

P1-017

Expression and localization of estrogen receptor-β in synovia of rheumatoid arthritis (RA) wrist

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Conflict of interest: None

[Objectives] To test hypothesis if estrogen affects development of rheumatoid arthritis. [Methods] We compared synovial specimens from 28 RA hands with specimens from a contol group of 20 hand with carpal tunnel syndrome. Analysis included histological synovitis grade (Krenn) and immunohisitochemical examinaiton for the distribution of estrogen receptor(ER) α, ER β, progesterone, Ki-67(MIB-1). [Results] Positive rate of ERα, ERβ, PgR, MIB-1 was 39.2%(11/28), 78.6%(22/28), 3.6%(1/28), 82.1%(23/28), respectively. The Peason's rank correlation coefficient between synovitis score and ERβ was 0.79($P<0.001$). [Discussion] These results demonstrate that ERβ are present in RA synovitis, suggesting a role for sex steroid hormone in the pathogenesis of RA.

P1-018

The evaluation of oxidative stress in synovial fluids in patients with knee hydroarthrosis.

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Conflict of interest: Yes

【Objective】To examine oxidative stress in synovial fluids in osteoarthritis (OA) and rheumatoid arthritis (RA) patients with knee hydrarthrosis.【Patients and Methods】Synovial fluid (SF) samples were obtained from patients with OA (28 cases) and RA (15 cases). Of 15 RA cases, 5 were treated with biologics (3 in etanercept, 1 in tocilizumab, and 1 in abatacept). Each SF sample was subjected to d-reactive oxygen metabolites (d-ROM) test by using Free Radical Elective Evaluator (Diacron, Italy). The significanct difference of d-ROM value was analyzed between OA and RA group statistically. In addition, the effect of biologics on d-ROM value was analyzed statistically.【Results】The d-ROM value in RA patients (209 U.CARR) was significantly higher than that in OA (124 U.CARR) ($p<0.01$, Mann-Whitney test). In RA patients treated with biologics, d-ROM value (110 U.CARR) was significantly lower than those without biologics (264 U.CARR).【Discussion】Significant increased level of d-ROM value in RA patients compared with that in OA patients indicates that oxidative stress is more associated with the pathogenesis of RA than OA. Biologics significantly decreased oxidative stress in RA patients but further examinations are required to clarify the detailed mechanism.

P1-019

Contribution of TNFα to the expression of circadian clock genes 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 tumor necrosis factor-alpha (TNFα) inhibited the mRNA expression of *Per2* in primary cultured human rheumatoid arthritis fibroblast-like synovial cells (RA-FLS). To clarify the molecular mechanism of Per2 inhibition by TNFα in RA-FLS, we examined the mRNA and protein expression of *Dbp* and *E4BP4*; a transcriptional activator and repressor of *Per2* gene, respectively. [Methods] Primary cultured RA-FLS were synchronized upon incubation with 50% horse serum for 2 hours, and then stimulated with 10ng/ml TNFα. Total RNA was extracted from RA-FLS to analyze quantitative mRNA expression of *Dbp* and *E4BP4* by real-time PCR with TaqMan probe. The nuclear protein level of DBP and E4BP4 were also examined by western blotting. [Results] TNFα significantly inhibited the mRNA and protein expression of *Dbp* gene and enhanced those of *E4BP4* in RA-FLS. [Conclusion] TNFα could modulate the expression of *Dbp* and *E4BP4* genes, thereby inhibits those of *Per2* in RA-FLS.

P1-020

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 extracted from the PBMCs were separated by two-dimensional gel electrophoresis. Then, all proteins and glycoproteins were detected by Sypro Ruby and ConA rectin, 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 1with *N*-glycans were detected. We found that glycosylation levels of 11 protein spots were significantly different between the healthy group and the RA group ($p<0.05$). Some of the proteins of these spots have been identified using MALDI-TOF/MS. There is a possibility that unusual glycosylation of these proteins may be involved in the pathogenesis of RA.

P1-021

Anti-CCP antibody and its clinical efficacy for predicting prognosis in RA

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Conflict of interest: None

Clinical utility of anti-CCP antibody (ACPA) was investigated for 733 patients with RA. Patients were classified in three groups using results of RF and ACPA: low value group showed RF(-) and ACPA<30U/ml, high group did RF>60U/ml and ACPA>80U/ml, and intermediate group between low and high groups. In the low value group, 55% of patients were treated with only DMARDs. In the high value group, immunosuppressive agents were added in 85 % of patients, and biological agents were added in 30 %. 147 cases could reexamine ACPA after more than six months, and changed slightly. ACPA is useful for the prediction of RA patients, refer to RF changing by disease activity.

P1-022

High titer of anti- cyclic citrullinated peptide antibody in early rheumatoid arthritis predict radiographic damage after five years

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Conflict of interest: None

[Objectives] To study the value of anti- cyclic citrullinated peptide (CCP) antibody in early rheumatoid arthritis (RA) and the radiographic damage after five years. [Methods] 17 patients with early RA onset, who were followed up for longer than 5 years, were subjected. We investigated the value of CCP antibody, Disease Activity Score (DAS) 28 CRP and modified Total Sharp Score (mTSS) at the first visit and five years after. [Results] Two patients possessed low titer of CCP antibody, 13 patients possessed high titers and 2 patients possessed negative. Nine patients were undergoing biological treatment after five years, they all presented CCP antibody positive. Their values of mTSS at the first visit were high, and increased after five years. However, the increase rate of mTSS in patients with biological treatment were lower than patients who were not undergoing biological treatment in spite of high titers of CCP antibody. [Conclusion] Joint damage in the patients with high titer of CCP antibody progress during early onset, aggressive intervention with biologics may help to inhibit joint damage.

P1-023

Associations between ratio of eicosapentaenoic acid and arachidonic acid (EPA/AA) and inflammation in rheumatic diseases patients

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Conflict of interest: None

Objectives: Fatty acids ratio of eicosapentaenoic acid and arachidonic acid (EPA/AA) has been reported to be associated with CVD event. We investigated the relationships between EPA/AA ratio and inflammation in rheumatic diseases patients. **Methods:** Among 316 consecutive outpatients visiting in our department between September 2009 and January 2010, we examined the fatty acid fraction 4 (EPA, AA, DHLA, DHA), cardiovascular risk factors, and serum levels of CRP. **Results:** Patients' characteristics are shown below;56.8 ±14.3 yrs, BMI21.6±2.9, M/ F;59/257, RA 103, SLE 55, MCTD 7, APS6, mean dosage of PRD 5.97± 3.6mg (203/316), HT116, HL94, DM33, EPA / AA 0.40 ± 0.29. EPA / AA ratio showed a significant difference in the presence of HL (0.47±0.34vs.0.38± 0.27, p = 0.028) CRP showed a significant difference compared with EPA / AA ≧0.4 and EPA / AA <0.4 groups (0.52±1.26vs.0.28±0.58mg/dl, p=0.043). In the absence of HL, serum AA levels were significantly high in RA group compared with SLE, APS and MCTD group (163.9±35.0vs.149.2±35.4μg/mL, p=0.04). Multiple regression analysis showed that serum levels of AA and CRP were negative correlation in RA group (r = 0.10, p = 0.0153) but not SLE group. These results suggest that serum AA levels were associated with inflammatory condition in RA patients.

P1-024

Plasma osteopontin levels decrease after successful treatment in patients with rheumatoid arthritis

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Conflict of interest: None

[Objectives] Osteopontin (OPN) is one of the key molecules in patients with rheumatoid arthritis (RA), due to its unique function bridging bone and the immune system. We reported in the last annual meeting that plasma OPN levels correlated significantly with levels of bone resorption markers, tartrate-resistant acid phosphatase-5b and C-terminal peptide of type I collagen. In this study, we measured plasma OPN levels before and after treatment in patients with RA to examine whether OPN levels associate with therapeutic effect. [Methods] A total of 36 patients with active RA were treated with disease-modifying antirheumatic drugs including biologics. Clinical response to the therapy was assessed before and after 6 months or 1year by ESR, CRP, and MMP-3, and patients were classified into responders (n=26) and non-responders (n=10). Plasma levels of OPN were measured by ELISA before and after the treatment, and changes in OPN levels were evaluated by Wilcoxon signed-ranks test. [Results] Plasma OPN levels were significantly decreased after therapy in responders (p=0.003). [Conclusion] Plasma OPN level may reflect not only bone destruction but also active arthritis in RA patients.

P1-025

Relationship between Monocyte Count and Radiologic Progression in Early Rheumatoid Arthritis

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Conflict of interest: None

Objective: Monocytes that generate inflammatory cytokines on stimulation by immune complexes, contribute to joint destruction in rheumatoid arthritis (RA). The aim of this study is to investigate the usefulness of serial measurement of peripheral monoctye count for monitoring the radiological progression in early RA. Methods:

Thirty one patients with RA who had not previously received disease modifying antirheumatic drugs (DMARDs) were studied. Area under curve (AUC) of monocyte count, erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) were calculated and compaired to the change of modified Sharp's scores of hands. Results: Mean monocyte count was 377.6 (5.7%±2.6) of peripheral WBC. During follow up period, D- Erosion score and D- joint space narrowing (JSN) score by modified Sharp's method were 15.6 and17.7, respectively. As already known, ESR-AUC and CRP-AUC were correlated to radiologic progression, monocyte count AUC was also significantly associated with radiological progression ($p=0.015$, $r=0.429$), in addition to that provided more accurate positive correlation in low ESR group ($r=0.678$) and low CRP group ($r=0.614$). Conclusions: Persistent elevation of monocyte count in early RA group, provide a short termcorrelation with radiologic outcome.

P1-026

Association between reactiveness of Abatacept and Rheumatoid factor

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Conflict of interest: None

[Objectives] Abatacept (ABT) which is a T-cell selective costimulatory modifier released in September, 2010. It is reported that ABT is effective, but there is not the report that discussed the association between ABT and rheumatoid factor (RF). Therefore we investigated an association between ABT and RF. [Methods] The data source was an observational cohort database of rheumatic disease in Japan known as Tsurumai Biologics Communication (TBC). We analyzed the data for 62 RA patients who used ABT and measured RF, who were observed for a period of 24 weeks after starting ABT. We divided the 62 patients two groups of good response group and the not good response group in response of SDAI in 24 weeks. We examined an association between reactiveness of ABT and RF. [Results] 21 patients were good response (GR) group, and 41 patients were not good response(NGR) in response of SDAI in 24 weeks. The average of RF in GR group was 140mg/dl, NGR group was 358mg/dl, and the RF at the ABT starting was significantly low in the GR group.7, however, the rate of change (RF at starting /RF at 24 weeks) of the RF did not show a significant difference between both groups.

P1-027

Expression of Toll-like receptors in synovial lining layer of rheumatoid patients with treatment of biological or non-biologic agents

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Conflict of interest: None

[Objectives] Toll-like receptors (TLRs), which play important roles in innate immune reaction as pattern recognition receptors, have been reported in the lining layer of rheumatoid synovial tissues. The aim of this study is to examine the immunohistochemical evaluation of synovial lining layer in rheumatoid patients with treatment of biological agents. [Methods] Mean counts of TLRs per area and histopathological grade were evaluated in synovial tissues, which were obtained from 16 rheumatoid patients treated by biological agents (BIO) at their surgeries compared to the synovial tissues from Non-BIO group. Mean duration of receiving biologics was 14 months. [Results] Mean score of histopathological grading system was 1.8 (0-3). The mean count of TLR1 was 17 cells/area (0-72), that of TLR2 was 20 (0-62), TLR3 was 17 (0-63), TLR4 was 18 (0-52), TLR5 was 19 (0-49), TLR6 was 15 (0-49), TLR7 15 (0-43), TLR8 11 (0-39), TLR9 3 (0-6) in BIO group. No TLRs in BIO group were correlated with histopathological grading system and were not significant compared to those in Non-BIO group excepting TLR9 ($p<0.05$). [Discussion] It seems the residual TLRs signaling pathway excepting TLR9 play in synovial lining layer in rheumatoid patients with treatment of biological agents.

P1-028

Serum TNF-α levels in rheumatoid arthritis patients treated with TNF inhibitors

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Conflict of interest: None

[Objective] To investigate changes in serum TNF-α levels and disease activity score (DAS-CRP) in RA patients treated with etanercept (ETN) or infliximab (IFX). [Methods] We recruited 15 RA patients treated with ETN, and 12 patients treated with IFX. Blood was collected before and after 1, 3 and 6 months of ETN treatment; and also collected before and after 2, 6, 14 and 22 weeks of IFX treatment. We assessed clinical results, and determined serum TNF-α levels by ELISA. TNF-a bioactivity was measured by investigating the influence on the expression of intercellular adhesion molecule-1 (ICAM-1) of normal human aortic endothelial cells (HAEC). [Results] CRP levels decreased remarkably 1 month after ETN or IFX treatment, and the improvement was found in DAS-CRP. On the other hand, TNF-a levels significantly increased after ETN treatment. However, very slight increases of them were found after IFX treatment. Recombinant human TNF-α (100pg/mL) promoted the expression of ICAM-1, but the ETN-treated patient serum containing TNF-α of the same concentration did not. [Conclusion] The present study suggests that the production of TNF-α is up regulated by ETN treatment; however, a good clinical effect is observed due to the neutralization of TNF-α's bioactivity by ETN.

P1-029

Influence of etanercept on the extracellular matrix-degrading activity in synovial fluids of RA patients

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Conflict of interest: Yes

[Objectives] Synovial fluids of RA patients contain the enzymes that degrade extracellular matrix. The aim of this study was to reveal the effect of etanercept (ETN) therapy on the extracellular matrix-degrading activity in synovial fluids of RA patients. [Methods] Synovial fluids from RA patients were pretreated with hyal-

uronidase and p-Aminophenylmercuric acetate (APMA). A silicon gasket with 12 wells was attached onto the gelatin-coated film. Two-fold serial dilutions of synovial fluid samples were applied into each well. After overnight incubation at 37°C, the gelatin-coated film was washed. Enzyme activity was determined by Ponceau S staining. [Results] During ETN therapy, some patients showed a decrease in gelatin-degrading activity, others showed no difference. DAS28 changed from 5.7 to 3.2 (ΔDAS 2.5) in the decreased activity group after an average of 4.5 months administration, and from 4.6 to 3.5 (ΔDAS 1.1) in the no different group after an average of 6.0 months administration. These results suggest that the decrease in the extracellular matrix-degrading activity in synovial fluid may be correlated with the clinical efficacy of ETN. Measurement of the extracellular matrix-degrading activity may become a predictive indicator for prognosis of RA patients.

P1-030

Effectiveness of etanercept in our patients

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Conflict of interest: None

Objective: Etanercept (ETN) treatment may vary from low dose to 50 mg QW. We report our retrospective study of ETN effectiveness by dose and after increase from low dose. Subjects & Methods: Analysis #1: Effectiveness by dose in 31 evaluable pts w/ RA on ETN for ≥3 months since Feb/2010; 7 men and 24 women (mean age 56.4 yrs; disease duration 8 yrs). Analysis #2: Effectiveness in 7 pts (mean age 66.3 yrs; disease duration 6 yrs) w/ poor response to 25 mg Q2W initiated before Feb/2010 and increased to 50 mg Q2W. Results: #1: DAS28 w/ 25 mg Q2W, QW and 50 mg QW was 3.63, 4.04, 3.35 at baseline and 2.63, 2.87, 2.82 at month 6, respectively. HAQ was 0.73, 1.04, 0.57 at baseline and 0.6, 0.92, 0.35 at month 6. Both showed improving tendencies. Compared to lower doses, 50 mg QW similarly improved DAS28 but was superior in HAQ. #2: DAS28 and HAQ at baseline and month 6 after dose increase comparison were 4.26 to 3.52 and 1.7 to 1.9, respectively. For these reasons, ETN given at sufficient dose from early disease may exhibit maximum efficacy. Selected pts may also achieve lower disease activity even w/ low dose. Further studies are needed to determine whether dose increase have additional effects in pts poorly controlled w/ low dose.

P1-031

Examination of the infliximab cases which were able to continuously administered more than three years

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Conflict of interest: None

[Objectives] We examined a dose change of IFX and MTX, in infliximab 70, report 24 cases that came by dosage continuation more than three years. [Method] At IFX introduction, for an average of disease period 14.5 years, average age 62.6 years old, at six man and 18 women. DAS28-ESR was an average of 5.66, it was HDA; a mean dose of MTX and PSL was 7.33 mg/week, 4.19 mg/day. [Result] DAS28-ESR was improved to 3.25 at three years. MTX dose was an average of 7.47 mg/week, and PSL 0.93 mg/day. The IFX increase was carried out positively in 14 cases. An average dose of 8.62 mg/kg at the first increase. In addition, seven of 14 increased twice. It was an average of 10.00 mg/kg. 24 IFX doses as of three years were an average of 8.38 mg/kg. [Discussion] The IFX continuation rate considerably decreases with 91.4% of one year, two years 61.4%, 34.3% of three years. There is the IV preparation reason immediate effect of the antiTNF α antibody and thinks that IFX is most suitable for first biologics. However, when the case that DA cannot control even if with high-dose MTX and IFX together passes more than two years, a biologics switch may be forced to make. I think that I use MTX every possible than an early stage together as measures and should perform IFX increase in quantity positively.

P1-032

Utility of etanercept for rheumatoid arthritis: A retrospective study

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Conflict of interest: None

Objective: To investigate the utility and efficacy of etanercept (ETN) in the treatment of rheumatoid arthritis (RA). Subjects: Subjects comprised 124 RA patients (27 men, 97 women; mean age, 56.7 years; mean disease duration, 9 years 4 months) who commenced ETN therapy at our department between June 2005 and July 2011. Results: The 1-, 3- and 5-year ETN adherence rates were 72.6%, 56.1% and 44.1%, respectively. A total of 54 patients discontinued ETN due to insufficient response (n = 32), adverse events (n = 16) or other reasons (n = 6). Mean DAS28 – 3CRP scores decreased from 4.01 at the start of treatment to 2.68 at the end of observation. Overall treatment responses according to EULAR response criteria were as follows: good response (GR), 34.2%; moderate response (MR), 36.7%; and, no response (NR), 29.1%. Of the 13 cases who were evaluated within 2 years of disease onset, 4 were GR, 7 were MR, and 2 were NR. Discussion & Conclusion: ETN therapeutic efficacy and relative safety were respectively indicated by treatment response of MR or better in approximately 70% of patients and discontinuation due to adverse events of only 12.9%. The present findings also demonstrate that active administration of ETN in early-stage RA may improve therapeutic response.

P1-033

Drug continuation rate of etanercept and related factors in patients with rheumatoid arthritis

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Conflict of interest: None

[Objectives] The aim of this study is to investigate the factor related to drug continuation rate of etanercept (ETN) in patients with rheumatoid arthritis (RA). [Methods] 102 RA patients (86female, 16male) treated with ETN were included in this study. Patients were separated to two groups using various patient characteristics. Drug continuation rates by Kaplan-Meier method were compared between groups and adverse events were also investigated. [Results] Mean age was 58.9 years old and RA duration was 11.1 years. Drug continuation rates of etanercept were 87.6% at 12 months, 80.0% at 36 months, 52.0% at 60 months in total. Mean continuation periods was 55.0 months. There was no significant difference between groups using stratified date (age, RA duration, baseline CRP and baseline DAS28-CRP). Continuation duration in non-PSL users was significantly longer than PSL user (68 months and 49 months respectively).15 cases stopped ETN due to adverse event, 14 cases due to inefficacy and 1 case hope for pregnancy. PSL users seemed to have serious bacterial infection compared

with non-PSL users. This study suggests that usage of PSL affects the continuation rate of ETN and reduction or stopping of PSL may lead to improvement of drug continuation rate of ETN.

P1-034

Etanercept (ETN) treatment indicated 95 RA patients with one remission

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Conflict of interest: None

[Objectives] Etanercept(ETN) is well indicated for treatment of RA. Ninety-five RA patients treated with ETN are reported. Within 95 patients, only one got remission is reported. [Methods] Complications and clinical results are retrospectively reported in 95 patients. [Results] Fifteen male and 79 female in all patients are 64 years old by average ranged from 23 to 86 y.o. Fourty-seven patients have been treated with ETN, 48 were stopped. One male patient had got complete remission for two years without treatment. Major complications are as follows. Two patients got abdominal perforation. One patient got sepsis. But, all patients were cured. One patient has got completely remission in 95 patients. Major complication is grate problem.

P1-035

Clinical study on etanercept in elderly patients with rheumatoid arthritis

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Conflict of interest: None

Objective: As the population ages, there is also a trend toward aging of rheumatoid arthritis (RA) patients. We studied the effectiveness and safety of etanercept (ETN) in elderly RA pts. Methods: We retrospectively analyzed changes in DAS28/4ESR scores, clinical remission rates, and mHAQ scores, etc., in 70-years or older RA pts treated at our hospital. Results: Of our 13 pts aged 70 years or older on ETN (3 men and 10 women), 12-week analysis was possible in 7 pts. Age ranged from 71 to 91 yrs (mean: 80.3). Disease duration ranged from 4 months to 47 yrs. There were 3 patients with Stage II, 2 with Stage III, and 2 with Stage IV. DAS28/4ESR improved from 4.63?1.87 before treatment to 3.43?2.27 with a significant difference ($P<0.02$). The clinical remission rate by DAS28/4ESR was 28.6%. Moreover, mHAQ before and after treatment improved from 0.87?1.19 to 0.77?1.43. Although mild urinary infection was noted in 1 patient, no particular serious adverse event was noted. Thus, aggressive ETN treatment was able to inhibit disease activity and improve ADL even in elderly RA patients. We consider that ETN treatment aiming to allow elderly RA pts to live their remaining life as normally as possible has a great significance.

P1-036

Etanercept for the treatment of elderly patients with rheumatoid arthritis in our hospital

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Conflict of interest: None

Objective: We often experience rheumatoid arthritis (RA) in elderly in which methotrexate (MTX) treatment is difficult due to complications. Appropriate treatment is required in order to reduce pain and improve activities of daily living (ADL). We evaluated 4 cases that improved symptoms after receiving etanercept (ETN). Methods: Disease activity was assessed before/after ETN treatment in 2 men and 2 women: mean age 82.8 years (range 80 - 86); mean stage 3.25; mean class 3.25. Mean treatment duration up to final assessment was 13.5 months (range 8 - 18). All pts could not receive MTX due to complications such as interstitial pneumonia and renal disorder. Previous medications included salazosulfapyridine and bucillamine. In addition to these, concomitant ETN 25 - 50 mg/w treatment was given. Results: Mean CRP was 3.53 and 1.13 before/after ETN treatment, respectively. Pts had a high level of satisfaction. No notable abnormality occurred during the study period. For these reasons active treatment w/ disease-modifying antirheumatic drugs plus biologicals, especially ETN, considering individual physical features and carefully monitoring adverse reactions can lead to the maintenance of QOL and ADL; thus, such therapy may be useful in elderly RA pts who cannot take MTX.

P1-037

Adalimumab therapy for 19 patients with rheumatoid arthritis: Our Hospital Experience (2nd Report)

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Conflict of interest: None

[Objectives] The aim of this study was to study the efficacy, response, and safety of adalimumab in patients who had on it during rather long period. [Methods] Nineteen patients (pts) with rheumatoid arthritis, 4 men and 15 women (average age, 59.7 years; range, 41 to 78 years) administered adalimumab (ADA) were studied retrospectively. Six patients were switched from etanercept; 7 pts from infliximab; 6 pts biologic-naïve. Fifteen pts were treated with methotrexate; four pts with tacrolimus. [Results] Seven pts (36.8%) continue to use ADA with moderate to good response, while 12 pts (63.2%) stopped ADA due to the following reasons: 1 pt primary failure, 5 pts secondary failure, 2 pts drug induced lupus (1pt pericarditis), 2 patients exanthema, 1 pt death (interstitial pneumonia), and 1pt transfer to a different hospital. [Discussion] ADA, fully human anti-TNF-a monoclonal antibody has been considered to be biocompatible, will lead to few secondary failures. However, secondary failures developed in 5 pts and drug induced lupus in 2 pts. We should pay attention these phenomena in pts administered with ADA.

P1-038

A one year follow-up study of adalimumab (ADA) treatment to RA patients in our Hospital.

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Conflict of interest: None

[Objective] To analyze the efficacy and the adherence of ADA on RA patients in our Hospital. [Patients & Methods] ADA was administered to 57 RA patients (6 males) from June 2008 to November 2010. Patients' backgrounds were as follows; mean age, mean disease duration, and mean DAS28-4/ESR were 61.09 years old, 10.0 years, and 5.87, respectively. It was retrospectively ana-

lyzed if the adherence rate of ADA was associated with background factors such as, age, disease duration, disease activity, prior-biologic use, and combination MTX therapy. [Results] Twenty-three patients continued ADA for one year, and reasons of discontinuation were ineffective (20 cases) and side effect (12 cases including 3 severe infection cases). The adherence rate was 43.4%. Mean DAS28-4/ESR was 3.56 after one year. The Odds ratios of biologics naïve to non-naïve and combination therapy to mono were 5.40 and 3.33, respectively. The adherence rate of patients switched from infliximab was higher than that switched from etanercept. The patients taking 6mg/week or more MTX significantly showed higher continuance rate than those with 4mg/week or less MTX. [Conclusion] The efficacy of ADA tended to depend on the concomitant MTX dosage and to be more prominent in biologics-naïve cases.

P1-039

Examine of adalimumab efficacy to rheumatoid arthritis patients.

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Conflict of interest: None

(Objectives) Examination of clinical use of adalimumab (ADA) on multicenter use started treatment of RA from August,2008 was examined. (Methods)85 cases of RA patients treated with ADA were average 59.8y.o and the duration were 12.9 years were examine for this study. The combination therapy with MTX were 68cases(80%) and the average dosage was 5.9mg/week. (Results) Total continuation rate at 52weeks was 72.9% and combination therapy with MTX and monotherapy were 76.5% and 58.8% respectively. MTX combination therapy with ADA showed better continuation rate. The average value of DAS28(CRP4) has improved from 5.0 to 2.8. DAS28(CRP4) at 52weeks improved a significant difference at 0 week($p<0.01$). DAS28(CRP4) of combination therapy with MTX at 52weeks improved difference from monotherapy. (Conclusion) For treatment of RA, ADA showed a high contination rate and clinical efficacy in the MTX combined therapy patients.

P1-040

Normalization of MMP-3 in patients on adalimumab treatment for 100 consecutive weeks at this hospital

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Conflict of interest: None

【Objective】Evidence on the suppression of the progression of joint destruction in Japanese by adalimumab (ADA) was accumulated for 3 years since its clinical application was launched in Japan. Normalization of MMP-3, which is an index of joint destruction, and disease activity were investigated. 【Methods】Changes in disease activity and MMP-3 were investigated in 25 patients that administered ADA for 100 consecutive weeks. 【Results】Of the 25 patients that administered ADA for 100 consecutive weeks, 21 took MTX concomitantly, and 20 were naïve patients. After 100 weeks of treatment, DAS28-ESR low disease activity(LDA) was 56% and remission(REM) was 32%. Of the 17 patients in whom MMP-3 was measured at week 100, MMP-3 normalized in 10 (normalization rate of 58%). 【Conclusion】Of the patients on ADA treatment for 100 consecutive weeks, 84% administered MTX concomitantly and 80% were Bio-naïve. Use of ADA resulted in long rate of treatment continuation, a high rate for the achievement of remission, and normalization of MMP-3. The above results suggest that ADA is a drug that can be used as a first choice drug for patients that can use MTX.

P1-041

Effects of adalimumab on rheumatoid arthritis and parameter analysis for diagnosis

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

[Objectives] We retrospectively investigated the clinical effects of adalimumab (ADA) in patients with rheumatoid arthritis (RA). [Methods] In our RA center, DAS28, MMP3, MHAQ, rheumatoid factor (RF), grip strength and morning stiffness were measured at 0, 1, 3 and every 3 month in RA patients (n=75~139) receiving ADA 40mg for 1and 2 years at every other week. The correlations among the six parameters were evaluated. [Results] ADA significantly improved all parameters measured when compared to the baselines. Remission rate (DAS28-ESR<2.6, LOCF) by ADA at 1 and 2 year were 32.2 and 30.3% in bio naïve patients, 22.2 and 15.2% in switch from other biologics, 32.2 and 27% with MTX and 20.0 and 22.2% without MTX, respectively. In the correlation analysis of 6 parameters, DAS28 well correlated with the others, and the parameter showing the highest correlation with DAS28 was MMP-3, and the next was grip strength that greatly correlated with MHAQ. (Conclusion) ADA in combination with MTX in bio-naïve patients has been shown the highest efficacy with early onset in the multiple parameters, and parameter analysis for diagnosis suggested that grip strength might be a useful tool in routine clinical practice.

P1-042

Efficacy of Adalimumab (ADA) for 54 weeks on rheumatoid arthritis (RA) patients who are not tolerate with high-dose MTX

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Conflict of interest: None

[Objectives] Evaluation of efficacy and continuation rate for RA patients who were administrated either ADA+MTX low dose (<6 mg) or ADA 80mg mono therapy [Methods] Efficacy and continuation rate were evaluated with 23 patients of 51 patients who

were able to analyze their DAS28-ESR data by LOCF analysis over 54 weeks. [Results] DAS28-ESR mean was significantly improved with 2.87 after 54 weeks, and clinical remission rate achieved 52.4%. The mean of MTX dose was 4.67±1.3 in LDA achievement group whereas 5.5±1.91 in LDA unachieved group. 54 week continuation rate was 68.2% and no serious adverse event was reported. [Conclusion] Generally, high dose MTX combination requires for ADA to achieve high efficacy and continuation rate. This report indicates that ADA 80mg monotherapy and the ADA40mg+MTX low dose (<6 mg) for the patients who were not tolerable for high-dose MTX could also show high efficacy and enough tolerability.

P1-043

The experience of Adalimumab in the treatment of rheumatoid arthritis in our hospital.

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Conflict of interest: None

Objective: To analyse the clinical features of Rheumatoid Arithritis (RA) patients recieved Adalimumab (ADA) therapy, and explore the Best Use of ADA. Materials and methods: We investigated 29 RA patients who received ADA in our hospital from Oct 2010 to Oct 2011. Seventeen patients showed a good response to ADA therapy,8 patients were redused response and 5 were no response. We analyse the crinical features among three groups. Result: Mean age 60.5 years (5 men and 24 women, mean duration 85.0 months). Thirteen patients were Stage II, 5 was Stage III and 11 were Stage IV. Thirteen had other biologics in prior, 17 were treated with MTX (mean 7.5 mg/week)), 18 with predonisolone (mean 7.9 mg/day) and 9 with Tacrolimus (mean 2.3 mg/day). No respose group showed high titer of the serum RF and DAS28-CRP, and had relatively longer duration than good response group. The rate of patients who recieved combined MTX therapy belongs to good response group was higher than whom not recievd.(82.4 % vs 41.7 %). And all Bio-naïve patients who has combined MTX therapy(8 patients) got good response. Conclusion: We should use ADA for early RA patients as first Biologics.

P1-044

Database analysis for our treatment of rheumatoid arthritis.

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Conflict of interest: None

Objective: To evaluate treatment-related complications in patients with RA and annual changes in our treatment measures in special reference to biologics. Methods: A database of our RA patients was used, which includes disease onsets, complications, and treatments. The database has been established since 2006 and updated continuously. By the present time, 694 patients have been registered. Results: SSZ or MTX had been applied in 77% or 75% of the patients, respectively. Discontinuation of SSZ therapy has been increased in biologics era. The Kaplan-Meier drug survival rate of MTX (1387 person-years) was 50% at 8.5 years. A total 267 patients were treated by biologics (125 infliximab, 86 etanercept, 20 adalimumab, 19 tocilizumab, 17 abatacept). There was no difference in the Kaplan-Meier drug survival rates among the biologics (505 person-years). Three patients developed tuberculosis by January 2004. No additional tuberculosis occurred under INH chemoprophylaxis started since February 2004. None of the patients treated by biologics had exacerbation of viral hepatitis or newly developed nontuberculous mycobacteriosis. Conclusions: In our patients, biologics-related complications were rare. There was no difference in the Kaplan-Meier drug survival rates among biologics.

P1-045

Efficacy of etanercept for pregnancy and delivery in patients with rheumatoid arthritis

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Conflict of interest: None

[Objective] To test the effect of etenercept for pregnancy and delivery in patients with rheumatoid arthritis, who hope to have children. [Methods] Eight patients (mean age; 33,8 y.o.) started etenercept therapy for rheumatoid arthritis. All had treated with glucocorticoid and NSAIDs, and 4 with MTX before etenercept theraphy. Glucocorticoid was tapered, and NSAIDs and MTX were discontinued. [Results] Six patients conceived 9.8 months(mean) after initial etenercept injection. Two patients became pregnant twice. Six pregnacy resulted 5 normal deliveries and 1 sponteneous abortion. Five babies were all healthy. Two patients keep their pregnancy now. Etenercept therapy was continued through pregnancy in 5 patients, but a patient, who suffered abortion, had stopped after conception. [Conclusions] Etenercept therapy seems to be very effective for pregnancy and delivery in patients with rheumatoid arthritis. Etenercept should be continued through pregnant period in patients with rheumatoid arthritis.

P1-046

Rheumatoid arthritis (RA) and Etanercept (ETN): a case report on pregnant patient.

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Conflict of interest: None

Though the prevalence of RA is commonly found in middle-age female patients, the occurrence among childbearing females is obvious. Since most of anti-rheumatic drugs including methotrexate (MTX) can cause teratogenicity, it is challenging to treat RA without such effect on pregnancy. We report the successful usage of ETN in pregnant patient. [Case info] 29 Y.O. Female suffered **from** RA since May 2005 (stage II, class II). Prednisolone (PSL) and MTX were prescribed to amelioratethe symptoms. We tapered MTX since the patient wished to get pregnantin June 2007. After the PSL failed to replace MTX, we shifted to ETN and the condition became controllable. ETN was replaced by PSL in Feb 2011 when pregnancy was confirmed. She delivered a healthy young boy in Sept 2011 without abnormalities. MTX was re-administered to control the condition. [Conclusion] ETN proves safety and useful for pregnancy and childbirth. [Discussion] The benefits of biologic administration are: 1) Allow tapering the dosage of anti-rheumatic drugs until cease; 2) Decrease the disease activities and promote remission; 3) Provide safe administration in female patient with possibility for pregnancy.

P1-047

An example of chronic tophaceous gout that was effectively treated with biweekly administration of 50 mg etanercept

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Conflict of interest: None

Objective: We report a case of chronic tophaceous gout in which biweekly 50 mg etanercept (ETN) administration was effective. **Case:** A 68 yr old woman had developed gout in her 40s and suffered repeated gout attack. Her uric acid level could not be controlled by allopurinol and NSAIDs administration. When she was 60 yr old, tophi appeared in DIP/PIP joints and lateral malleoli, & the number of tophi had gradually increased. As symptoms of polyarthralgia, multiple subcutaneous nodules & chronic cough worsened, she consulted our hospital. Hand & digit X-ray images showed bone destruction at the sites corresponding to subcutaneous nodules. Her serum creatinine level was 1.15 & estimated GFR was 37, indicating renal function impairment. Instead of treatment intensification, biweekly administration of 50 mg ETN was started aiming to improve pain relief & reduce nodule size. In 4 months short period, CRP decreased from 7.6 to 0.03, MMP3 from 144 to 61.6, and SAA from 751 to 3.4. Over time, arthralgia & tophi became less severe, w/ tophi size reduced. Concomitant NSAIDs dose was reduced to half, & high pt satisfaction has been achieved. **Conclusion:** Biweekly administration of 50 mg ETN may be effective for chronic tophaceous gout pts w/ complications such as renal function impairment.

P1-048

Etanercept therapy for rheumatoid arthritis in two patients with past history of malignant tumor.

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Conflict of interest: None

(Case1) A 65 year-old male. In 2006, he diagonosed as urinary bladder cancer, and surgical removal was done. In 2007, he was affected with RA. Low disease activity had kept by MTX therapy. In March of 2010, acute exacerbation of RA was occuerd. Additional steroid and DMARDs agnets was not effective, and Etanercept (ETN) was started. ETN was very effective and remission was induced, and steroid was stopped. ETN also was stopped in 2011. Recurrence or metasis of bladder cancer is not occurred. (Case2) A 76 years-old female, duration of RA was 30years. RA had been good control using Bucillamine. In 2009, chemotherapy was done for malignant lymphoma, and induced remission. Acute severe flare up of RA activity occured, and response to additional steroid and DMARDs was not seen. Then, 25mg/week of ETN was induced, but response to therapy was not appeared, and increased up to 50mg/week. However, sufficient effectiveness was not seen, then 4mg/week of MTX was added. A good response to treatment was seen, after then, steroid was decreased successfully. MTX and ETN were continued because of recurence of inflammation by decreasing dosage. (conclusion) In short term observation, no recurrence or metastasis of malignant tumor had occured in RA patients treated with ETN.

P1-049

After "T2T" management with biologic agents in patients with rheumatoid arthritis in Miyazaki

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Conflict of interest: None

【Objective】The goal of the study was to research therapeutic changes after the "treat to target (T2T) recommendation", and the types of changes that occurred in biologic treatments for rheumatoid arthritis.【Patients and Methods】Based on the data, which included patient profile lists gathered every March in the Miyazaki Rheumatoid Arthritis Biologic Agents Research Meeting, we compared "after T2T" with "before T2T" for new biologic treatments in patients with rheumatoid arthritis. We examined the treated age, sex, disease duration, the selection of the biologic agents, and other drug treatments.【Results】The treated age and disease duration were significantly different after the T2T recommendation. In the "before T2T" group, infliximab and etanercept were prescribed in 82% of patients, but in the "after T2T" group the agents used were infliximab (26%), etanercept (35%), adalimumab (21%) and tocilizumab (18%). Otherwise, treatment rates with MTX and corticosteroid did not change significantly.【Conclusion】After the T2T recommendation, the treated age and clinical stage were younger and earlier, and the selection of biologic agents used was greater. T2T definition together with biologic agents and treatment strategies may change therapeutic management plans.

P1-050

Infliximab therapy reduced anti CCP antibody titer in RA remission

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Conflict of interest: None

[Objectives] To study the utility of anti CCP Antibody as marker of Infliximab therapy [Methods] 56 patients with rheumatoid arthritis(RA) who received Infliximab therapy. Infliximab therapy became not effective in 19 patients (14patients received other biologics. Five patients recived no biologics). Infliximab therapy was stopped due to adverse effects, pregnancy and changing address. Six patients stopped Infliximab therapy due to remission. Infliximab therapy was continued in 26 patients(46%). Methods:Remission is defined less than 3.2 DAS-CRP28. Anti CCP antibody was checked before Infliximab therapy and in remission. Stage, disease duration and MTX doses were also checked. [Results] 18 patients(32%) became remission. Remaining 8 patients(14%) continued Infliximab therapy. Anti CCP antibody was positive in 15 remission patients and decreased in remission. Stage I 14 case, stage II 2cases, stage III one case disease duration was 3.2years, Infliximab 5mg/kg, more than 8mg / week MTX was used. Remission was easily achieved in patients of short disease duration, radio logically less damaged. Infliximab therapy reduced anti CCP antibody titer in RA remission. Anti CCP antibody is useful marker of deep RA remission.

P1-051

Remission successfully maintained for two years after leukocytapheresis in a rheumatoid arthritis patient with a reduced response to etanercept

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Conflict of interest: None

[Backgrounds] There are some RA patients who show a reduced response to biological DMARDs. We describe a RA patient with a reduced response to etanercept, who maintained complete remission with ETN only. [Case] A 50-year-old female RA patient who was diagnosed eight years ago. MTX was administered, but, subsequently, lymphadenopathy syndrome due to MTX was revealed. After discontinuing MTX, the activity of RA aggravated with only the use of DMARDS. Then, LCAP was performed in 2,400 ml under PSL5-10 mg combination, but it was not effective. When ETN became covered by authorized insurance, it was immediately introduced and was good effective. About two years later, ETN showed reduced the effectiveness. At that time, only a few agents were available with insurance coverage. Then, the second LCAP was performed with 4,800 ml in 2006. Her joint pain and CRP gradually reduced, and we were able to taper PSL. Two years after the 2nd LCAP, PSL was stopped without any reccurence. Now, four years have passed since the 2nd LCAP, and her RA activity remains controlled without any symptoms. [Discussion] LCAP showed a favorble effect to improve the ETN response. LCAP may be one of the choices in patients with attenuation of the effect of biological DMARDs in whom MTX combination is not possible.

P1-052

Adalimumab in combination with methotrexate can be useful in remission induction and sustainment for bio-naïve rheumatoid arthritis patients.

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Conflict of interest: None

[Objectives] We clarified the advisable indication and the efficacy of adalimumab on rheumatoid arthritis (RA). [Methods] Consecutive nineteen RA patients receiving adalimumab were recruited. Bio-naïve group included 2 males and 11 females of mean 54 years old and disease duration of 8.7±9.7 years. 11 cases (85%) of them had a combination therapy with methotrexate (Ave. 6.6 mg/week). Switch group included 6 females of mean 69 years old and disease duration of 14.2±8.6 years. 4 cases (67%) of them had methotrexate (Ave. 4.0 mg/week). Clinical responses, remission rates and drug survival rates were assessed. [Results] In bio-naïve group, drug survival rates were 92% and 70% after 6 and 12 months. DAS28 improved from 5.2±1.1 to 2.9±1.2 and 2.2±0.6. DAS28 remission was achieved in 50% and 42%, ACR50/70 response in 75%/50% and 75%/58% after 6 and 12 months. In switch group, only one case from infliximab efficacy loss sustained remission for two years, but other three cases had no response, 1 case inadequate response and another case adverse effect and drug survival were 33% (6M) and 17% (12M). [Conclusion] Adalimumab achieved high rates of treatment response, disease remission and a long drug survival rate if used for bio-naïve RA patients with methotrexate combination therapy.

P1-053

The effects of the presence and dose of methotrexate on remission induction rate during adalimumab therapy in patients with rheumatoid arthritis

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Conflict of interest: None

[Objective] To investigate the effects of the presence and dose of methotrexate (MTX) on the remission induction rate during the treatment with adalimumab (ADA) in patients with rheumatoid arthritis (RA). **[Subjects and methods**] Forty-nine patients with RA (10 males and 39 females) treated with ADA in our hospital were stratified by the presence/absence of combination with MTX (8 and 41 patients were treated with and without MTX, respectively) and by dose of MTX (12 and 29 patients received at <8 mg/week and ≧8 mg/week, respectively), and the subgroups were compared for remission induction rates at year 1 based on DAS28, SDAI, and CDAI. The LOCF method was used in each analysis. **[Results**] The remission induction rates in all patients, patients without and with MTX, and patients with MTX at <8 mg/week and ≧8 mg/week were as follows: 57%, 25%, 63%, 50%, and 69% for DAS28; 53%, 0%, 63%, 50%, and 69% for SADI ($p<0.01$ for MTX(+) vs MTX(-) and MTX ≧8 mg/week vs MTX(-)); and 53%, 0%, 63%, 50%, and 69% for CDAI ($p<0.01$ for MTX(+) vs MTX(-) and MTX ≧8 mg/wk vs MTX(-)). **[Conclusion**] The remission induction rate during ADA therapy can be expected to be increased when MTX is used or used at higher doses.

P1-054

adalimumab plus DMARDS imprvove remission rate

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Conflict of interest: None

[Objectives] The goal of treatment in rheumatoid arthritis is remission, But in real world, the patients and clinicians was satisfied tto reach good response without remission, even if using adalimumab. We retorospectively evaluated that the patients with good responese but no remission, who were treated by adalimumab, were achieved remission by conventional DMARDS. [Discussion]. [Methods] 13 patients after three months with good response to adalimumab added more DMARDS. Added DMARDS were tacrolimus 4cases, mizoripin 5cases, and bucillamine 4 cases. Results: [Results] The number of remission after 3 months is 7 cases, and 10cases showed a decrease in disease activity.

P1-055

Early clinical results of adalimumab administration for the rheumatoid arthritis patients, as a biological agent of the first choice.

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Conflict of interest: None

(Objectives) Adalimumab (ADA) was used as one of the 1st biological agent (BIO) for the rheumatoid arthritis (RA) patients of disease modifying anti-rheumatic drugs failure, and the adaptation

/ usefulness of ADA was examined. (Method) Considering safety / convenience, et al, patients were allowed to select infliximab (IFX) or ADA. Patients' background and clinical results were investigated. (Results) The patients treated with ADA had mean age of 63.4 and more comorbidities than those of INF, and 87% (47/54) were BIO naïve. Patients with ADA who continue to show efficacy, but duration was less than 1 year were excluded from analysis, along with lack of efficacy and adverse effects (n=7). The average DAS28 of 34 patients was 5.53 at baseline, 3.07 at 3 month and 3.16 at 6 month. The majority were able to maintain the low disease activity with significant decrease of CRP and MMP-3. Though the improvement of the disease activity was slower than IFX, the equivalent efficacy was obtained with ADA after 6 months. 5 patients with flare after 1 year were switched to other BIO. ADA is convenient and effective, but the secondary issue of flare might be a topic for future research.

P1-056

Intra-articular steroid injection therapy to achieve or sustain remission

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Conflict of interest: None

[Objectives] Despite successful drug therapy few residual arthritis episodes may interfere w/ remission. Relapse often occur in the course of RA. Our study showed combination w/ intra-articular steroid injection known as temporal adjunctive therapy was greatly effective in such pts. [Methods] 98 pts on ETN received triamcinolone acetonide injection aqueous suspension as steroid, 10 mg per fingers/toes joint & 20-40 mg per wrists/ankles/shoulders/knees joint, not exceeding 40 mg per session. Evaluation based on ETN survival rate, RA disease activity & SDAI as clinical remission criteria. Modified Sharp score for plain X-ray of joint destruction to assess annual progression & steroid-injected joint changes. [Results] ETN survival rate at month (mth) 12, 24, 36, 48: 93.4%, 86.7%, 71.7%, 64.4%, respectively. DAS28-CRP at mth 0, 12, 24, 36, 48: 5.7, 2.9, 2.3, 2.7, 2.2. Proportion of pts w/ DAS28-CRP <2.3 & those w/ SDAI ≤3.3 at mth 12, 24, 36, 48: 38%, 18%; 42%, 20%; 37%, 16%; 44%, 24%. Sharp score of annual progression at baseline, mth 24 & 48: 3.8, 1.3, 0.9. Steroid-injected joint score: -1.3, -1.5 at mth 24, 48; showing osteosclerosis or relief of bone erosion in most joints. Intra-articular steroid injection is useful in tight control strategy to achieve or sustain remission.

P1-057

The clinical results of adalimumab treatment for rheumatoid arthritis -Comparison of combination treatment with and without MTX, or a experience of biologics-

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Conflict of interest: None

[Objectives] A purpose of this study is to clarify efficacy of ADA treatment for RA patients concerned of use experience of other biologics, presence of MTX treatment. [Methods] 26 rheumatoid arthrotis patients whom it was administered ADA and and were follow up for 24 weeks. We investigated DAS 28(exclusion of VAS) in 24 weeks, presence of continuation, presence of use of other biological preparation as patient background, the use situation of MTX after beginning of dosage. [Results] In DAS28 (exclusion of VAS), before administration for 4.16 decreased to after administration for 2.11 in results after 24 weeks. The continuance rate of ADA was 76.9%. MTX was used for the patient of 73.1%, and the continuance rate was 42.9% in MTX non-use group and 89.4% in a group of MTX use. In presence of use of biologics, it was a continuance rate of group of switches 66.7% for 80.0% in a group of naïve. [Conclusion] Use of MTX was necessary to raise the effectiveness of ADA. There was a little connection with use experience and availability of biologics.

P1-058

The factors associated with achievement of low disease activity one year after the biologic therapy.

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Conflict of interest: None

[Purpose] To identify the factors associated with achievement of low disease activity (LDA) (DAS28(ESR) <3.2) one year after the biologic therapy in RA patients. [Materials and methods] It was examined whether LDA achievement rate was related to age, disease duration, ESR, CRP, DAS28(ESR), MMP-3, MTX use, MTX dose at baseline and the history of biologic therapy in 48 infliximab (IFX), 31 etanercept (ETN), 17 adalimumab (ADA) and 27 tocilizumab (TCZ) therapy patients. [Result] Achievement rate of LDA were 41.7%, 26.7%, 35.3% and 77.8%, in IFX, ETN, ADA and TCZ respectively. The factors of LDA achievement were ESR and CRP in IFX, DAS28 (ESR) in ETN, MTX use and the history of biologic therapy in ADA, MTX use and MTX dose in TCZ. IFX, ETN and ADA had similar LDA achievement rate under MTX combination in bio-naive patients who did not show high ESR, CRP or DAS28(ESR). LDA achievement rate were deterorated by high ESR and CRP in IFX, high DAS28 score in ETN, previous biologic therapy and no MTX use in ADA, and no MTX use in TCZ patients. [Discission] The main factors of LDA achievement were ESR, CRP, DAS28(ESR), MTX combination, and the biologic therapy history. These factors differ by agents, and could be one of indexes for bioligic agent selection.

P1-059

Validation of algorithms using genome-wide SNP analysis for prediction of remission criteria for infliximab (IFX) or etanercept (ETN)-treated RA patients using multiple medical cohorts

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Conflict of interest: None

[Objectives] Achievement of remission in IFX and ETN treatment is currently one of the most important matters in RA treatment. However, there is no method for prediction of remission criteria. 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. Remission criteria 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-remission 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 remission and non-remission, and the total score in the third cohort. [Results] Although only 18.1-43.8% of the patients achieved remission with IFX and ETN, the SNP algorithms can predict remission with 54.8-66.7% accuracy in the third cohort samples. These highly accurate algorithms using SNP analysis may be useful in the prediction of remission before treatment with IFX or ETN.

P1-060

Treatment Outcoms Based on increase the dosage of Methotrexate in Patients with Rheumatoid Arthritis receiving Anti-TNF-α-agents

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Conflict of interest: None

<Objectives> To examine the effect of increase the dosage of MTX (10mg/weeks) in Patients with Rheumatoid Arthritis receiving Anti-TNF-α-agents <Methods> MTX dose were increased 8mg/week to 10mg/week, in 9 patients with RA treated Anti-TNF-α-agents (Infliximab:5, etanercept:4). The effect of treatment were assessed prior and after 12 weeks. Disease status was assessed using the Disease Activity Score(DAS28). <Result> After 12 weeks, increase the dosage of MTX (10mg/weeks) produced a significant reduction in DAS28 among 9 patients with RA, 8 achieved good response based on EULAR response criteria. A significant reduction in SJC, TJC were seen in the response group. Sideeffect with increase the dosage of MTX (10mg/weeks) was not seen in all 9 patients.

P1-061

A case of mesenteric paniculitis with RA patient who had been treated with tocilizumab for eight years

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Conflict of interest: None

76 years-old man, who had been treated with tocilizumab for eight years, was pointed out the high-inflammatory reaction (high CRP and WBC elevation) by blood examination when he visited the hospital for the usual monthly infusion of tocilizumab. No clinical infectious sign was observed, especially with his abdomen. But computer-tomography scanning on his abdomen and pelvic space revealed the existence of inflammation in the leftside of mesentery. Combined with the result of Ga scintigraphy, he was diagnosed as mesenteric paniculitis. Mesenteric paniculitis is a rare and self-limiting disease characterized by the inflammatory nodules in fat tissues of mesentery. Usually cortico-steroids improve the clinical symptoms and reduce or diminish the tumors. But in some cases, perforation or massive hemorrhage at the affected sites occurs during the course of the disease. Careful observations are required not to miss the chance of starting cortico-steroid treatment and/or surgical interventions. Among biologics, tocilizumab is known to have a unique adverse effect of gut perforation. This is the first report of mesenteric paniculitis accompanied with tocilizumab treatment.

P1-062

Repeated Hypoglycemic Attacks to An Rheumatoid Arthritis Patient Complicated Diabetes Mellitus Type 1 by Abatacept

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Oita Redcross Hospital

Conflict of interest: None

[Objectives]1 [Methods] [Results]

P1-063

Biological therapy for rheumatoid arthritis (RA) patients with renal dysfunction

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Conflict of interest: None

Objective: Treatment for RA patients with renal dysfunction is controversial, but biological therapy could be one choice for such patients. This objective is to confirm the effectiveness of biological therapy for RA patients with renal dysfunction. Methods: All RA patients with renal dysfunction (eGFR 40 ml/min./1.73m^2 or on dialysis) who received biological therapy from January 2006 were enrolled and their clinical course was investigated. Results: 25 patients (6 male, 19 female; 8 on dialysis) were enrolled. Mean age is 67.0±10.2 years old. 20 patients were administered etanercept and 4 patients achieved CR, 2 patients improved partially. 14 patients did not show enough improvement and switched to tocilizumab. 18 patients were administered tocilizumab and 12 patients achieved CR, 5 patients improved partially. One patient did not show enough improvement and switched to abatacept. 2 patients administered adalimumab and improved partially. In 3 of 4 patients with AA-amyloidosis, renal function improved after starting tocilizumab. Conclusions: Most patients receiving biological therapy showed improvement of their symptoms. Especially, many patients achieved CR in patients administered tocilizumab. Tocilizumab was also effective for renal dysfunction associated with AA-amyloidosis.

P1-064

Tocilizumab treatment in patients of rheumatoid arthritis with renal insufficiency.

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Conflict of interest: None

[Objectives] The aim of this study is to elucidate the safety and efficacy of Tocilizumab (TCZ) in patients of rheumatoid arthritis (RA). [Methods] We evaluated the renal function of patients with RA treated with TCZ in our hospital from June 2008 to August 2010. A total of 41 patients with RA (9 male and 32 female, mean age of 66.4±8.2 years old, and mean disease duration of 15.1±14.0 years) were enrolled in this study. We devided patients into two groups, with (n=21, including 6 dialysis patients) or without (n=20) renal insufficiency (estimated glomerular filtration ratio (eGFR) <60 ml/min./1.73m^2), and compared the safety and efficacy be-

tween the two groups, 24 weeks after administration of TCZ. [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. Our results suggest that TCZ is a safe and effective treatment for the patients of RA with renal insufficiency.

P1-065

Tocilizumab treatment in a patient with rheumatoid arthritis on haemodialysis a case report

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Conflict of interest: None

[Case] A 67-year-old Japanese man, who was diagnosed as rheumatoid arthritis (RA) in 1986, stage 4, class 3, was put on haemodialysis due to chronic renal failure in 2004. At 2009 Mar, his disease activity was suddenly flared up, bilateral shoulder and wrist pain increased, inflammatory marker level got high. Sulphasalazine and predonisolone was ineffective, and so etanercept was started at 50mg/week from 2009 Nov with isoniazide and sulfamethoxazole/trimethoprim. After introduction of etanercept, bilateral shoulder joint destruction was rapidly progressed, shoulder hemiarthroplasty was undergone at 2010 Mar and Jul. However bilateral wrist pain and inflammatory reaction were not improved. Then tocilizumab was started at 8mg/kg from 2010 Sep every four weeks with itraconazole. After two months, arthralgia was almost none, and CRP, MMP-3 level, and DAS decreased. One year after tocilizumab introduction, clinical remission could be kept (DAS-28ESR 1.7), and no adverse event was happened during that period. Discussion] Few case reports were described about treatment with biological agents for RA patients on hemodialysis. With careful attension for adverse events especially for infection, tocilizumab treatment is useful for refractory RA patients on hemodialysis.

P1-066

A case of colitis with peritonitis during tocilizumab therapy for rheumatoid arthritis

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Conflict of interest: None

A 69-year-old woman was diagnosed with RA in 1992. She suffered from urinary tract infection and hemophagocytic syndrome during etanercept therapy in 2008. Methotrexate was discontinued because of thrombocytopenia. Although she was treated with tacrolimus 3 mg/day and prednisolone 5 mg/day since August 2010, her disease activity was high. Tocilizumab (TCZ) therapy (8 mg/kg) was added in November 2010. In April 2011, two weeks after 6th administration of TCZ, she complained of lumbago and myalgia. After she was admitted to our hospital, she had a high fever and vomiting. The CT scan revealed edema of the right colon, inflammation of the pericolic fat and ascites, but there was no sign of diverticulitis. Although she had no abdominal tenderness, she was diagnosed with colitis and peritonitis. By the conservative management including antibiotics, her condition and CT image improved. In September 2011, three weeks after 7th administration of TCZ, she complained of abdominal pain, vomiting and diarrhea. The CT scan showed edema of total colon, inflammation of the pericolic fat and ascites. She was diagnosed with colitis and peritonitis again. By the conservative therapy including antibiotics, her symptom and CT image improved. No pathogenic bacteria detected from fecal culture.

P1-067

Two severe infection cases in Tocilizumab RA therapy

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Conflict of interest: None

We experienced two severe infection cases in 26 tocilizumab(TCZ) treating RA cases. One case was suppurative arthritis in bilateral knee joint, another case was bacterial meningitis. The diagnosis did not attach when either case also consulted a physician the emergency out patient, and it was diagnosed as the significant infection later. One case had been three weeks since TCZ was administreted, she had hemolytic streptococcal infection in her foot. Her symptom did not recover only by the antibiotic injection. After all, she had revision surgery. Another case had been two days since TCZ was administreted, she underwent the gastrocamera inspection. Afterward, she had developed high grade fever and gastroenteritis. For a while, she had recovered by the oral antibiotics. But, after all, she had paravertebaral abcess and bacterial meningitis. The treatment of the infectious disease treating TCZ requires noting very much.

P1-068

Two cases of Tocilizumab therapy for rheumatoid arthritis patients complicated MTX-related lymphoproliferative disorders (MTX-LPD).

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Conflict of interest: None

[Objectives] Evaluation effectiveness and safety of TCZ for RA patient with MTX-LPD [Methods] Two patients who therapies our hospital describe. [Results] Case 1 is a 62-year-old man who had a history of RA for ten years. He was given at MTX, SASP and PSL and he focused 4cm of subcutaneous tumor at right elbow for month, and diagnosed diffuse large B cell lymphoma by biopsy. By Ritxmab therapy and stop MTX, lymphoma was improved but his RA was aggravation. After Tocilizmab started, his RA was improved not with lymphoma relapsing. Case 2 is a 54-year-old woman with RA for twenty years who was treated with the combination of Inflixmab and MTX. She developed fever, nausea and general malaise from a month. The patient was diagnosed Hodgkin lymphoma by biopsy, and lymphoma was improved by MTX stop, but RA was worsened. She successfully treated with Tocilizmab for one year, but stopped TCZ because lymph nodes were swelling again. TCZ therapy is considered for RA patient with MTX-LPD.

P1-069

Rheumatoid arthritis treatment in high risk patients - HBV carriers

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Conflict of interest: None

Treatment is a problem in rheumatoid arthritis (RA) patients who are hepatitis B virus carriers (HBs antigen positive). Methotrexate (MTX) is contraindicated in patients with exacerbated hepatitis and biological products, especially TNF inhibitors, are also contraindicated for de novo fulminant hepatitis with HBV reactivation. Case 1: 44 year old man with Stage 1, class 3 RA referred to our hospital because of high disease activity with MTX. He was found to be a HBV carrier by blood sampling. Tocilizumab was started after 2 months of treatment with the nucleoside analog entecavir. RA disease activity decreased and no HBV reactivation has occurred in 14 months. Case 2: 71 year old woman with Stage 3, class 2 RA referred to our hospital because disease activity remained high after treatment with DMARDs. Blood sampling showed she was an HBV carrier and entecavir was initiated. No HBV reactivation has been found after 12 months on MTX. Case 3: 69 year-old woman with Stage 4, class 2 RA referred to our hospital because disease activity remained high after treatment with DMARDs and she had a history of non-tuberculous mycobacteriosis. She was an HBV carrier and entecavir was started together with MTX. All three patients undergo monthly monitoring of HBV-DNA blood levels.

P1-070

Kinetics of Viral loads and risk of hepatitisi B virus reactivation in rheumatoid arthritis patients already infected hepatatis B unedergoing biololegics

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Conflict of interest: None

[purpose] The Kinetics of vital loads and risk of hepatitis B virus (HBV) revitalization are considered for the rheumatoid arthritis patients of HBsAg(-) HBc antibody (+) who received biologicals. [materials and methods] It was aimed at of HBV previous infection of the rheumatoid arthritis patient who did biologicals. Age was of 55.8 (50-60) and sex was all women and the concomitant drug of age are four of MTX medication, other two of DMARS combined use, and two of steroid combined use. Biologicals are one infliximab, two etanercepts, and two abatacept. The inspection measured AST/ALT, a HBV-DNA, and a hepatitis B surface antigen. [Results] There was none of a biologicals medication stop during a progress observation period. Two rises of AST/ALT were accepted from the standard value. None of detection did not have a HBV-DNA, Although hepatitis B surface antigen change-to-positive-ized accepted by one example, and prescribed emtecavir. Then, hepatitis B does not accept at present. [Conclusion] Revitalization was not accepted in biologicals use of the rheumatoid arthritis patient of the infected hepatitis B. However, a HBV-DNA is not detected, but has the case which only the hepatitis B surface antigen change-to-positive-ized, and needs cautions for future progress.

P1-071

Complications and the side effects by administration of biological DMARDS

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Conflict of interest: None

Of late 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. We examined the side effects and complications and its treatment about the cases that a side effect and complications appeared in our hospital. There were seven cases that the side effects and complications appeared in administration of biological DMARDS in our hospital sinse 2008. The side effects and complications were rash, cellulitis, herpes zoster, buttocks abscess, hypotension, and angina, decreased body temperature, et al. Operative treatment was performed for buttocks abscess and papilla mammae cartinoma. About these cases, we examine its treatment and its subsequent course.

P1-072

Case report of a patient with rheumatoid arthritis who developed Henoch-Schonlein purpura due to treatment with abatacept

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Conflict of interest: None

The patient was a 73-year-old woman who was diagnosed with rheumatoid arthritis (RA) 15 years ago. The patient was given methotrexate to treat RA and infliximab was administered from October 2006 due to poor control. However, she developed tuberculosis that resolved after treatment with oral medication for 1 year. Subsequently, tocilizumab was administered from January 2010. However, the patient developed pneumonia in March and tocilizumab was withdrawn. Abatacept was administered from July 2011. Purpura developed in both lower extremities 2 weeks after the third injection. Proteinuria and hematuria were found in a urine test. Henoch-Schonlein purpura (HSP) was suspected and a skin biopsy was performed. Leukocytoclastic vasculitis and IgA deposition were detected in the dermal vessel walls by immunofluorescence, confirming the diagnosis of HSP. Treatment with abatacept was discontinued and purpura disappeared approximately 2 weeks later. Hematuria and proteinuria also remitted. Development of HSP has previously been attributed to drugs and it is likely that this patient developed HSP due to treatment with abatacept. This case suggests that HSP should be considered as an adverse reaction of abatacept.

P1-073

Survey of the Status of Use of Biological Preparations to Treat Rheumatoid Arthritis Patients in our Institution (second report)

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Conflict of interest: None

[Objectives] We conducted a survey on the status of use of four biological preparations to treat rheumatoid arthritis in our institution. [Subjects] Biological preparations were used to treat 107 cases, and consisted of infliximab (INF) in 61 cases, etanercept (ETA) in 53, tocilizumab (TCZ) in 27, and adalimumab (ADA) in 14. [Results] Treatment was discontinued in 6 INF cases (9.8%), 19 ETA (35.8%), 3 TCZ (11.1%), 2 ADA(14.3%), and the proportion of the ETA cases was the highest. Treatment was switched to another drug in 26 INF cases (42.6%), 13 ETA (24.5%), 5 TCZ (18.5%), and 5 ADA (35.7%), and the proportion of INF cases was the highest. Cases in which more than one drug was used because of attenuated or inadequate efficacy or adverse events consisted of 1 case in which 4 drugs were used, 8 cases in which 3 drugs were

used, and 30 cases in which 2 drugs were used. The longest periods of use were: INF, 7 yr 5 mo; ETA, 6 yr 2 mo; TCZ, 3 yr; ADA, 2 yr 11 mo. Administration was discontinued because of infection in 8 cases, but there were no deaths. [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.

P1-074

Evaluation of the use of Biologics [IFX, ETN, ADA, TCZ, ABA] for rheumatoid arthritis [RA] in our hospital

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Conflict of interest: None

[Objectives] To evaluate the efficacy and our tendency of Biologics(IFX, ETN, ADA, TCA, ABA) in the treatment of rheumatoid arthritis(RA). [Methods] We evaluated 54 patients of RA treated with biologics. Infliximab(IFX) 20, Etanercept(ETN) 26, Adalimumab(ADA) 7, Tocilizumab(TCZ) 7, Abatacept(ABA) 3. [Results] The mean MTX dose were IFX 7.5 mg/week, ETN 7.5 mg/week, ADA 6.8mg/week, TCZ 5.4 mg/week, ABA 10 mg/week. The mean PSL dose were IFX 5.5 mg/day, ETN 4.6 mg/day, ADA 5.2mg/day, TCZ 2.5 mg/day, ABA 5.0 mg/day. Drug retention rate of TCZ was highest, ADA, ETN, IFX higher in the order. TCZ had highest negative-conversion rate of CRP. ABA had highest decreasing rate of MMP-3 in early period. There was no significant in SDAI during 5 biologics in 6 months after treatment. [Discussion] This study suggests that TCZ was used in patient with MTX low dose and the use of ABA decreased MMP-3 early.

P1-075

Clinical factors related to the efficacy of abatacept in rheumatoid arthritis

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Conflict of interest: None

To investigate what factors relate to clinical efficacy of abatacept in RA, 52 patients treated with abatacept were assessed DAS28, CDAI and SDAI up to 52 weeks. We found significant correlation between CRP and DAS28(24W) (R=0.39, P=0.025), disease duration and DAS28(24W), CDAI(24W) (R=0.467, P=0.006), SDAI(24W) (R=0.521, P=0.002) respectively. Therefore CRP before treatment and disease duration are clinical factors to predict the efficacy of abatacept.

P1-076

Efficacy and safety to use halfdose abatacept therapy between 24weeks in patients with rheumatoid arthritis

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Conflict of interest: None

[Objectives] Clinical Phase II trials in Japan, ACR improvement rates, compared with placebo showed significantly improvement in the group of ABT (abatacept) 2mg/kg and 10mg /kg. The purpose of this research was to evaluate the patient who reduced the dose of ABT by 250mg (5 mg/kg). [Methods] The efficacy, safety, continuity were evaluated of nine cases in TBC registry which treat half amount (250mg) dose of ABT from the first time. [Results] Background Patients - average age 60.1 and average disease duration 12.4 years, six females, three males, 53.7kg average body weight, the dosage is 5.3mg/kg body weight in terms of average, 7 cases combined with MTX, 8 cases of Bio naive. Disease activities before the start of treatment, 6 patients were high disease activity, 2 patients were moderate disease activity, and 1 patient was remission. At 24 weeks after treatment, three patients because of inadequate response, which was continued back to the normal dose, 6 cases were continued at half dose, all patients confirmed the improvement in disease activity. Serious adverse events in all 9 cases have not been observed. [Conclusion] In our reports, half dose of ABT treatment is potentially as an alternative treatment to the patients such as elderly patients or in response to economic reasons.

P1-077

Efficacy and persistence rate of abatacept in bio-naive and bio-experienced rheumatoid arthritis patients

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Conflict of interest: None

OBJECTIVE: To study the efficacy and persistence rate of abatacept (ABT) among rheumatoid arthritis (RA) patients undergoing treatment at our department. MATERIALS AND METHODS: Subjects comprised 16 of 23 RA patients treated with ABT in our department, who had received the drug for ≧ 12 weeks (mean treatment period, 33 weeks). Classified into bio-naïve (n=6) and bio-experienced treatment groups (n=10), patients were compared on the basis of the European League Against Rheumatism DAS28-CRP and shift in serum MMP-3 levels. RESULTS: ABT persistence rate at 48 weeks was 59.8%. In the bio-naïve treatment group, 3 patients had good response, 3 patients had moderate response, and 0 patients had no response. In the bio-experienced treatment group, 4 patients had good response, 4 patients had moderate response, and 2 patients had no response. Mean serum MMP-3 improved by 40% (152.3 ng/ml) in the bio-naïve group and by 38% (38.4 ng/ml) in the bio-experienced group. No significant intergroup differences were observed (p=0.14, p=0.94, respectively). CONCLUSIONS: ABT produces good therapeutic response and is an important treatment option for both bio-naïve and bio-experienced RA patients.

P1-078

Treatment with abatacept in biologics naive 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 naive. [Methods] This retrospective study investigated 18 patients with RA who were treated with abatacept. At baseline, 10 of them had already been treated with biologics (7 patients after one biologic (switched group) and 3 patients after 3 or 4 biologics (more switched group)), and 8 were biologics naive (naive group). Treatment responses to abatacept at week 12 and the last observation carried forward (LOCF) were compared between the switched and naïve groups using the disease activity score 28 (DAS28). [Results] Eight (100%), 7 (100%) and 2 (66.7%) patients in the naïve, switched and more switched groups, respectively, completed 12 weeks of abatacept treatment. One patient discontinued abatacept due to no effect in more switched groups. The mean DAS28-ESR values at weeks 12 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 12 were 50% (4 patients), 28.6% (2 patients) and 0% in the naive group, switched group and more switched group, respectively.

P1-079

Efficacy of low dose or low frequency administration of abatacept

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Conflict of interest: None

[Objectives] We analyzed whether low dose or low frequency of abatacept (ABT) therapy respond to RA patients. We defined low dose ABT therapy that administrated 250mg/body and defined low frequency ABT therapy that omitting 2nd intravenous infusion at 2weeks. [Methods] 10 (all women, average age 59.8 years old) of RA patients treated with ABT at our clinics. RA activities were evaluated by CDAI. [Results] 5 patients(50%) achieved remission. 3 of the 10 patients treated with low dose ABT. There is no difference in remission rates between low dose and regular dose of ABT (67% vs 50%). 5 of the 10 patients treated with low frequency of ABT. There is no difference in remission rates between low frequency of ABT and regular treatment (60% vs 50%). Conclusion: Low dose or low frequency of ABT therapy was effective of RA patients and possible to achieve clinical remission.

P1-080

Results of 24-week Abatacept Treatment, Including Radiographic and Functional Evaluation

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Conflict of interest: None

[Objective] To analyze the effects of abatacept (ABT) treatment on rheumatoid arthritis (RA) at Week 24 of treatment by the LOCF. [Method] Twenty-two patients who started ABT between November 2010 and May 2011 were included in the analysis. The mean age and mean duration of illness were respectively 67.6 and 12.8 years. The mean baseline DAS28-ESR, SDAI, and HAQ-DI scores were 3.43, 17.89, and 1.33, respectively. Fourteen patients switched from TNF inhibitors, and the other 8 were biologic-naive. Nine concomitantly used MTX, and 13 received ABT alone. [Results] Adherence to ABT at Week 24 was 86.4%. The mean DAS28-ESR and SDAI were 2.35 and 10.92 at Week 24. The mean changes in mTSS (erosion score/JSN score) and HAQ-DI were respectively -1.33(-1.56/+0.22) and 1.13. Three patients discontinued ABT due to inefficacy (1), economic reasons (1), and an adverse event (nosocomial infection) (1). Two patients skipped one dose (one each due to herpes simplex and abdominal pain), but have taken subsequent doses according to schedule.. [Conclusion] Patients treated with ABT showed clinical improvements as well as suppression of joint destruction and functional improvements at Week 24 of treatment.

P1-081

Clinical efficiency and safety of combination therapy of Abatacept and Tacrolimus

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Conflict of interest: None

[Objectives] We investigate the efficiency and safety of combination therapy of Abatacept (ABT) and Tacrolimus (TAC) for rheumatoid arthritis (RA). [Methods] Among RA patients treated with ABT in our department after Octobar 2010, the subjects were 5 serial patients who had been treated with TAC. Clinical efficiency was retrospectively assessed by DAS28, CDAI and SDAI in 3 month and 6 month after the initiation of ABT. Adverse events, including infection, lymphopenia, renal dysfunction and glucose intolerance, were evaluated during the follow-up period. [Results] Two of five patients were treated with mexotrexate. DAS28-CRP and DAS28-ESR were significantly decreased at 3 month (P=0.0043, P=0.0134) and 6month(P=0.0146, P=0.0058) after the iniciation of ABA. CDAI and SDAI were significantly decreased at 3month (P=0.0055, P=0.0067) before the initiation of ABT, too. Adverse events are recorded as infection (one case), renal dysfunction (one case) and glucose intolerance (one case). Serious adverse events were not observed during follow-up period. [Conclusion] The combination therapy of ABA and TAC may be effective and safety for RA patients.

P1-082

Short-term study of efficacy and safety in rheumatoid arthritis treated with abatacept

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Conflict of interest: None

[Objective] To investigate the short-term efficacy and safety of abatacept (ABT) in rheumatoid arthritis (RA). [Method] Fifteen RA patients who had received ABT for at least three months were enrolled. Patients demographic data (mean) were as follows: age, 65.1 years; disease duration, 11.4 years; bio-naive 8, switched 7. Most of the enrolled patients were in stage 3 (73.1%) and class 3 (93.3%). There was a past history of pneumonia in three, pleuritis in one, and respiratory complications in six. The DAS28-ESR, HAQ-DI and Sharp / van der Heijde method were used in evaluation of these patients. [Results] The DAS28-ESR based on LOCF at baseline, after one month, three months was respectively 5.6, 4.8, and 4.8 for overall, 5.4, 4.7, and 4.1 for bio-naive patients and 5.9, 5.7, and 5.4 for “switched” patients. Both the naive and “switched” patients showed greater improvements in number of swollen joints, VAS, and HAQ-DI than ESR and CRP. Almost no progression of joint destruction was recognized. Adverse events were observed in nine patients, included worsening of arthritis in two, increased KL-6 in one, urolithiasis in one, and interstitial pneumonia in one. [Conclusion] Short-term efficacy of ABT was observed. However, its use requires caution when patients have respiratory symptoms.

P1-083

Effect and safety of abatacept on patients with RA in our department

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Conflict of interest: None

Abatacept (ABT) is the fifth biologics (BIO) that was released in September 2010. We studied the effect and the safety of ABT on RA. Subjects were 18 patients with RA (male/female = 2/16) to whom ABA was introduced. The mean age was 60 years and the mean duration of illness was 7.9 years. The number of BIOs previously used before introduction of ABT was 0 in 1, 1 in 3, 2 in 9, 3 in 2 and 4 in 1, respectively. Evaluation of efficacy and safety was done during 12 months of administration for the patients who used ABT for at least 6 months. ABT was withdrawn in 1 patient because of operation. Two patients were affected with respiratory infection but ABT was not discontinued with short postponement. SDAI decreased from 19.4 (SD 5.9) to 12.7 (SD 6.4) at 6 months and 12.0 (SD 5.8) at 12 months, respectively, and the change was statistically significant. DAS28ESR and MMP-3 concentration decreased significantly during the 12 months treatment, but the change was not large. The dose of PSL and MTX did not change significantly. The parameters of RA activity improved significantly, but 6 months treatment was needed to reach a significant level. Studies involving more active patients are needed to evaluate the effects and the safety of ABT accurately.

P1-084

Clinical Efficacy of Abatacept in Rheumatoid Arthritis at Our Hospital

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Keiyu Orthopedic Hospital

Conflict of interest: None

[Method] The efficacy and safety of ABT were evaluated in 10 RA patients (all women) who were observed for at least 24 weeks out of 28 patients who received ABT for the first time at our hospital. [Results] The mean DAS28-CRP scores improved from 3.96 at baseline to 2.51 after 24 weeks of treatment. The scores indicated that 2 patients had low disease activity and 3 were in remission. On average, SDAI decreased from 18.69 to 7.99, and 5 and 1 patient were respectively considered to have low disease activity and be in remission. The average HAQ scores also decreased from 1.14 to 0.87, indicating that 3 were in remission. The average MMP-3 scores decreased from 279 to 92.3. One patient who was naive to biologics achieved remission based on the Boolean definition. Adverse events were a decreased lymphocyte count and an immediate post-injection reaction in 1 patient each. No serious adverse events occurred. The persistence rate was 80%. Two patients who switched from another biologic discontinued ABT due to lack of efficacy [Conclusion] ABT seems as effective as other existing biologics, and patients treated with the drug have had favorable clinical courses. The present findings suggest that ABT may provide a new option for biologic-naive patients.

P1-085

Result of abatacept (ABT) treatment for rheumatoid arthritis (RA) in our Hospital

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Conflict of interest: None

【Purpose】To examine the usefulness of ABT treatment on RA patients.【Objectives】There are 9 patients with RA who have continued ABT treatment at least 8 weeks. Breakdown, 2 males and 7 females, mean age 62.2 years, mean disease duration 158 months, stage average 3.1, class average 2.2. In addition, other biological drugs before ABT treatment had been used 8 patients.【Results】5 patients have been ongoing ABT treatment, and 4 patients were discontinued because of no responce. DAS28-ESR (average) is 5.25 before the start of ABT treatment, 2 patients with high activity(≧ 5.1), 7 patients with moderate activity(5.1 ~ 3.2), respectively. Finally, DAS28-ESR(average) at the last administration decreased to 4.10. In addition, 2 patients obtained EULAR Good Response (GR), and one obtained clinical remission. They who obtained GR were both in high activity and reached at 16, 20 weeks from first administration respectively. The adverse effects was pharyngitis in one case.【Conclusion】Therapeutic effect of ABT is compared with other BIO tends to take hold slowly and surely.

P1-086

Safety and efficacy of abatacept comparable with adalimumab in rheumatoid arthritis

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Conflict of interest: None

[Objectives] To detect the safety and the efficacyof abatacept (ABT) comparable with adalimumab (ADA) in RA. [Methods] We followed 60 RA patients with ABT (ABT group) in multicentre open clinical trial (FIT-RA) and 66 RA patients with ADA (ADA group) in our offices. ESR, CRP, DAS28-ESR, DAS28-CRP, SDAI, CDAI, MMP3 were evaluated at base line, 1, 3, and 6 months after ABT or ADA treatment started. We compared ABT group with ADA group. [Results] At the data of the base line there were no remarkable difference between two groups, except the ABT group has higher rate of biologics using history and higher prednizolone dose. Four % in the ABT group and 12% in the ADA group withdrew due to safety reasons. ABT group: There were remarkable differences in the changes of all variable at any points except the changes of ESR at all point and CRP at one month and 3 months. ADA group: There were remarkable differences in the changes of all variables at any points. There was no remarkable difference between two groups at any points except the ESR. The ABT group had significantly higher ESR than ADA group at any points. [Conclusion] ABT was as safe and effective as ADA. But the reduction rates of acute-phase reactants in patients receiving ABT were less than ones in patients receiving ADA.

P1-087

Short-time therapeutic results for abatacept in our hospital

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Conflict of interest: None

【Objective】The efficacy and safety of abatacept in RA patients treated in this unit on an ambulatory basis was investigated.【Methods】Included in the present study were 20 patients followed

up for at least 12 weeks of treatment with abatacept from October 2010 in this unit, including 18 women (mean age: 58.8 years; mean duration of illness: 10.3 years).【Results】All patients had previously used at least one DMARD (biologics in 7 patients). PSL was used by only one patient at 5 mg. MTX (8-12 mg/week) was concurrently used by 16 patients. Two patients used other concurrent drugs. Two received monotherapy. At the baseline, Week 12 (n=19) and Week 24 (n=9), DAS28 (ESR) was 5.2±1.4, 3.3±1.5 and 2.4±1.09, respectively, while SDAI was 23.2±15.4, 7.4±10.0 and 2.7±2.9. The remission rate (DAS28 (ESR<2.6)) at Weeks 12 and 24 was 32% and 56%, respectively. Treatment was continued in 90% of patients. It was discontinued in one patient due to inefficacy and in another due to hepatic dysfunction. In the evaluation of safety, herpes zoster, hepatic dysfunction and hyperlipidemia were reported from one, one and two patients, respectively.【Discussion】Abatacept offers great therapeutic benefits in routine medical practice as well as previous data.

P1-088

Cinical efect of abatasept in patients with rheumatoid arthritis: data from Fukuoka RA biologics treatment study group

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Conflict of interest: Yes

[Objectives] To evaluate clinical efficacy and safety of abatacept in RA patients in 16. facilities at Fukuoka city and nearby. [Methods] Observation data from Fukuoka biologics treatment study group was collected for September 2010 to October 2011. Efficacy was evaluated based on DAS28 (ESR) and SDAI [Results] 114patients were enrolled for the period concerned.. In this meeting, 49 patients treated with abatacept for 24 weeks were evaluated. 28 patients were switched (S), 21 patients were bio-naive (N). Average DAS28 at baseline was 4.77 in S group, 4.72 in N group. DAS28 improved 4.34 at 4 weeks, 4.35 at 12 weeks and 4.05 at 24 week in S group. In N group, 3.85 at 4 weeks, 3.59 at 12 weeks and 3.29 at 24weeks. Average SDAI at baseline was 21.41 in N group and SDAI improved 12.65 at 4weeks, 11.85 at 12 weeks and 10.26 at 24 weeks. 8 adverse event was shown and 4 cases discontinued abatacept. Conclusion: Abatacept was effective in patients with RA and the effect was swifter in N group.

P1-089

Clinical evaluation of abatacept in our hospital

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Conflict of interest: Yes

[Objectives] We reviewed the efficacy and safety of abatacept (ABT) therapy in patients with rheumatoid arthritis(RA) in our Hospital. [Patients] 13RA(4 males), Average age; 47±16 years old, Average disease duration; 9.6±6.5 years. Nine patients were switched and 4 were biologics-naïve patients. Eight used methotrexate(MTX); average dose 8.3±2.3mg/w. [Methods] Efficacy and safety of ABT were evaluated by SDAI, and CDAI at 0, 14, 26 and 38w after injection of ABT. [Results] The number of low disease activity (LDA): 6w; SDAI 4/10, CDAI 3/11(remission (R) 1/11), 14w; SDAI 4/10, CDAI 5/10(R 2/10), 26w; SDAI 2/6, CDAI 1/6. The number of LDA in the group of MTX 8mg/w≦: 6w; 0/7, 14w; 3/6(R 1/6). The number of LDA in the group of MTX 8mg/w>: 6w; SDAI 2/6, CDAI 3/6(R 1/6) and at 14w, no cases newly became LDA or R. Although the switched patients did not become LDA at 6 and 14 w, in biologics-naïve patients, 3/4 became LDA and 2/4 became R. Although no patients with high disease activity became LDA at 6 and 14w, in the other cases, the number of LDA is 2/6(R 1/6) at 6w and 3/7(R 2/7) at 14w. Adverse events did not occur in all patients. [Conclusion] ABT in the patients of LDA, biologics-naïve and using MTX or at 14w rather than 6w tend to be more effective.

P1-090

Treatment using abatacept for RA patients

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Conflict of interest: None

[Objectives] Biologic agents have been changing dramatically the course of the treatment for rheumatoid arthritis (RA). We can use abatacept as the fifth biologic agents in Japan since September 2010. As the pharmacological mechanism of abatacept is different from those of other biologics, it has lately attracted considerable attention. The purpose of this study is to evaluate the effectiveness of the treatment of RA patients with abatacept. [Methods] Twenty-five RA patients treated with abatacept were evaluated. They have been treated with this drug more than 3 months at November 2011. The mean age at introduction of abatacept was 59.2 year-old, 5 men and 20 women. It was the first time using biologic agents for 3 patients. [Results] At the time of follow-up, serological markers as CRP and ESR decreased, although there was the differences among the patients. No serious side effects related to this biologic agents were observed. In conclusion, this biologic agents' therapy is thought to be safely performed and useful for RA patients. As abatacept has the different target for inflammatory pathology, this drug will be considered as an option for RA treatment. The experiences and clinical inframations about this biologic drug will be needed more in future.

P1-091

A treatment outcome of abatacept (ABT) in Rheumatoid arthritis (RA) in our hospital

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Conflict of interest: None

We examined efficacy and safety of ABT which is biologics with new mechanism of action to inhibit the co-stimulatory of T cells in 27 patients in our hospital by September, 2011 from October, 2010. ABT has many clinical trials reports in foreign countries. The efficacy, safety are confirmed in the class of wide patients from biologic naive case to a TNF inhibitor-resistant case. It is appreciated about the safety among other things. It has been already used than 5,000 patients in Japan, and accumulation about the safety data in the all cases investigation is performed. The study patients in this hospital are 4 cases for men, 23 case for women. The mean age of the patients was 59 years (range 32-84years), and they had had RA for 11.3 years (range 3 months-31years). The clinical stages were I in 1, II in 12, III in 6, IV in 8 patients. The functional status of the patients was class 1 in 15, 2 in 10, 3 in 2. 20 of them used MTX (an average of 8.3mg/week). Other biologics was used for 22 cases as previous treatment. ABT is superior in efficacy and safety, and it is thought with an effective option of RA

treatment.

P1-092

Clinical features and investigation of abatacept for rheumatoid arthritis

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Conflict of interest: None

[Objectives] Treatment for rheumatoid arthritis (RA) has been dramatically altering, because biological agents have been approved in Japan in these several years. Abatacept, a selective T-cell co-stimulation modulator, is a unique agent, whose mechanism is different from other biologic agents. But it has not been reported about abatacept for Japanese RA patients. We evaluated clinical characteristics of abatacept. [Methods] We analyzed 19 patients (18 women, 57.5±11.4 yr), who were treated with abatacept for over 24 weeks. [Results] Average DAS28 score improved from 3.91±1.18 at start to 2.80±0.96 at 24 weeks later. Abatacept therapy achieved good response. 19 RA patients included 15 cases (78%) in class 1+2, 12 cases (63%) in stage I + II, and average disease duration was 7.0±7.8 years (under 5 years : 12 of 19 cases). There were 15 cases (78%) treated with MTX, 6 cases without previous biological treatments, and 8 cases with previous only 1 biological agent. [Conclusion] The results suggested that abatacept is useful drug for patients in relatively early stage, or with moderate disease activity.

P1-093

The efficacy of abatacept for arthritis with Sjogren's syndrome (Sjs)

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Conflict of interest: None

[Objectives] A substantial number of patients with Sjs have an arthritis which inadequate or unsustained response to usual therapy. We evaluate the efficacy and safety of abatacept, a selective co-stimulation modulator, in patients of Sjs with active arthritis and an inadequate response to MTX or DMARDs. [Methods] 5 patients with Sjs arthritis inadequate response to other medication were assigned to receive abatacept. DAS28(4ESR), S-DAI, C-DAI were assessed. [Results] although 1 patient was dropped out from this study by cessation of abatacept administration, because of allergic response, other 4 patients completed the study. 12 weeks after, DAS28(4ESR) were significantly lowered from 5.23±0.44 to 2.73±0.27, and achieved the good response by EULAR criteria in all cases. The effect of abatacept for salivary flow rate evaluated by VAS remained unclear. Our data suggests that abatacept was useful for treatment of patients with Sjs arthritis.

P1-094

A case of improvement of joint damage in bilateral ankles of patients with rheumatoid arthritis during abatacept therapy

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Conflict of interest: None

We started abatacept therapy for a 62-year old female with refractory rheumatoid arthritis (RA) who withdrew from other four biological agents due to adverse events. Before administration, she had a high disease activity and no walking because of severe bilateral ankle pain. Clinical Disease Activity Index (CDAI) and Health Assessment Questionnaire (HAQ) improved from 31 to 15 and from 2.75 to 2.0 at 1 year of abatacept therapy. Although ankle range of motion reduced, her symptoms improved such as loss of tenderness and decrease of swelling. Moreover, bilateral ankles with pre-existing radiographic damage of Larsen grade III showed improvement of erosion and subchondral bone structure after 1 year of abatacept therapy. We reported a patient who showed improvement of joint damage in bilateral ankles during abatacept therapy. Reduced ankle range of motion may be associated with healing of ankle joint damage.

P1-095

Reduction of mRNAs associated with antigen presenting and cell adhesion during large volume leukocytapheresis for rheumatoid arthritis.

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Conflict of interest: None

[Objectives] Leukocytapheresis(LCAP) is a safe, unique therapy prevail to intractable rheumatoid arthritis(RA) even in case of drug allergy or infectious state. Various findings have been reported estimated to concern with LCAP efficacy (i.e. recruitment of CD34+ cells, reduction of IL-6, TNFalpha, etc.), but the details are still unknown. To investigate how to come up LCAP efficacy, we have conducted genes expressions analysis from peripheral blood of RA patients treated with LCAP. [Methods] Peripheral blood samples were collected immediately before and after treatment from 16 RA patients who received LCAP (all responders). Gene expression analysis was done with high resolution DNA microarray (3D-Gene®, Toray Industries Inc., Tokyo, Japan). Calculations were performed with statistical software R using Welch's t-test. MetaCore® program (GeneGo Inc., division of Thomson Reuters, St Joseph, MI, USA) was used for further pathway analysis. [Results] In comparison of 25,370 genes expression, 43 genes have shown significant change in down-regulating genes groups (i.e. B2M, HLA-C, ITGB1). These reductions of mRNAs associated with antigen presenting and cell adhesion observed following LCAP treatment. These findings may relate with previously unknown LCAP efficacy for RA patients.

P1-096

ïClinical significance of abatacept

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Conflict of interest: None

[Objective] To investigate the clinical significance of abatacept (ABT) in clinical practice. [Subjects and Methods] 26 subjects infused with ABT by July 2011, after ABT went to market. 12 were

naïve subjects and 14 were switching from a drug. DAS28(ESR), CDAI and SDAI were used in the clinical assessments. [Results and Discussion] The mean changes in DAS28(ESR), CDAI and SDAI just before infusion and at examination (last day of September 2011) were 5.12 to 3.97 for DAS28(ESR), 25.1 to 13.7 for CDAI, and 26.44 to 14.60 for SDAI; these were major improvements. The switching subjects had a poor or inadequate response, with the mean duration after infusion being 4.7 months (shortest: 1 month, longest: 10 months), 11 subjects (78.6%) were switched to another drug. As for ABT's safety, company reports at 1 year post-marketing showed a tendency for few SAEs to be associated with ABT compared to 4 earlier drugs. This suggests that ABT is a good candidate drug for RA of up to moderate activity and is unsuitable for switching subjects. It also suggests that is a first-bio drug that tends to be associated with few SAEs.

P1-097

The case of successful therapy with Rituximab to a RA patiant associated with MTX induced adrenal Malignant lymphoma.

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Conflict of interest: None

[Objectives] We report the case of RA with high disease activity wich is associated with MTX induced malignant lymphoma. [Methods] 75 y/o Male. Right shoulder joit pain developed 5 years ago, and he was diagnosed with RA 2 years ago. The therapy of MTX6mg started and infliximab was added 1 year later. After 16 months of therapy of MTX, left adrenal tumor and right pleural effusion appeared on chest CT. The tumor size grew 2 months later, and it is diagnosed with Malignant lymphoma by biopsy. MTX and infliximab was discontinued. Although the adrenal tumor dicreased in size after discontinuation of the drugs, the activity of RA got higher. He visited ER because of joit pains and dyspnea. He was diagnosed with high acticve RA, and RA pleuritis. We started mPSL 60mg/day and Rituximab 500mg/day1, day15. The score of DAS28(CRP) decreased from 7.27 to 2.15. [Results] MTX and anti-TNF therapy might be associated with an increased risk of lymphoma. In Europe and the United States, Rituximab has received approval for use in combination with MTX for patients with active RA that has not responded to anti-TNF therapy. Although Rituximab has not been allowed to use for RA in Japan, this case sowed safety and efficacy of Rituximab for RA. Rituximab is expected to be one of the treatments for RA with malignat lymphoma.

P1-098

Efficacy and Safety Evaluation of Iguratimod, a Novel Anti-rheumatic Agent – A Double-blind, Comparison Study of Iguratimod-MTX Combination in Rheumatoid Arthritis Patients with an Inadequate response to MTX

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Conflict of interest: Yes

[Objectives] This study evaluated the efficacy and safety of a combination of iguratimod (T-614) and MTX in rheumatoid arthritis patients with an inadequate response to MTX. [Methods] This study was a placebo-controlled, double-blind, comparison study (24 weeks) in patients who had been treated with MTX at 6–8 mg per week for over 12 weeks. T-614 was orally administered in 165 patients at 25 mg/day for 4 weeks followed by 50 mg/day until Week 24. A matching placebo treatment was given in 88 patients. Folic acid was orally administered in all patients at 5 mg/week. [Results] ACR20 response rate at Week 24 was 69.5% (114/164) in T-614 + MTX Group (TM) and 30.7% (27/88) in placebo + MTX Group (PM), demonstrating superiority of TM to PM. ACR50 and ACR70 response rates were 38.4% and 17.1%, respectively in TM and 15.9% and 5.7%, respectively in PM, with TM showing significantly higher response rates. Incidence of adverse events was 80.5% in TM and 75.0% in PM and the difference was insignificant. Serious adverse events were reported by 5 patients in TM and 3 patients in PM. [Discussion] A combination therapy of T-614 and MTX is promising to become an alternate effective treatment for rheumatoid arthritis patients with an inadequate response to MTX.

P1-099

The combined effects of iguratimod, a nobel DMARD, and MTX on adjuvant arthritis in rats

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Conflict of interest: Yes

[Objectives] Iguratimod (T-614), a novel DMARD, was discovered by Toyama Chemical Co., Ltd. Using adjuvant arthritis model, we examined the combined effects of iguratimod with MTX focusing on therapeutic effects on arthritis and anemia as a side effect. [Methods] Adjuvant arthritis was induced at the right hind paw in rat (Lewis, male, 7-week old) by injection with *M. tuberculosis* and evaluated by measurement of paw volume. Erythrocytes and reticulocytes were counted to evaluate anemia. [Results] MTX at 0.3 mg/kg/day inhibited the arthritis but induced the anemia. MTX at 0.1 mg/kg/day decreased reticulocytes but did not decrease erythrocytes. This dose of MTX weakly suppressed the arthritis on adjuvant-injected paws. When combined with iguratimod, MTX at 0.1 mg/kg/day was able to suppress the arthritis on injected paws. MTX at 0.07 mg/kg was not found to suppress the arthritis. When combined with iguratimod to MTX at 0.07 mg/kg, significant therapeutic effects on non-injected paws were observed compared with each drug alone group. [Conclusion] It was expected that the combined administration of iguratimod with low-dose MTX would enhance the inhibitory effect of arthritis and reduce the side effects of MTX.

P1-100

Iguratimod, a new DMARD, Inhibits Osteoclastgenesis *in vitro*.

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Conflict of interest: Yes

Objective: Iguratimod (T-614), a new DMARD, was discovered by Toyama Chemical. To elucidate the mechanism for improvement effect of Iguratimod on the progression of articular destruction, we investigated its effect on osteoclastgenesis *in vitro*. Methods: Osteoclastogenesis was assessed using murine bone mar-

row cultures and RAW 264.7 cells. TRACP-positive multinucleated (>3 nuclei) cells (MNCs) were counted as osteoclast-like cells and TRACP activity in the cell lysate was measured. Expression of NFATc1 was determined by Western blot analysis. DNA binding activity was assessed using TransAM NFATc1 Transcriptional Factor Assay Kit. Results: Iguratimod remarkably inhibited the increase of TRACP activity in a dose dependent manner (RAW264.7 cells, IC_{50} = 0.7 μM), and decreased the number of TRACP-positive MNCs at 1 μM in RANKL-stimulated RAW264.7 cells. Iguratimod did not inhibit DNA binding activity of NFATc1, whereas the NFATc1 expression induced by RANKL-stimulation was significantly suppressed. Conclusion: Iguratimod showed the inhibitory effects on osteoclastgenesis via the suppression of NFATc1 expression and it was suggested that such action would contribute the clinical effect on articular destruction in RA patients.

P1-101

Combination effects of a c-Fos/AP-1 inhibitor T-5224 and methotrexate on mouse type II collagen-induced arthritis

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Conflict of interest: Yes

[Objectives] We have reported the preventive and therapeutic effects of T-5224 on mouse type II collagen-induced arthritis (CIA). In this study, the effects of T-5224 in combination with methotrexate (MTX) were investigated on mouse CIA. **[Methods]** CIA was induced in DBA/1J mice by the immunization with collagen type II twice on day 0 and 21. T-5224 and/or MTX were orally administered once daily from the day of the 2nd immunization (day 21). Efficacy was determined by arthritis score, X-ray examination and serum biochemical analysis on day 35. **[Results]** MTX dose-dependently suppressed the arthritis development at 0.5 to 5 mg/kg/day (the inhibition rate on day 35: 15%–58%). MTX at 0.5 and 1.5 mg/kg/day in combination with T-5224 at 3 mg/kg/day (the inhibition rate: 24%) showed the equivalent inhibitory effect of a high dose of MTX (5 mg/kg/day). The combination of MTX with T-5224 also showed the enhancement of inhibitory effect on the joint destruction. In addition, the serum IL-1β decreased in mice treated with the combination of T-5224, but not with a low dose of MTX alone. **[Conclusions]** The combined use of T-5224 and MTX with a different mode of anti-arthritic action is expected to augment anti-rheumatic and anti-joint destructive effects in the therapy of rheumatoid arthritis.

P1-102

Relevance of tofacitinb in T cell subsets to clinical courses in patients with rheumatoid arthritis

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Conflict of interest: None

[Objectives] Tofacitinib (tofa), a Janus kinase (JAK) inhibitor has demonstrated clinical efficacy on RA. JAK is involved in intracellular events for cytokines involved in lymphocyte development and activation. We herein analyzed lymphocyte subsets and proliferation at week-0 and -52 to elucidate the factor affecting efficacy and risk factors for infectious adverse events. [Methods] Twenty-nine patients were enrolled (6 with tofa, 23 with tofa and MTX). [Results] During 52 weeks, 21 events of infection (17 viral, 3 bacterial and 1 local fungus) were observed. Change was seen in total lymphocyte counts nor proportion of lymphocyte subsets at week-52. However, proliferation of CD4+ T cells *in vitro* was significantly reduced at week-52 (p=0.02) and correlated with both ΔCRP (p=0.02) and ΔSDAI (p=0.03) at week-52 but not with the incidence of infections. Surprisingly, the number of CD8+ T cells at week-0 was extracted as a predictive factor affecting incidence of infections (odds ratio 5.33, 95% CI 1.02-27.8). Cut off value was <210 /μl (sensitivity 0.72, specificity 0.82) to predict at least one infection per year. Our results indicate that suppression of CD4+ T cell proliferation contributes to clinical efficacy, and patients with low CD8+ T cell counts is at risk for infections.

P1-103

JAK inhibition suppress production of IL-6, IL-17 and MMP-3 as well as cartilage destruction in patients with RA

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Conflict of interest: None

[Objectives] We have previously reported that a JAK inhibitor tofacitinib (tofa) reduced disease activity, IL-17 production by CD4+ T cells and MMP-3 in RA patients at week-12. [Methods] We herein investigated the serum levels of multiple cytokines at week-0 and -12 and cytokine production by CD4+ T cell in vitro at week-0 and -52. To evaluate the direct effect of tofa on synovitis and cartilage destruction, synovium and cartilage from RA patients were implanted into SCID mice (SCID-huRAg). [Results] In patient serum, IL-6 and IL-8 tended to decrease at week-12, with IL-6 correlating with the reduction of MMP-3. IL-17 production by CD4+ T cells in vitro was suppressed at week-52 as it was at week-12. In SCID-huRAg, marked growth of RA-derived synovium and its apparent invasion into cartilage were suppressed with decreased production of human IL-6 and IL-8 as well as MMP-3 when tofa was administered. As a result, serum IL-6 and IL-8 concentration was decreased in connection with reduced MMP-3 in both RA patients and SCID-huRAg. Moreover, cartilage destruction in SCID-huRAg were markedly suppressed. These results indicate the potential of tofa to suppress cartilage destruction as well as T cell-medated synovitis from the initial several months of administration in patients with RA.

P1-104

Effectiveness of Biolactis powder for rheumatoid arthritis

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Conflict of interest: Yes

[Objectives] The purpose of this study was to analyze the effectiveness of probiotics (Biolactis powder) for rheumatoid

arthritis(RA). [Methods] RA patients who agreed to join this study were randomly divided into two groups. For Group A patients (probiotics group; 19 patients), 3 grams of Biolactis powder/day were administered orally. For group B patients(non-probiotics group;18 patients), Biolactis powder was not administered. The DAS-28 CRP(4) score and mHAQ score were calculated at pre-, 1, 3, 6, and 12 months after administration in both groups and DAS-28 CRP(4) score and mHAQ score of Group A patients were compared to those of Group B patients. [Results] The DAS-28 score in both groups at pre- administration showed no difference, but at 12 months, Group A showed significantly lower score than pre-socre and Group B showed significantly higher score than pre-score. The mHAQ score in both groups at pre- administration showed no difference, but at 12 months, there were significantly lower score in Group A than Group B.

P1-105

Effects of irbesartan on IMT in the patients of connective tissue disease or rheumatoid arthritis with hypertension. (3rd 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 102patients for 52weeks). We continued to follow them (10 more patients enrolled) and examine the efficacy and safety next 52weeks. [Results] As a result, we found that irbesartan was effective and safe for 3-years. In conclusion, irbesartan is useful for secondary hypertension of connective tissue disease and rheumatoid arthritis.

P1-106

Rheumatoid orthopaedic operation with biologic agents and non-biologic agents

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Conflict of interest: None

[purpose] It was for that purpose that we analyze rheumatoid orthopaedic operation in yamanashi prefectural central hospital. [method] rheumatoid orthopaedic operation in yamanashi prefectural central hospital analyze between January, 2008and september, 2011, cases 41.41cases divide used of biological agents(Group A) and non-biological agents (Group B). We examined about the changes of perioperative body temperature and CRP, postoperative complications. [result] Compared to the Group A group B had risen both significantly next day body temperature and CRP after operation. One cases had experience of surgical site infection (Group A). One cases had experience of late wound healing(Group B). [conclusion] although attention for masking of fever and CRP of postoperative infection used of biological agents, careful perioperative treatments should be taken for rheumatoid orthopaedic operation under biologic agents.

P1-107

Surgical Treatments in Rheumatoid Arthritis Patients Taking Abatacept Therapy

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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 since 2010 in Japan. The clinical safety in Japanese is still unknown. We studied perioperative adverse events in RA patients with ABT therapy. [Methods] Twelve patients who took orthopedic operations were included, in the 153 patients with ABT therapy in the Tsurumai Biologic Communication (TBC), which is the multicenter registry for RA patients taking biologics. [Results] Total knee arthroplasty in five, total hip arthroplasty in two, resection arthroplasty in foot in three, lumber fixation in one, osteosynthesis in two cases were observed. Mean age was 64.8 years and mean disease duration was 13.2 years. Ten patients were taking methotrexate, in mean dose of 7.1mg/week, and stopped a week before their operations. Nine patients were taking predonisolone, in mean dose of 3.9mg/day, and they kept on taking perioperatively. The mean dose of ABT was 9.3mg/kg, and the last administration was 23.5 days (14-46) before operations on the mean. No specific adverse events, such as surgical site infection or wound trouble, were observed in this study. Current results would be important information for patients with ABT therapy who need to plan to be performed operations.

P1-108

Perioperative management of rheumatoid arthritis (RA) patients with adalimumab (ADA) from multicenter study data

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Conflict of interest: None

[Objectives] We investigated RA patients who underwent elective orthopedic surgery during ADA treatment. Data were retrieved from Tsurumai Biologics Communication, TBC. [Methods] 319 RA cases which started ADA after post market were evaluated. Orthopedic surgeries were performed in 26 cases. Surgical treatments were including 8 TKAs, 3 THAs, 1 TEA, 2 spine surgeries, 1 synovectomy, 3 fractures, and 8 other operations. We investigated the mean age and the mean dose of MTX at operation, and timing of surgery. DAS28-ESR, CRP, infection ratio and complications were assessed 24 weeks after surgery. [Results] The mean age was 30.5 years. The mean dose of MTX was 6.4 mg/week, and the MTX utilization was 76.9%. DAS28-ESR was improved from 4.4 to 3.6. CRP was also improved from 1.27 to 0.91. In terms of ADA pre- and post-operative administration, the final administration days in

all cases were determined at 2 weeks before surgical operation and the administration was performed again between 2 and 4 weeks after surgical operation. In all cases, neither surgical infections nor complications were observed. [Conclusion] Despite a low number of cases, wound healing was achieved without any infection signs in all cases, and the similar results were obtained from patients with normal operation.

P1-109

Does the use of biologics induce perioperative complications? - a multiphasic comparison with non-biologic DMARDs -

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Conflict of interest: None

Objectives To assess the dose of Biologics induce perioperative compication rising patients with rheumatoid arthritis(RA), a multiphasic comparison with non-biologic DMARDs A total of 478 patients receiving operative treatment for RA from 2004, January to 2010, December at Kyoto University Hospital were evaluated. The operative complication, infection. Poor wound healing were evaluated. Results A total of 98 patients receiving Biologics treatment and 380 patients receiving non-biologic DMARDs treatment. The infection rate that was receiving Biologics treatment were 3cases, and receiving DMARDs was 0%. The poor wound healing rate that was receiving Biologics was 1 case, receiving DMARDs was 3 cases. The infection rate was significant difference between two groups. Conclusions The Biologics treatment have the potential of increasing infection rate, so we have to take account of perioperative risk and benefit.

P1-110

A study on surgical treatment operated under the biological agent use

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Conflict of interest: None

[Objectives] According to the survey of postoperative infection conducted by The Japanese Orthopaedic Association, there's no significant difference between the use group of biological agent and the nonuse group. However, it shows more infection cases limited on Replacement Arthroplasty in the use group. On the basis of above findings, we researched the results of operations under the biological agent use. [Methods] We researched the 13 cases, which includes 16 joints, performed surgical treatment under the biological agent use in our department. The details are as follows; TKA: 4 cases 5 joints, THA: 2 cases 3 joints, Finger replacement arthroplasty: 1 case 1 joint, Ankle replacement arthroplasty: 1 case 2 joints, foot resection arthroplasty: 2 cases, Thumb CM joint suspension arthroplasty: 1 case, Wrist arthrodesis: 2 cases. We examined these cases for infection, would healing delays and the postoperative results. [Results] These cases showed no infection nor would healing delays. Moreover, there's no significant postoperative difference compared to the nonuse group. It became obvious that proper administering biological agent contributes to the result as well as the standard procedure.

P1-111

Characteristics and complications of surgical procedures for patients with rheumatoid arthritis under treatment with biologic agents in a single institute

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Conflict of interest: None

[Objective] The purpose of this study is to examine the characteristics and complications of surgical procedures for patients with rheumatoid arthritis under treatment with biologic agents in our institute [Method] Among the RA related surgical procedures in our institute between from 2003 to 2011, we select the patients who were treated with biologic agents and examine the kinds of biologics, surgical sites, perioperative resting period, surgical site infection, delayed wound healing, and postoperative flare up of disease activity. [Result] 60 surgical procedures of RA patients treated with biologic agents were undergone during that period. The kinds of biologics were 29 infliximab (IFX), 23 etanercept (ETN), 5 adalimumab, 6 tocilizumab (TCZ), 1 abatacept. Surgical sites were shoulder 6, elbow 6, wrist/hand 16, hip 7, knee 10, ankle/foot 18, spine 1, and wrist/hand and ankle/foot surgeries occupied the majority. One superficial infection was recognized and deep infection was none. 4 delayed wound healing were observed, 2 foot, 1 wrist, 1 knee. Post operative flare up was observed 11patients (IFX 1, ETN 8, TCZ 2). Patients of TCZ were conducted too long resting period before surgery, while patients of IFX and ETN were flared up despite of appropriate resting period before surgery.

P1-112

Prevalence of surgical site infection in rheumatoid arthritis under biological treatment

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Conflict of interest: None

[Background] Some studies suggest that use of biologic agent in rheumatoid arthritis (RA) increase risk of surgical site infection (SSI), but details remain unclear. We report the incidence of SSI in patients with rheumatoid arthritis in our hospital. [Method] We made a comparative analysis between biological treated group and non-biological group of RA in the incidence of SSI since 2008. [Results] Biological agent user group contained 65 cases. SSI occurred in 4 cases 3 cases is superficial SSI required second sutures and debridement. One case is deep incisional SSI needed screw removal. The non-user group contained 120 patients. SSI occuredoccurred in 2 cases. One case is superficial incisional SSI required debridement and second suture. One case is deep incisional SSI needed implant removal. Statistically significant difference was not observed between two groups. [Conclusion] In our study, biological treatment does not increase the risk of SSI. Appropriate washout period before surgery is essential for this kind of surgery.

P1-113

Role of biological products in total knee arthroplasty

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Conflict of interest: None

Introduction: We studied the relation between total knee arthroplasty (TKA) and BIO in this department after the appearance of BIO. Subject and methods: In the period from 2002 until December 2011 when BIO were on the market, TKA for RA was performed on 216 knees in 160 patients in this department. The Bio introduction group consisted of 63 knees in 86 patients with Bio introduced at any time. The timing of BIO introduction, department of introduction, and MMP3 and CRP values (before TKA, at survey) were examined. Results: The timing of introduction of BIO was before TKA in 27knees, within one year after TKA in 17 knees and more than one year after TKA in 42 knees. MMP3 and CRP values were high in the group with BIO already introduced at the time of BIO introduction, but they decreased at the time of TKA. In the group with BIO introduced within one year after TKA, MMP3 and CRP values were higher at BIO introduction than at TKA. Discussion: Introduction of BIO was given priority in the department of internal medicine for cases of poorly controlled gonitis, but the stance in the department of orthopedic surgery was that if introduction of BIO is decided, TKA should be performed beforehand in consideration of infections after TKA, and BIO should then be introduced.

P1-114

Effect of total knee arthroplasty with capsulosynovectomy on disease activity in rheumatoid arthritis patients treated with biological therapy

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Conflict of interest: None

[Objectives] We evaluated effect of total knee arthroplasty (TKA) with capsulosynovectomy on disease activity in RA patients treated with biological therapy. [Methods] Seventeen RA patients with severe joint destruction underwent TKA with capsulosynovectomy. Nine of these patients were preoperatively treated with biological agents including infliximab (2 patients), etanercept (5 patients), or tocilizumab (2 patients) (Group B). No biologic therapy was used in the other eight patients (Group N). Preoperative and postoperative RA disease activity was measured using the Disease Activity Score 28 (DAS28). Synovial tissue was histologically assessed using Rooney's scoring system. [Results] Rooney's score in Group B was significantly lower than in Group N (Group B = 16.4+/-6.4; Group N = 22.5+/-8.6; $P < 0.05$). DAS28 in Group B was significantly decreased from 4.2+/-1.0 preoperatively to 3.1+/-0.8 postoperatively ($P < 0.05$). DAS28 in Group N was significantly decreased from 4.1+/-0.7 preoperatively to 2.9+/-1.2 postoperatively ($P < 0.05$). There was no significant difference between two groups. This study suggested that TKA with capsulosynovectomy has a secondary systemic effect on RA disease activity in patients with moderate or high disease activity.

P1-115

Risk management of bleeding in patients with rheumatoid arthritis used biologics

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Conflict of interest: None

[Objectives] Perioperative management in patients with rheumatoid arthritis is important. Biologics improve clinical outcome for the treatment of RA. However the effect of the biologics in perioperative management remains incompletely understood. [Methods] We investigated the changes of values in inflammatory markers including WBC, CRP and Fibrinogen in 36 RA patients who have been treated with infliximab (IFX) or tocilizmab (TCZ), 19 and 17 patients respectively. Furthermore, we examined postoperative complications and laboratory data in biologics received 15 RA patients who were undergoing total knee arthroplasty (TKA), 13 patients in IFX group and 2 patients in TCZ group. [Results] There are significant differences in values of WBC and fibrinogen between groups treated with IFX or TCZ but not in CRP value. Compared to IFX group, increased total amounts of bleeding during postoperative period were observed in TCZ group, associated with low values in fibrinogen. [Discussion] Biologics inhibiting IL-6 signaling could be a risk for increased bleeding during perioperative period in patients who undergone TKA because of the protective role of IL-6 in coagulation system in inflammation

P1-116

Posterior lumbar interbody fusion for rheumatoid arthritis patients

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Conflict of interest: None

[Study Design] A retrospective case-control study. [Objective] To determine if outcomes were similar between patients with and without rheumatoid arthritis (RA) who underwent posterior lumbar interbody fusion (PLIF). [Methods] Subjects comprised 20 patients who underwent one-level PLIF, and were divided into an RA group (n=10) and a non-RA group (n=10). The incidence of postoperative complications, and the rate of non-unions, loss of correction at the fused level, and adjacent segment degeneration (ASD) at one-year follow up were investigated. Clinical results were evaluated by the JOA score and JOABPEQ. [Results] There were no complications or non-unions in either group, and there were no significant differences in the loss of correction at the fused level and clinical outcomes between the RA and non-RAgroup. ASD was observed radiologically in two cases in the RA group. [Conclusions] Although outcomes of PLIF in patients with RA were equally favorable to those of patients without RA, the presence or absence of lumbar rheumatoid lesion affected ASD after PLIF. A prospective study to determine if a predictor of ASD in patients with RA can be identified, and to examine the influence of biological agents on ASD is planned.

P1-117

Clinical outcome after lumbar surgery in patients with rheumatoid arthritis

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Conflict of interest: None

[Objectives] To describe operative procedures, Japanese Orthopaedic Association (JOA) score, postoperative complications, and concomitant cervical spinal disease in patients with rheumatoid arthritis (RA) who underwent lumbar surgery. [Methods] Seven RA patients with lumbar spinal diseases (degenerative spondylolisthe-

sis in 3 patients, lumbar spinal stenosis in 3, isthmic spondylolisthesis in 1) were performed surgery. The patients were all women with a mean age of 58 years and mean follow-up of 56 months. The medical records and imaging studies of all patients were reviewed retrospectively. [Results] The operative procedures were simple posterior decompression in 2 patients and posterior decompression and fusion with instrumentation in 5. The mean JOA score was 12.2 preoperatively and 21.0 postoperatively. Two RA patients with spinal instrumentations who had postoperative complications (deep infection and adjacent segment problem, respectively) underwent revision surgeries. Four of 7 patients had concomitant cervical spinal disease. Surgeons and their RA patients who undergo an instrumented lumbar fusion should pay attention to postoperative complications which may be related to osteopenia and immunosuppression, along with concomitant cervical spinal disease.

P1-118

Solid Bolt Fixation of the Medial Column in Charcot Midfoot Arthropathy

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Conflict of interest: None

BACKGROUND: The primary goal of surgical intervention for Charcot midfoot deformity is to realign and stabilize the plantar arch. We employed a solid intramedullary bolt for a medial column fusion. METHODS: Eight cases were retrospectively reviewed. The patients consisted of six men and two women with a mean age of 63 years, and the mean duration of postoperative followup was 27 months. Four patients had recurrent plantar ulcer. RESULTS: No breakage of the bolt was observed. The mean radiographical correction of lateral talar-first metatarsal angle and the dorsal midfoot dislocation was 15 degrees and 9 mm, respectively. The correction was maintained until the last followup. At the last followup, no case presented recurrent ulcer and all patients were able to walk, with cane in two cases and without cane in six cases. Bolt removal was done in three cases. One was due to deep infection, and the other two were due to axial migration of the bolt into ankle joint. CONCLUSION: The use of a solid intramedullary bolt is a feasible procedure for realignment of the medial column in Charcot arthropathy. A rigid fixation can be expected and no implant failure occurs. However, implant migration is an issue which needs to be addressed by future design modification.

P1-119

Clinical results of knee arthroplasty in hemodialysis patients

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Conflict of interest: None

[Objectives] We retrospectively evaluated the clinical outcomes and clarified the usefulness of knee arthroplasty performed in hemodialysis (HD) patients. [Methods] Between 2003 and 2008, we performed 7 TKA (Scorpio/PS) on 6 patients and 1 UKA (Zimmer-uni). OA in 6 knees and RA in 1 knee. The etiologies of renal failure were CGN in 3 patients, DM in 2, HT in 1 and IgA nephropathy in 1, respectively. The average age was 70 yrs. The average duration of HD was 9.5 yrs. Average postoperative follow-up period was 4.0 yrs. [Results] One patinet died of gastrointestinal hemorrhage on the 11th postoperative day. Another patient died of systemic complications 2.6 years after the operation. One patient had a TKA infection which was successfully controlled after debridment and continuous irrigation procedure. No loosening was recognized. No revision surgery was required. The preoperative ROM was 118 while the postoperative ROM was 111. The JOA score sightly improved from 49.3 to 56.4 pts. There was not significant difference between preoperatively and postoperatively both in ROM and JOA score. Despite of these results, concerning that HD patients have various general and musculoskeletal complications, knee arthroplasty can be an acceptable option to maintain knee functions in HD patients.

P1-120

Rheumatologic Backgrounds in Candidates for Valvular Heart Surgery in Iran

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Conflict of interest: None

Aim & Objectives: This study was design to evaluate incidence of rheumatologic clinical demonstration and serology in patients candidate for heart valvular surgery in Alzahar cardiovascular center, Yazd, Iran. **Materials & Methods:** 120 patients candidate for valvular heart surgery who had not any known rheumatologic diagnosis enrolled this study. All of patients were examined separably, Careful history and physical examination taken from rheumatologic stand point. Tests such as CRP, ESR, UA and CBC, plus most sensitive screening serologic tests (rheumatologic tests) were evaluated before surgery. **Results:** The mean age of patients was 48.1 ±12.65. 64 cases (53.3%) were male and 56 cases (46.7%) were female. Males to females ratio was 1.14. 45.8% of patients had history of non-mechanical joint disease, 14.2 % had history of rheumatologic conditions in their family, and 30% had history of constitutional symptoms. 29.8% had positive joint findings in their physical exam. 5% of patient had abnormal urine. 52.5% of all patients had positive rheumatologic serology (rheumatoid factor 34.2%, Anti CCP 2.5%, ANA 4.2%. ANCA and APL were positive in a few cases). Amount of positive CRP was 26.7% and elevated ESR was 36.7%.

P1-121

The efficacy of suprascapular injection using ultrasoud guided system in chronic shoulder pain with rheumatoid arthritis

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Conflict of interest: None

[Objectives] We evaluated that the effect of suprascapular nerve block using ultrasound guidance systems for shoulder joint pain in rheumatoid arthritis [Methods] Shoulder joint pain with rheumatodi arthritis in 22 cases (33 joints) underwent suprascapular nerve block using ultrasound to guide. We evaluated the visual pain scale at baseline at one day after the injecton (whole day pain, night pain), morning stiffness, and CRP. [Results] The whole day pain, night pain, and morning stiffness was notable improvement. [Discussion] This rusults suggested the possibility of some impact on night pain and morning stiffness by suprascapular nerve.

P1-122

Relationship between calcium pyrophosphate dihydrate crystal and osteoarthritis of the knee

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Conflict of interest: None

[Objectives] To investigate the relationship between CPPD crystal and knee OA. [Methods] One hundred forty-four TKAs were performed for over grade III OA of knees classified by Kellgren-Lawrence grading scale. At the operation, joint fluids were collected from 138 knees (average age 74.9: male 19: female 119). We evaluated the relationship between CPPD crystals and age, BMI, CRP, ESR, MMP-3, degree of osteophyte formation and alignment. [Results] CPPD crystals were detected from 43 OA knees (31.2%). There were no significant differences between CPPD(+) and (-) groups about age, BMI, CRP, ESR and MMP-3. CPPD(+) rate in female (34.5%: 41/119) was significantly higher than that in male (10.5%: 2/19). The more severe osteophyte formation became, the higher CPPD(+) rate was, significantly. Although CPPD(+) rate in valgus knees (62.5%, 5/8) was higher than that in varus knees (31.5%, 35/111), it wasn't significant. CPPD arthritis causes incident OA. Although there was no report about gender influence, CPPD(+) rates in female and severe osteophyte formation were significantly higher in this study. It is suggested that CPPD arthritis is the one possible pathogenesis of knee OA and makes it worse through severe osteophyte formation.

P1-123

The Effect of intraarticular steroid injection on glucose metabolism

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Conflict of interest: None

[Objectives] The effect of intraarticular steroid injection on glucose metabolism is unclear. The purpose of this study is to observe the glucose metabolism after intraarticular injection. [Methods] 14 patients were enrolled in this study. Patients with frozen shoulder, osteoarthritis of the knee joint and rheumatoid arthritis were included. HbA1c, CRP, C-peptide immunoreactivity (CPR), immunoreactive insulin (IRI) and fasting blood glucose (FBG) were obtained before injection. Meal challenge test was done. Homeostasis model assessment ratio (HOMA-R) was calculated. Patients with CRP≧0.5 or IRI<0.1 or HOMA-R>2.5 were excluded. 40mg of triamcinolone acetonide was injected to knee joint or shoulder joint. FBG and IRI were obtained and meal challenge tests were done 1day and 30 days after injection. FBG, two hour blood glucose (2h-BG), IRI and HOMA-R were compared between pre-injection (Day 0), one day after injection (Day 1) and 30 days after injection (Day 30). Wilcoxon signed- rank test was used for evaluation. [Results] 2 were excluded. Data was evaluated among 12 patients (female; 11 male; 1). FBG, 2h-BS, IRI and HOMA-R were significantly higher on Day 1 compared to Day 0 and Day 30. It was revealed that intraarticular steroid injection worsen the glucose metabolism.

P1-124

Incidence of acetabular dysplasia without history of treatment for developmental dislocation of the hip

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Conflict of interest: None

Background Most Japanese patients have secondary osteoarthritis, mainly because of developmental dislocation of the hip (DDH) or acetabular dysplasia (AD). However, the precise pathomechanism and relationship between DDH and AD remains unknown. The purpose of this study was to investigate frequency of the past history of treatment for DDH in the patients with AD. **Method** A total of 206 patients with prearthritis or early-stage osteoarthritis caused by AD were examined radiographically and their history of treatment for DDH during infancy was reviewed. There were 187 women and 19 men included in the study, and the mean age at examination was 37.6 years (range, 20 to 49 years). **Result** Seventy-two patients (35%) had a history of treatment for DDH and the remaining 134 patients (65%) had no history of DDH. **Conclusion** To prevent the treatment by total hip arthroplasty for young patients with AD, they have to be operated by periacetabular osteotomy before osteoarthritis stage of the hip progressed to advanced stage. Usually AD has been diagnosed by x ray radiographs when patients admitted the hospital after they have continuous hip pain. The screening and detection of DDH at group medical examination without using x ray radiographs before patients have continuous hip pain must be proposed.

P1-125

Radiographic stage in patients with hip osteoarthritis in different position

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Conflict of interest: None

[Objectives] Radiographic staging systems for Osteoarthritis (OA), for example, those of To¨nnis, Kellgren and Lawrence, and the Japanese Orthopaedic Association (JOA), are based primarily on narrowing of joint space width as seen on anteroposterior radiographs. [Methods] To address the existing controversy in the literature, we asked whether radiographic stage is different in the supine and standing position. Radiographic stage was classified 77 hips with OA. Subjects had a mean age of 52.0 years (range, 22–84 years). [Results] 12 of 77 hips (15.6%) was classified different stage in the supine and standing position. To evaluate radiographic stage for hip OA, radiographs should be obtained with the patient in the standing position.

P1-126

Saggital spinal alignment and its impact on spinal degenerative deformities in a female cohort

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Conflict of interest: None

[Objectives] The purpose of this study was to investigate the influence of sagital spinal alignment on the development of degenerative spondylolisthesis (DS) and kyphosis (LDK) in a prospective cohort. [Methods] A final total of 227 community-based female volunteers were followed for more than 8 years. Standardized entire spine radiographs were taken and used for measuring sagittal spinal alignment. Magnitude of spondylolisthesis was also evaluated in a subgroup of 142 women without DS at baseline radiograph, and development of more than 5% slip was diagnosed as newly-developed DS. LDK was diagnosed by the angle of L1-S1<15°. [Results] Subjects' baseline age was 57.5 and mean follow-up period was 12.0 years. DS was diagnosed in 12.7%, and pelvic incidence (PI) was significantly bigger in DS patients (DS 62.4° vs. normal 54.7°, p=0.0056). LDK was diagnosed in 13.7%, and PI was significantly smaller in LDK patients (LDK 48.2° vs. normal

56.3°, p=0.0021; Student t-test). [Conclusion] This is the first to study the relationship between PI and spinal pathologies in a mean 12-year follow-up. PI determines the capacity of pelvic retroversion, and smaller PI led to the development of kyphotic deformity, while bigger PI led to the development of spondylolisthesis.

P1-127

Study of Rheumatoid Arthritis in Patients with Knee Arthritis

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Conflict of interest: None

[Objectives] To clarify whether patients with knee arthritis develop RA. [Methods] Prospective study in Yamanote do-ri Yagi hospital, Sapporo, Japan. 23 cases with knee arthritis were registered, which were RF or CRP positive but no diagnosis of RA and which were done knee joint operation (artificial joint operation, synovial membrane resection or meniscal resection) from April/2009 to October/2010. 18 cases in 23 cases, followed up in 1 year after operation, could be analyzed.(5 males and 13 females, 49-84 years old) [Results] 6 cases in 18 cases were diagnosed as RA at the 1 year after an operation, (RA group: 6 cases v.s. non-RA group: 12 cases). There were signigicant difference in 3 factors, the anti-CCP antibody positive rate (RA group 60% vs non-RA group 0%), RA classification criteria of 2010 ACR/EULAR (RA group 33.3% vs non-RA group 16.7%), histological change of synovial membrane (RA group 100% vs non-RA group 33.3%).

P1-128

Preoperative screening for deep venous thrombosis using serum D-dimer levels in patients with rheumatoid arthritis

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Conflict of interest: None

[Objectives] Measurement of D-dimer level is useful screening test for deep venous thrombosis (DVT), but limited reports are available for RA patients. The purpose of this study was to analyze the relationship between preoperative D-dimer level and the presence of DVT in RA patients. Also, the cut-off value of D-dimer for DVT screening was estimated. [Methods] D-dimer levels were measured in 176 and 162 patients with RA and OA preoperatively. For patients with their D-dimer levels were higher than standard value, either venography or ultrasonography was performed to detect DVT. Level of D-dimer and the incident rate of DVT for RA and OA were analyzed. The cut-off value of D-dimer for DVT screening for RA was calculated using the receiver operating characteristic (ROC) curve. [Results] The mean D-dimer level was significantly higher in RA patients (3.3μg/ml) than OA (1.5μg/ml) ($p<0.001$). In D-dimer positive cases, the incident rates of DVT were 19.8% in RA and 18.0% in OA (n.s.). Positive correlation was observed between CRP and D-dimer levels ($r=0.54$, $p<0.001$). For RA patients, when a D-dimer level was set at 2.4μg/ml as a cut-off value, ROC analysis revealed 80% in sensitivity and 76% in specificity (negative predictive value: 95%, odd ratio: 7.8).

P1-129

The effect of arteriosclerosis on joint power Doppler ultrasonography in rheumatoid arthritis.

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Conflict of interest: None

[Objectives] Joint power Doppler ultrasonography (PDUS) is useful to evaluate synovitis in rheumatoid arthritis (RA), and many RA patients have arteriosclerosis and poor peripheral circulation with diabetes and/or hyperlipidemia. We evaluated the effects of cardio-ankle vascular index (CAVI) and ankle brachial index (ABI) as indicators of arteriosclerosis on joint PDUS in RA patients. [Methods] We performed finger joint PDUS on 2919 patients between Oct. 2009 and Nov. 2011. We evaluated CAVI, ABI, total points (TPs) of finger joint PDUS (Point method), total vascularity (T-Vs) of finger joint PDUS (Box method), and the number of positive finger joint power Doppler (PD) signals in 37 RA patients with positive finger joint PD signals among 78 RA patients with CAVI and ABI examination within 180 days before or after finger joint PDUS. [Results] TPs and T-Vs of finger joint PDUS, and the number of positive finger joint PD signals were not decreased in RA patients with arteriosclerosis ($CAVI \leqq 9.0$ or $ABI \leqq 0.90$). [Discussion] At first, we concerned about the difficulties to detect synovitis in RA patients with severe arteriosclerosis and poor peripheral circulation. These findings suggest that joint PDUS could detect synovitis regardless of arteriosclerosis and peripheral circulation.

P1-130

Usefulness of peak grade in power Doppler sonography in the assessment of disease activity in rheumatoid arthritis

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Conflict of interest: None

Purpose: Joint ultrasound is increasingly important in evaluating the pathology and progression of rheumatoid arthritis (RA). Gray-scale ultrasound is useful in assessing synovial thickening and bone erosion, and blood flow signals in power Doppler sonography are important in evaluating disease activity. We investigated the usefulness of peak grade (PG), the highest grade of blood flow signals obtained in a patient. Patients: The study enrolled 204 patients (45 males and 159 females; 25~94 years of age; mean age 21 years). Methods: Using a Toshiba Aplio XG a 12 MHz linear probe, blood flow signals in inflammatory joints were obtained using power Doppler sonography, and were graded (grade 0~3) with Klauser's method. The correlations of PG with CRP, erythrocyte sedimentation, MMP-3, and rheumatoid factor (RF) were evaluated. Results: The coefficients of correlation (r) with PG were 0.2165, 0.2594, 0.3235, and 0.2035 for CRP, erythrocyte sedimentation, mMP-3, and RF, respectively. Conclusion: The positive correlation of PG with MMP-3 suggests that PG reflects the severity of synovitis. PG, which can be obtained quickly by assessing joints with significant swelling and pain, is useful as an adjunctive diagnostic method and in the assessment of disease activity in RA patients.

P1-131

Liver dysfunction and fatty liver in gout and hyperuricemia patients

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Conflict of interest: None

[Objectives and Methods] We investigated the liver dysfunction and fatty liver in 106 male gout and hyperuricemia patients who underwent abdominal ultrasonography (US). [Results] 40 patients were no fatty liver (G0), 26 patients were mild fatty liver (G1), 28 patients were moderate fatty liver (G2) and 12 patients were severe fatty liver (G3) in US findings. Serum ALT level correlated with BMI and west size and these factors significantly elevated with the degree of fatty liver. Fasting IRI and HOMA-R significantly increased with the degree of fatty liver. None of Go and G1, 20% of G2 and 50% of G3 were above 10μU/mL IRI which was reported the risk factor of non-alcoholic steatohepatitis. 2.5% of Go, 27% of G1, 21% of G2 and 83% of G3 were above the upper limit standard value.

P1-132

Relationship between oxidative stress and clinical data or the disease activity in patients with rheumatoid arthritis

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Conflict of interest: None

[Objectives] Oxidative stress is a state in which balances between oxidative and anti-oxidative reaction are broken down. In this study, relationship between oxidative stress and clinical data or the disease activity in RA patients was investigated. [Methods] Twenty-two patients (average age, 60.6 y), who had relatively high disease activities (average DAS28, 4.33) and induction or switching of biologics was considered, were included in this study. Oxidative stress was evaluated using a d-ROMs test that measures the serum hydroperoxide. D-ROMs in DM patients (average age, 60.3 y) were also measured. [Results] The d-ROMs value in RA patients was 504 U.CARR of average, which was significantly increased in comparison to DM patients with an average 380 U.CARR ($p<0.01$). In RA patients, the d-ROMs were strongly correlated with CRP ($r=0.651$, $p<0.01$) but not with MMP3 or DAS28. The value of d-ROMs was reduced by induction or switching of biologics. [Discussion] In RA, persistence of inflammation increases oxidative stress, which may further amplify the inflammation. Since RA is often complicated with metabolic syndromes including diabetes, hyperlipidemia and arteriosclerosis, anti-oxidative therapy could also be important for the control of the disease activity.

P1-133

Clinical features and treatment strategies of autoimmune-associated hemophagocytic syndrome

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Conflict of interest: None

[Objectives] To understand clinical features and treatments of autoimmune-associated hemophagocytic syndrome (AAHS). [Methods] By searching in the literature, we analyzed adult cases of AAHS, in which medication and outcome were clearly described. Underlying infection or malignancy was excluded. [Results] 154 cases (M:F=1:3, mean age 42 ys) were studied. Underlying disorders included SLE (n=79), AOSD (n=39), DM (n=10) and others. Fever, lymphadenopathy, hepato- and splenomegaly occurred in 85, 43, 41 and 42%, respectively. Most of cases showed cytopenia. Coagulopathy were less frequent (24%). AST, ALT and LDH levels were elevated in 77, 62 and 73%, respectively. CRP levels were elevated in majority but >50% of cases underlying SLE showed low CRP levels. Although ferritin levels were high, 21% revealed low levels (<500μg/l). As an initial treatment, corticosteroids (HD corticosteroids or mPSL pulse) were given, and >60% responded. Resistant cases underwent other immunosuppressive therapies, including cyclosporine, IVIg or IVCY. Recently, biological agents were administered with good response. 15 cases died (9.7%). [Conclusions] Clinical features of AAHS are not always similar to other HPS. Corticosteroids may be first line therapy. The standard treatments should be established.

P1-134

HLA-B7 positive seronegative spondyloarthritis associated with colitis.

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Conflict of interest: None

[Objectives] HLA-B7 loci is known to be associated to certain diseases. Among them, RS3PE syndrome is well-known by the first report of McCarty D.MD with arthritic condition. We reported two cases of seronegative spondyloarthritis (SNSA) with colitis who showed HLA-B7 positive. Case 1: A 45 year-old-male was been to our hospital because of back pain and lumbago. He noticed stomatitis, acne, migratory arthritis. CRP was positive (0.3-4.7mg/dl), RF(-), HLA-B7(+). The Colonoscopy (CS) showed multiple ulceration in colon, compatible with ulcerative colitis. Case 2: A 52 year-old-male was suffered from recurrent bloody bowel discharge. At the age of 51, he complained backache, lumbago, and ankle pan (Achilles' tendinitis). CRP level varied between 0.3-23.1mg/dll, and RF(-), HLA-B7(+). His CS revealed diverticula and colitis. [Results] Our two cases of SNSA with colitis showed HLA-B7 positivity. Conclusion: We should pay much attention to HLA-B7 in addition to HLA-B27 on diagnosis of SNSA.

P1-135

Analysis of serum 25-hydroxy-vitamin D (25-OH-D) level in Japanese patients with rheumatoid arthritis

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Conflict of interest: None

[Background] Vitamin D is well known to have immunomodulatory effect for immune competent cells. Several studies indicated that 25-hydroxy-vitamin D (25-OH-D) insufficiency had been associated with several autoimmune disorders, including rheumatoid arthritis (RA). [Objectives] To examine the prevalence of vitamin D insufficiency and the associations of vitamin D concentration with type of disease, disease activity in Japanese patients with RA [Methods] We enrolled 15 Japanese patients with RA, no supplementation of vitamine D. Serum samples from those patiens were tested for 25-OH-D levels by RIA method. Association between serum levels of 25-OH-D and age, gender, type and disease dura-

tion and disease activity were assessed. [Results] The mean serum 25-OH-D level was 26.4ng/ml. The prevalence of 25-OH-D insufficiency (defined as <30ng/ml) was 53%. Significantly lower serum 25-OH-D levels were found in ACPA and/or rheumatoid factor positive RA patients. There was no significantly correlation between serum levels of vitamin D and age, gender, disease duration. Disease activity score(including SDAI, DAS28ESR) were tend to be inversely correlated with 25-OH-D levels, but not significant. [Conclusion] Vitamin D insufficiency was also common in Japanese patients with RA.

P1-136

Importance of marker of bone formation in rheumatoid arthritis patients: efficacy of intact (P1NP) measurement.

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Conflict of interest: None

Objective: Clinical importance of high sensitive marker of bone formation was studied since teliparatide: novel agent stimulating bone formation launched recently. Method: 52 of RA patients in outpatient clinic of Osaka City University Hospital were enrolled. Correlation of iP1NP and marker of bone metabolism, clinical parameters was analized. Results: RA patient showed quite high bone turnover. Marker of bone turnovers were positively correlated with markers for systemic inflammation in RA patient. However, magnitude of increase of bone formation was less than that of bone absorption marker since iP1NP/TRAP5b showed negative correlation with disease duration of RA. These results suggested that bone formation is uncoupled with bone absorption in RA patients with long term disease duration. In conclusion simultaneous measurement of markers of bone formation and absorption in RA patients.

P1-137

A case report of juvenile idiopathic arthritis with advanced joint destruction even after clinical and functional remission.

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Conflict of interest: None

A 15-year-old woman with a 2-month history of polyarthritis showed multiple erosions and joint space narrowing of radio-carpal joint on radiograph of her right wrist. Laboratory studies showed elevation of C-reactive protein, rheumatoid factor, anti-CCP antibody and MMP-3. She was diagnosed as polyarticular JIA by clinical findings and manifestations. Her symptoms remarkably improved and achieved clinical remission after administration of MTX for 4 months. However, erosions and joint space narrowing of right wrist progressed at the 1-year-follow-up. Power Doppler ultrasonography analysis revealed the presentation of active inflammation in right wrist. Etanercept 50mg/week was added on to do tight control. This case suggested the necessity of the continuous follow-up for affected joints using conventional radiograph and ultrasonography even in the case under clinical and functional remission. We reconfirmed the importance to suppress joint destruction from the earlier stage of disease course.

P1-138

Rheumatoid synovitis mimicing neoplastic lesion: A case series

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Conflict of interest: Yes

[Objectives] It is sometimes quite challenging to make a proper diagnosis in cases with mono-arthropathy presenting soft-tissue swelling. We reviewed the cases who initially presented as solitary mass lesion, which turned out to be synovitis by histological examination, and finally diagnosed as rheumatoid arthritis later on. [Methods] Between 1985 and 2010, eight cases with solitary mass lesion were histologically diagnosed as synovitis. All patients were female, and the average age at the biopsy was 49 year. [Results] The involved joints were shoulder (1), ankle (2), MTP (4) and calcaneous (1). Osteolytic lesions were radiographically observed in six cases, and biopsy was performed with diagnosis of suspected pigmented villonodular synovitis or giant cell tumor of tendon sheeth. Elevation in CRP level was observed in three cases preoperatively. Rheumatoid factor was positive in six cases with bone erosion, and all these six patients developed polyarthritis later on and met the 1987 ACR criteria for RA. Physicians are encouraged to be aware that rheumatoid arthritis could be presented as a solitary mass lesion.

P1-139

Preliminary study of three dimensional quantitative evaluation of bone erosion over time using CT on rheumatoid arthritis patients

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Conflict of interest: None

[Objectives] To investigate the feasibility of three dimensional quantitative evaluation of bone erosion (BE) using CT on rheumatoid arthritis (RA) patients. [Methods] CT scanning covering the area from bilateral wrists to metacarpal bones was performed (0.250mm thick slices, 0.234mm pixels, 512×512 matrixes) on 6 RA patients (male 1, female 5, average age 53.5 y.o. ranging from 37 to 70 y.o.) twice with an interval of one year. BE area of bilateral distal parts of radius and ulna was extracted from each image of CT and the total bone erosion volume of 4 epiphyseal lesions was calculated. [Results] The averages of total BE volume for the initial exam and for the one-year-after exam were 184.8 ± 127.4mm3 and 232.2 ± 175.6mm3, respectively, and tended to increase over one year ($p = 0.127$). The averages of CRP (0.187 ± 0.249mg/dl) and ESR (16.3 ± 7.37mm/hr) at the initial exam tended to be positively correlated ($r = 0.348$ and $p = 0.499$, $r = 0.381$ and $p = 0.457$, respectively) with the average of total BE volume increase (47.4 ± 63.6mm3). The average of total BE volume increase of 4 patients treated with no biological products (14.8 ± 11.7mm3) tended to be higher than that of 2 patients treated with biological products (63.7 ± 75.1mm3) ($p = 0.286$).

P1-140

MRI findings in patients with rheumatoid arthritis one year following tocilizumab treatment

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Conflict of interest: None

[Objectives] The purpose of this study was to examine changes in MRI findings in rheumatoid arthritis (RA) patients who were treated with tocilizumab (TCZ) for one year. [Subjects] Subjects were seven women with RA who were treated with TCZ for more than one year. Mean age at TCZ therapy was 64.6 years. Two cases were bionaïve, four switched from infliximab, and one switched from etanercept. [Methods] MRIs were taken of each patient's hands prior to TCZ therapy and one year after TCZ. We determined RAMRIS scores, and carried out evaluations using DAS28 and CDAI. [Results] Prior to TCZ therapy, the mean synovitis, bone erosion, and bone edema scores were 8.4, 25.3, and 22.0, respectively; DAS28 and CDAI were 4.88 and 18.4, respectively. One year after treatment, synovitis, bone edema scores, DAS28, and CDAI improved in six cases. Mean synovitis, bone erosion and bone edema scores were 4.4, 21.0 and 10.7, respectively, while DAS28 and CDAI were 2.87 and 9.0, respectively. [Conclusions] MRIs taken one year after TCZ therapy revealed alleviation of synovitis and bone edema. DAS28 and CDAI also improved, but bone erosion remained unchanged. These results suggest that MRI findings of synovitis and bone edema may be useful for assessing the effects of RA treatments.

P1-141

Diagnostic Impact of Magnetic Resonance Imaging of the Shoulder in the Diagnosis of Polymyalgia Rheumatica

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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. The characteristic laboratory findings in PMR are high erythrocyte sedimentation rate (ESR) level and elevated serum C-reactive protein (CRP) level. There is no laboratory or other test, including ESR and CRP, specific for the diagnosis of PMR. New classification criteria for PMR had been presented by the ACR/EULAR. After exclusion of other diagnoses, patients aged ≥50 years with the 'polymyalgic syndrome' (defined as new-onset bilateral shoulder pain and elevated acute-phase reactants) are classified as PMR cases if they fulfill point scoring algorithm without or with ultrasonography. 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 that criteria. We investigated diagnostic impact of shoulder MRI for the diagnosis of PMR in our institution.

P1-142

Two cases of monoarthritis-type rheumatoid arthritis diagnosed by MRI

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Conflict of interest: None

【Case 1】A 59-years-old female has suffered right ankle pain and swelling for 5 years. Serological exam : ANA x40, RF <3, CCP antibody 1.3 U/ml, CRP 1.3 mg/dl, and ESR 21 mm/h. A foot MRI study revealed bone erosion of talus with synovitis, leading to a diagnosis of early RA based on Nagasaki University criteria (NUC). Treatment with bucillamine was commenced and followed by administration of MTX andPSL. Synovial tissues resected by arthroscopic synovectomy revealed the papillary proliferation of synovial membrane, mononuclear cell infiltration and lymphoid follicles, which were pathologically compatible with RA.【Case 2】A 64-year-old male has suffered right knee pain and swelling for 9 months. Serological exams : ANA x160 (homogeneous pattern), RF 236 IU/ml, CCP antibody 1522.9 U/ml, CRP 6.8 mg/dl, and ESR >100 mm/h. A knee MRI study revealed bone erosions of femur and tibia with bone edema and synovitis, leading to a diagnosis of early RA based on NUC. The patient was treated with MTX and PSL.【Discussion】We experienced two cases of monoarthritis-type RA, which was diagnosed by MRI. The diagnosis was performed based on NUC for early RA, instead of the ACR/EULAR (2010) criteria. We here report the significance of early diagnosis of monoarthritis-type RA by MRI.

P1-143

The magnetic resonance imaging (MRI) findings of rheumatoid arthritis in clinical remission treated with biological therapy.

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Conflict of interest: None

[Objectives] The purpose of study is to investigate MRI findings of rheumatoid arthritis patients in clinical remission. [Methods] Eight RA outpatients were enrolled in the study. Three patients were treated with infliximab (IFX group), two with etanercept (ETN group), and three patients with Tocilizumab (TCZ group). Clinical disease activity was determined using the DAS28–ESR. Magnetic resonance imaging examinations were performed twice, once before biological therapy and the other at clinical remission. MRI findings were currently scored using the RA MRI scoring system (RAMRIS) as reported in the Outcome Measures in Rheumatology Clinical Trials (OMERACT). [Results] DAS28-ESR was 5.08 before therapy and improved to 2.10 at clinical remission. TThe total RAMRIS score was decreased in all patients. The synovitis score and bone edema score in RAMRIS MRI score was improved remarkably. But, only two cases disappeared the synovitis and bone edema scores. [Discussion] This study suggests that some cases in DAS28-ESR clinical remission with biological therapy still remain inflammatory arthritis.

P1-144

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: None

Objective:The aim of this study was to evaluate the efficacy of abatacept (ABT) by using low field compact magnetic resonance imaging (cMRI) in patients with rheumatoid arthritis (RA). Methods:Four RA patients treated with ABT were included. All patients had insufficient responses to one or more anti-TNF therapy. The clinical response to the therapy was evaluated by simplified disease activity index (SDAI). Hand images were taken by 0.3T cMRI in 2 sequences; coronal T1 weighted image and coronal short tau inversion recovery image, without gadolinium enhancement. Two examinations were performed before and after the administration of ABT, and bone erosion, bone marrow edema and synovitis were scored by cMRI scoring system. Results:There was a tendency of improvement in SDAI after the ABT therapy (20.15±28.02 to 7.61±12.66, p=0.11). Synovitis score were significantly decreased after the ABT treatment (16.75±22.05 to 5.75±22.37, $p<0.05$), whereas no significant change was found in erosion score and bone marrow edema score. Conclusion:ABT may improve synovitis and suppress the progression in bone erosion observed by cMRI in RA patients.

P1-145

Ultrasonography and Magnetic Resonance Imaging in 4 patients with mimicking polymyalgia rheumatica

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Conflict of interest: None

[Objectives] We examed that Ultrasonography and MRI in assessment of patients with mimicking polymyalgia rheumatica are useful tools to distinguish elderly onset RA. [Methods] Four patients whose PMR diagnosis was confirmed at onset were recruited. When Their polymyalgia symptom flared up during tapering of PSL treatments, we examed clinical, laboratory, US, and MR data and reconsider their diagnosis. [Results] 2 of 4 patients were classified with ACR/EULAR2010 Rheumatoid Arthritis criteria. 2 patients were not classified, but showed characteristic findings of MRI and US for RA. US demonstrated tenosynovitis in 1, subacromial-subdeltoid bursitis in 1, LHB tenosynovitis in 1 and peripheral synovitis in 4. MR demonstrated synovitis in 2, scapulohumeral periarthritis in 1, and erosion in 2.

P1-146

Four cases of seronegative RA with significant US and MRI findings

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Conflict of interest: None

With the 2010 ACR/EULAR criteria for rheumatoid arthritis, we can make diagnosis of RA in earlier stage. But in seronegative cases, its diagnostic sensitivity is not so high. And some of the early RA cases don't present any bone erosion in X-ray. In these cases, US or MRI may reveal active synovitis or bone erosion, which can support the diagnosis of RA. Here we present four cases of polyarthritis, focusing on US and MRI. Three are male, and three are over 65 years old. DAS28-ESR was over 5.1 in all patients, but the bone erosion was not detected by X-ray of hand and foot. Two of four cases were scored as 7 with the 2010 criteria, and the others were scored as 5. So two cases didn't match the criteria, but in all cases, US revealed active synovitis and bone erosion on multiple joints, and MRI bone edema was detected in two cases. We administered some DMARDs for all these patients. PDUS score and MRI bone edema are reported to be prognostic factors of joint destruction, so these findings are very helpful to make therapeutic decision.

P1-147

Comparison of ^{18}FDG-PET and MRI of shoulder in patients with rheumatoid arthritis

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Conflict of interest: None

[Objectives] It has been reported ^{18}FDG-PET(PET) findings for the rheumatic disease including rheumatoid arthritis (RA), and we had reported the relationship between disease activity, the progress of the joint destruction and PET. However, it is not yet clear about the cut-off line of standardized uptake value (SUV). The aim of this study to assess PET findings and synovitis of shoulder joint of MRI in RA patients. [Methods] 43 shoulders in 42 patients with RA were assessed with PET and MRI. Mean age (range) was 54 (36–75) years and mean disease duration was 9 (1–40) years. 18F-FDG uptake was quantified using the maximum pixel value of the SUV. Synovitis were examined in axillary pouch(AP), subacrominal bursa(SAB), subdeltoid bursa(SDB), rotator interval (RI) and acromioclavicular joint(ACJ). We examined having either synovitis or not and relations of SUV max using ROC curve. [Results] In SUV max, 0.87-6.17 (an average of 1.99), the synovitis in MRI are AP: 8/43, SAB: 17/43, SDB: 12/43, RI: 16/43, ACJ: 5/43. It was thought that it was 0.88, and the AUC was relatively high in the predictive ability of the SUV with the ROC curve. If cut-off line was 1.50, sensitivity was 0.833 and specificity was 0.842 [Conclusion] Cut-off level of the SUV was thought 1.50 in RA shoulder joint.

P1-148

The usefulness of the whole body screening using 18FDG-PET/CT to a biological products prescription cases

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Conflict of interest: None

[Objectives] It's being increased that biologics is employed as drug treatment to rheumatoid arthritis(RA) and spondyloarthrits such as ankylosing spondylitis(AS). But anxiety of participation with susceptibility and malignant tumor is pointed out to biologics, and it's necessary to make the screening enough. The present paper

concerns the results that 18FDG-PET/CT of the whole body was performed as a screening before biologics prescription. [Methods] 86 patients with RA and 2 patients with AS who scheduled new installation of biologics and did a screening in the whole body were selected for this study. It was considered presence of infection, without medical history and clinical condition, tumor and all that. [Results] A malignant tumor(malignant lymphoma), 7 benign tumors(2 myoma of the uterus, an ovarian tumor, a parotid tumor, 2 renal tumors and an elastofibroma), 3 active infection(a deep abscess, a pharyngitis and a maxillary sinusitis) and others(3 pulmonary node, a cholelithiasis, a urolithiasis, a hydronephrosis and an old cerebral infarction) were pointed out by 18FDG-PET/CT. [Discussion] The results showed that 18FDG-PET/CT is effective in screening before biologicics prescription.

P1-149

Usefulness of ultrasound-Doppler guidance for image-guided injections of temporomandibular joint in rheumatoid arthritis.

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Conflict of interest: None

[Objectives] We assessed the efficacy an ultrasound-Doppler guided technique for visualization of needle placement within the temporomandibular joint in patients with rheumatoid arthritis (RA). [Methods] The efficacy of temporomandibular joint corticosteroid injection and a liniment as a positive control were compared. Randomization was performed and 14 outpatients with RA were treated with their respective treatment. The mouth opening length at 4 weeks was compared with those at baseline in each treatment group. [Results] At the 4 week assessment, participants in the temporomandibular joint injection group (n=8) demonstrated significantly increased mouth opening length ($P<0.0001$) in comparison with their baseline assessments. The significant differences were not found in the group with the liniment (n=6), ($P=0.61$). [Conclusion] Ultrasound-Doppler guided technique for temporomandibular joint injection with corticosteroid is suitable for patients with RA who complained severe pain in her jaws when chewing.

P1-150

The bone erosion depiction sensitivity and utility that are observed by joint ultrasonography and other imaging studies

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Conflict of interest: None

[Introduction] In recent years, the bone erosion image and joint synovitis in small joints that were difficult to observe by using conventional roentgenographic examination of a joint can be more easily observed now with the dramatic improvement in performance of the diagnostic imaging equipment of various modality. But, since each modality has advantages and disadvantages, the image information obtained should be analyzed synthetically, and it seems important that the clinical view is added further to get a grasp of clinical state of rheumatoid arthritis. [Method] The joint ultrasound examination by the real-time 3D method was performed to three RA patients whose bone erosion and a blood-flow signal were detected by conventional joint ultrasound examination at the fingers MCP and a PIP joint. [Result] (1) The expanding of bone erosion was observed in three dimensions by using real-time 3D Gray Scale Ultrasound. Moreover, the distribution of blood flow in a joint cavity is also observed by using Power Doppler Ultrasound examination. The bone erosion and the surrounding blood-flow signal was able to be depicted by using Fine Flow mode.(2) In case of joint ultrasound examination, it was possible to observe small bone erosion in finger joint at all of 5 cases.

P1-151

About the optimal setting method of the equipment in blood-flow signal detection

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Conflict of interest: None

“Background” In rheumatoid arthritis, appearance of blood-flow signal in articular cavity is a sign of active inflammation. To detect blood flow signal in variable joints, optimal machine setting are important. There has been no specialized software for rheumatoid joint observation. In this study, we examined to figure out the optimal machine setting in blood-flow signal detection using high resolution color flow function (Fine Flow)(Avius Hitachi Aloka Medical Ltd.). “Method” Several parameters such as basic application, PRF (the flow velocity range), probe frequency, and a filter were examined. <Result> (1) In the basic application, “orthopaedics mode” was most suitable to observe rheumatoid joints. (2) 7.5 MHz was most suitable. (3) 500-800 Hz as PRF is most detectable for blood flow in articular cavity. “Conclusion” Detection of a blood-flow signal is greatly influenced to the machine setting, but also the differences in the performance of each model. Our investigated setting enable to avoid the differences in performance of each model to a minimum. In the future plan, checking tool for probe degradation or blood-flow phantom are strongly needed to standardize optimal setting for each machine.

P1-152

Using novel high resolution mode to detect synovial vascularity in rheumatoid joint ultrasonography

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Conflict of interest: None

“Background” PDUS (Power Doppler Ultrasound) is an important examination to observe synovial vascularity that reflects joint inflammation level and its progress. Conventional PDUS has weak points in observation for small vessel flow due to low ability in time-course and three-dimensional resolution. Novel high resolution mode (Fine Flow) has been developed. In this study, we compared conventional PDUS with Fine Flow in ability to visualization for synovial vascularity. “Method” Rheumatoid finger joints with active inflammation were observed. The machine parameters were setted for small organ. “Result” Fine Flow image had less blooming and ability to visualize detailed blood flow. Assessing vascularity with scoring systems such as semi-quantitative 4-grade method, 7-grade method and quantitative method, there were few cases with different scoring between conventional PDUS and Fine Flow. “Conclusion” In Fine Flow, the blood flow signal was visualized more clearly with less blooming than conventional PDUS. Fine Flow could provide precise blood flow information.

P1-153

Analysis of angiogenesis factors in patients with rheumatoid arthritis.

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Conflict of interest: None

Objective: To evaluate the clinical significance of serum levels of vascular endothelial growth factor (VEGF), angiopoietin-1 (Ang-1), angiopoietin-2 (Ang-2) in patients with rheumatoid arthritis (RA). Methods: The subjects were RA patients who fulfilled the diagnostic criteria of the American College of Rheumatology. Ten joints: the bilateral wrists, elbows, shoulders, knees, and ankles, were examined by power doppler ultrasonography (PDUS). The blood flow signals at synovial sites of each joint were scored 0-2, and the total blood flow scores of the 10 joints was calculated as the total signal score (TSS). The vascular endothelial growth factor (VEGF), angiopoietin-1 (Ang-1), angiopoietin-2 (Ang-2), Interleukin-1 (IL-1), IL-6, IL-8 levels were determined by ELISA. Results: Significant correlations were observed between the serum VEGF and serum IL-6, and TSS. There were also correlations between Ang-1 and IL-6, and between Ang-2 and IL-6, and IL-8. Conclusion: The increases in the synovial blood flow signals in joints of RA patients observed by PDUS are likely to be caused by vascularization in synovial proliferation areas. They are particularly likely to represent the pathology in the period of marked vascularization, in which Ang-2 plays a dominant role.

P1-154

Reliability of physician evaluation of swollen joints in rheumatoid arthritis: A comparison study with ultrasound.

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Conflict of interest: None

Objective: The evaluation of inflammation is the keystone for the therapy in rheumatoid arthritis (RA). However, whether physicians could accurately evaluate swelling joints or not is uncertain. The assessment of synovial volume using ultrasound (US) is an important point in the quantification of the joint swelling. This study evaluated the reliability of patients' and physicians' assessment of swollen joints versus those by US. Method: Eighty-one RA patients self-assessed 22 joints/ 26 sites (wrists: three sites, MP and PIP: one site) for swelling. They were then assessed by two physicians and US. Semiquantitative scoring of synovial hypertrophy (Gray scale, GS score: 0-3) and Power Doppler (PD, score: 0-3) signals were performed. We defined swollen joints as GS score >=2. Results: DAS28 correlated well with total of GS score ($R=0.512$, $p<0.001$). Swollen joints assessed by US were observed in 18% of all joints and of which 80% were demonstrated positive score in PD. The sensitivity for swollen joints assessment by two physicians and patient were 48%, 49%, and 34% respectively. The sensitivity for the joints which showed both GS>=2 and PD>=1 were 66% and 69% in the two physicians. Conclusion: US examination appears to be a useful imaging technique to detect swollen joint in RA.

P1-155

Survival rate and causes of death in SLE patients

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Conflict of interest: None

【Objective】 Recent advances of management of Systemic lupus erythematosus(SLE) has changed the prognosis, and the cause of death may have been changed. In this study, we analyzed the survival rate and the cause of death. 【method】 We used our database of SLE patients registered between 1991 and 2011, and estimated the Kaplan-Meier survival rate and the Kaplan-Meier observation-period from the SLE onset. In the latter analysis, dropped-out cases were excluded from the survival curve. Referral patients for emergent hospitalization and of no later follow-up in our clinic were excluded from the study. 【Result】 The number of SLE patients was 297 (observation 5346 person-years). Of these, 39 patients died. The survival rates at 5, 10, 15 years were 99.6%, 98.2%, 94.1%, respectively, and the Kaplan-Meier observation-period were 93.1%, 87.8%, 80.2%, respectively. Patient-deaths were caused by active SLE in 13 of 17 patients before 2000, or in 2 of 22 patients after 2001, and the difference was significant ($p=0.00002$). After 2001, stroke (6), cardiovascular disease (3), malignancy(5) were major causes of deaths. 【Conclusion】 Prognosis of SLE has been improved in recent years.

P1-156

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-induing 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). Sera were collected to detect RF, anti-Sm and anti-dsDNA antibody. To assign CD number on the *ai*CD4 T cell, expression of effector/ memory markers on splenic CD4 T cell were studied. These CD4 T cells were further isolated referring to CD45RB, CD27 and CD122 markers, and were adoptively transferred into naïve recipients. Autoantibodies were measured in sera of the recipients 2 weeks after transfer. **[Results]** Upon repeated immunization >12x with KLH, OVA or SEB, varieties of autoantibodies including RF, anti-Sm and anti-dsDNA antibodies were increased. We also noted that CD45RB^{lo}, CD27^{lo} and CD122^{hi} CD4 T cells were significantly expanded after repeated immunization with any antigens. Further, the transfer of CD45RB^{lo} 122^{lo} CD4 T cells induced RF and anti-dsDNA antibodies in the recipient mice. **[Conclusion]** The *ai*CD4 T cell that induces SLE belongs to CD45RB^{lo} 122^{lo} CD4 T subpopulation.

P1-157

Effect of SAP-deficiency on B cell-mediated autoimmune disease

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Conflict of interest: None

[Objectives] SLAM family molecules exist on various immune cells and control a variety of immune functions. In T cells, SLAM signal is mediated by SAP (SLAM associated protein). It has been reported that T cell-mediated SLE is completely inhibited by SAP-deficiency. In the preset studies, we examined the effect of SAP-deficiency on B cell-mediated SLE. [Methods] We have established SAP-deficient BXSB mice by introducing *rpl* gene, which is SAP-deficient mutant gene spontaneously occurred in MRL/lpr mice. This mutation completely inhibited autoimmune phenotypes in MRL/lpr mice. [Results] In BXSB/*rpl* mice, serum autoantibody levels and the incidence of proteinuria were significantly suppressed as compared with BXSB mice. In contrast, there were no significant differences in B cell activation, splenomegaly and germinal center formation between two strains. BXSB disease is B cell-dependent because of *Yaa* gene, which is due to the TLR7 duplication. Our data indicate that SAP-deficiency is not enough to suppress B cell-mediated SLE.

P1-159

Serum levels of beta 2-microglobulin in systemic lupus erythmatosus patients

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Conflict of interest: None

[Objectives] To examine serum levels of beta 2-microglobulin (β_2-m) in systemic lupus erythmatosus (SLE) patients. [Methods] Serum levels of β_2-m were measured in 21 patients with SLE in active and inactive disease states. The relationships between serum β_2-m levels and the laboratory markers of disease activity in macrophage activation syndrome (MAS) were evaluated. [Results] Serum β_2-m levels decreased significantly after the treatment (3.8±1.5 versus 2.2±0.76mg/L; $p<0.01$). A statistically significant positive correlation was observed between serum β_2-m levels and serum serum lactate dehydrogenase (LDH) ($rs=0.51$ $p=0.02$), ferritin ($rs=0.49$ $p=0.04$), aspartate aminotransferase (AST) / alanine aminotransferase (ALT) ratio ($r=0.62$ $p<0.01$), plasma fibrin degradation products (FDP) ($rs=0.52$ $p=0.04$), D-dimer ($rs=0.66$ $p<0.01$). Serum β_2-m levels in patients with serositis were higher than its levels in patients without serositis (5.0±1.8 versus 3.2±0.81mg/L; $p=0.04$). Serum β_2-m levels in two patients with MAS were very high levels. [Conclusion] It is suggested that serum β_2-m levels may be a useful indicator of disease activity and complications of MAS in SLE patients.

P1-160

Is this case sero-negative SLE?

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Conflict of interest: None

We report here an unusual case of sero-negative SLE presented as spiking fever and C4 hypocamplementemia. A 63-year-old Japanese woman was admitted because of a 10-days history of spiking fever. Her laboratory data showed remarkable inflammatory signs and C4 hypocomplementemia, but ANA, ds-DNA Ab, Sm Ab, Lo/Ra Ab, ANCAs or elevation of serum ferritin were not detected. After oral steroid therapy (prednisolone 30 mg per day) her spiking fever and hypocomplementemia promptly improved. When prednisolone was tapered to the dose of 20 mg per day, mononeuritis multiplex: left sural palsy suddenly occurred, indicating that she might have vasculitis. Therefore, we finally diagnosed she might have sero-negative SLE. Further clinical observation is required to confirm this diagnosis. In conclusion, we presented this patient to remind the possibility of SLE because she presented with steroid-sensitive C4 hypocomplementemia and vasuculitis.

P1-161

A case of Klinefelter's syndrome with systemic lupus erythematosus

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Conflict of interest: None

[Case] A 23-year-old man with a 2-year history of SLE was admitted to our hospital for fever and dyspnea. Over the previous year, he had not taken prescribed prednisolone (PSL) or tacrolimus after self-discontinuation. Based on malar rash, pleuritis, renal failure, nephrotic syndrome, pancytopenia, and high anti-dsDNA and -Sm antibody titers, he was diagnosed with SLE relapse. Coincidentally, bone marrow aspiration, done as a pancytopenia work-up, revealed 47, XXY karyotype, indicative of Klinefelter's syndrome (KS). For progressive renal failure, he received methylprednisolone pulse therapy, followed by high-dose oral PSL combined with monthly intravenous pulse cyclophosphamide and hemodialysis. His symptoms and laboratory data significantly and promptly improved with the treatment, weaned off hemodialysis after 3 months, and PSL dosage was gradually tapered. [Discussion] KS, which results from 47, XXY karyotype, is characterized by abnormal sexual development and infertility. There are several case reports of KS with SLE. A recent study predicted a higher risk of developing SLE among KS patients. The comparison of SLE incidence with other karyotypes implies a dose effect of X chromosome on SLE susceptibility. SLE patients may require a careful consideration about KS.

P1-162

A case of SLE with frequent alveolar hemorrhage despite of aggressive treatment

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Conflict of interest: None

Case: 27 y.o female who has history of SLE and anti-phospholipid syndrome diagnosed when she was 16 y.o. She also had three times histories of respiratory failure treated with anti-bacterial and high dose steroid therapy. In July 2009, she was admitted because of fever and dysnea in our hospital. Bronchial fiber (BF) showed a sign of alveolar hemorrhage (AH). She was treated with pulsed steroid therapy (PS) and improved remarkably. But 4 days after admission, AH recurred more severely requiring ventilator, plasma exchange, and monthly IV cyclophosphamide (IVCY). She needed 6 times of IVCY, and azathioprine as maintenance. In August 2011,

She was admitted again because her respiratory condition became worse and AH had revived which confirmed by BF. We treated with PS and immune-globulin therapy and she improved again without any sequela. In this patient, at least 3 times of AH was occurred in spite of aggressive therapy. Treatment for recurrence of AH in SLE patients was not clearly established, although some article reported cases of frequent AH in SLE patients. This case indicated necessity of further investigation for frequent AH in SLE in future.

P1-163

A case of SLE with ASD, PH and portal hypertention who developed chronic diffuse alveolar hemorrhage

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Conflict of interest: None

The case is a 31-year-old female, who was diagnosed with SLE and ASD in 2000 and has been followed by our cardiology department. She visited our rheumatology department in 2007 and was found to have pulmonary hypertension (PH). SLE had remitted by 5-10mg/day of PSL and 200mg/day of Mizoribine with normal level of serum anti-ds-DNA Ab. In the meantime, she was admitted to our hospital with rupture of esophageal varices due to idiopathic portal hypertension. In May 2011, she started to suffer from bloody sputum and chest CT showed pattern of ground-glass opacity. The bronchoalveolar lavage fluid revealed that she developed diffuse alveolar hemorrhage. However, she had had no sign of anemia, dyspnea, nephritis, or abnormal lab data indicating the exacerbation of SLE for 4 months. In September 2011, she was admitted again due to bloody sputum and dyspnea. Since cardiac catheterization showed no exacerbation of PH, she was treated with steroid pulse therapy because it was possible that SLE might cause the diffuse alveolar hemorrhage. Her symptoms and CT findings of lung were getting better with the therapy. Herein we report a rare case of SLE with ASD, PH and portal hypertention who developed chronic diffuse alveolar hemorrhage.

P1-164

Alveolar hemorrhage in an SLE pt

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Conflict of interest: None

A-42 year old woman was diagnosed as having SLE in1990. Since 2009, pulmonologist followed her bronchial asthma like symptoms. Low platelet count was seen in Feb 2011. A diagnosis of autoimmune thrombocytopenic purpura (ATP) was made on June 2011 then PSL (30mg/day) was initiated. From July 2011, persistent pneumonia were seen and she was admitted to our hospital on 10 August due to infiltration on the chest X ray and hypoxia. Originally, hypersensitivity pneumonitis was suspected because temporarily flair up was occurred when she returned home. On 9 Sep, hypoxia was seen and bronchofiberscopy was performed. Alveolar hemorrhage was confirmed then PSL pulse therapy was initiated on the next day followed by plasma pheresis and cyclophosphamide pulse therapy. When the dosage of PSL and cyclophosphamide were taperd, alveolar hemorrhage was occurred again on 14 Oct. Plasma pheresis was once performed followed by 2nd cyclophosphamide pulse therapy and administration of Intravenous immuno globulin. After the therapy, her condition was under control. We had difficulties in making a diagnosis of alveolar hemorrhage in this SLE pt. Plasma pheresis and cyclophosphamide pulse therapy may be of value in the treatment of alveolar hemorrhage in SLE which was refractory to PSL.

P1-165

A case of systemic lupus erythematosus with refractory peripheral neuropathy that was successfully treated with rituximab and that relapsed after 6 years with peritonitis, enteritis, and cystitis

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Conflict of interest: None

A 57-year-old woman was admitted to our hospital because of fever and polyarthritis with cold-like symptoms. She was diagnosed as systemic lupus erythematosus (SLE) based on arthritis, leukocytopenia, and anti-dsDNA antibody and anti-nuclear antibody positivity. She then suffered paresthesia and paralysis in her extremities. A diagnosis of sensory and motor neuropathy due to vasculitis was made by nerve biopsy. High-dose glucocorticoid (GC), cyclophosphamide pulse therapy, plasma exchange, and intravenous immunoglobulin were not effective. Her neuropathy deteriorated and she became bed-ridden. However, a single infusion of 1000 mg rituximab (RTX) dramatically ameliorated her symptoms. Prednizolone(PSL) dosage was tapered to 5 mg/day. In 2011, she felt abdominal pain after experiencing cold-like symptoms. Computed tomography showed thickening of intestinal wall, ascites, and hydronephrosis. A blood test showed anti-dsDNA antibody positivity with hypocomplementemia. On the basis of these findings, she was diagnosed as lupus enteritis, peritonitis, and cystitis. Her symptoms improved after commencement of GC pulse therapy and PSL (50 mg/day). Although her SLE relapsed, it is interesting to note that GC resistance was resolved after the long-term, RTX-induced SLE remission.

P1-166

Long-term survival and prognosis in lupus nephritis; a retrospective analysis in our institute.

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Conflict of interest: None

[Objectives] Aggressive use of immunosuppressant has been introduced for the treatment of proliferative lupus nephritis(LN) since 1990's in our institute. We investigated its effect on survival. [Methods] Patients with LN from 2000 through 2010 who underwent renal biopsy were retrospectively analyzed in terms of WHO classification, response to treatment and flare rate. Mean follow-up was 13 months. [Results] A total of 71(mean age of 36 year-old) patients with LN had renal biopsy. The mean serum creatinine was 0.9mg/dl and mean amount of proteinuria was 2.6g. Five(7%) patients had WHO II, 10(15%) had III, 27(39%) had IV and 11(16%)

had V by WHO classification. Another 16(23%) showed mixed with WHO IV and V. Intravenous cyclophosphamide(IVCY) and mycophenorate mofetil(MMF) were introduced as induction therapy in 36 and 10 patients, respectively. Among patients who had achieved remission, 50% and 18% of the patients had IVCY and MMF therapy. In contrast, 67% of patients who had flare of LN received steroid monotherapy. Only one patient died from infection during the follow-up. Surprisingly, no patients needed maintenance dialysis. [Sonclusion] The prognosis of LN patients in our institute was favorable, maybe because aggressive introduction of immunosuppressants such as CY or MMF.

P1-167

Renal pathological findings do not predict clinical response to induction therapy in patients with lupus nephritis

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Conflict of interest: None

[Background] Early response to induction therapy is predictive of good long-term renal outcome in lupus nephritis. There are few reports which evaluated the prognostic factors according to the details of pathological findings. [Objectives] To evaluate the response to induction therapy in Japanese people with class III and IV lupus nephritis depending on renal pathological findings. [Methods] We evaluated 23 patients with biopsy-proven focal or diffuse lupus nephritis according to the 2003 ISN / RPS classification of lupus nephritis. We studied retrospectively their clinical data from 0 to 3 years after the induction therapy, and analyzed the clinicopathological factors affecting response to induction therapy. We also evaluated pathological findings according to NIH activity / chronicity indices. [Results] Ten patients were classified with class III, 13 with classIV. Intravenous Cyclophosphamide (IVCY) was initiated in 10% with class III and 69% with class IV. Complete remission rate at 6 months were 30% and 62%. There were no significant differences in pathological factors according to NIH scores between patients treated with IVCY and those without. [Conclusion] Our results suggest that consideration of pathological activity is not always meaningful in induction therapy.

P1-168

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] We histopathologicaly evaluated samples of renal biopsy (RBx) form 117 patients with LN (34.0 y.o, 108 females) according to ISN/RPS classification. Tubulointerstitial involvement (TII) was also assessed. Treatment response at 2 years was evaluated by SLICC renal activity and response index score. [Results] Mean age of SLE onset was 25.0 years. The patients received RBx within 2 years, 2-5 years and more than 5 years was 47, 25 and 28%, respectively. Biopsy specimens included 18.8 glomeruli at average, though only less than 10 glomeruli were found in 7.6%. The RBx samples were classified into Class I/II/III/IV/V/VI (3/21/15/53/25/0). TII was found in 62 % of the samples. Corticosteroids (CS) and cyclophosphamide (CY) have been the first line agents as the induction therapy. Interestingly, the initial dose of CS was increased with higher frequency of pulse therapy against Class III and IV after 2004. Similarly, intravenous infusion with CY was more frequently used for Class III, IV and V after 2004 than before. Complete response rate was 41.9% and 36% in class III and IV, respectively. Unfavorable renal prognosis was associated with class III, IV in addition to TII.

P1-169

The association between the histological analysis in patients with lupus nephritis and the clinical parameters.

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Conflict of interest: None

[Objectives] Although it is important to evaluate the renal histology in the patients with lupus nephritis (LN) for adjusting the treatment, it is difficult to procedure the renal biopsy (RB) in some situations because of contraindications. Our aim is to predict the activity of LN from the clinical parameters. [Methods] Thirty-four cases of LN (27 females and 7 males) performed RB in our hospital were analyzed in the association between the activity of LN and clinical parameters. [Results] The mean age was 39 ±14.8 years. The number for each class of the ISN/RPS classification was as follows; Class II: 1 case ; Class III: 5 cases; Class IV-S: 9 cases; Class IV-G: 14 cases; Class V: 5 cases. Sixty percent of LN had extracapillary proliferation, necrosis and crescents that were reported to be histological predictors of poor renal outcome and had the association with active urinary cast (p= 0.007), urinary occult blood (p =0.068) and SLEDAI (p=0.025). The other active lesions such as intracapillary proliferation, hyaline thrombi, and wire loop didn't have association with any clinical parameters. In this study, the presence of active urinary cast and urinary occult blood are important to predict the active lesion related with poor renal outcome of LN.

P1-170

Urinary λ-Free Light Chain Concentration Is Associated with Disease Activity and Response to Treatment in Proliferative Lupus Nephritis

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Conflict of interest: None

[Objectives] To evaluate whether serum and urinary free light chain (FLC) is a useful biomarker for ISN/RPS classIII, IV lupus nephritis. [Methods] 43 SLE patients in whom renal biopsy was performed from 2004 to 2006 were enrolled. The evaluation of parameters included renal and immunological markers, SLEDAI and FLC. Clinical characteristics were compared between class III, IV and non-class III, IV. Serum and urinary FLC were measured before and after immunosuppressive treatment in 6 class III, IV nephritis patients. [Results] Anti-dsDNA Ab, urinary protein/creati-

nine ratio, SLEDAI, serum κ-FLC, urinary κ-FLC, and urinary λ-FLC were significantly higher in class III, IV. C3, Anti-dsDNA Ab, and urinary λ-FLC were correlated with SLEDAI (P = 0.02, <0.01, and 0.04, respectively). Correlation was not found between serum and urinary λ-FLC (P = 0.75). Urinary λ-FLC was significantly correlated with the urinary protein/creatinine ratio in class III, IV (P = 0.02). But no association was shown in non-class III, IV (P = 0.60). Serum and urinary FLC were significantly decreased after treatment in all patients, and urinary λ-FLC was not detected in any patient. The decline index in urinary λ-FLC was more significant compared with those in anti-dsDNA Ab (P<0.01).

P1-171

Clinical study of lupus nephritis (LN) in our hospital

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Conflict of interest: None

[Objectives] Systemic lupus nephritis(SLE) patients have a 50~60% incidence kidney disease. It is affected by prognosis of SLE. We have investigated the activity, laboratory data of the onset and recurrence time of LN. [Patients and methods] We investigated 27 patients (male4, female23) with LN who had diagnosed in our hospital, during March 2000 to October 2011, retrospectively. [Results] The average age was 33.7, SLEDAI was 3 to 43. All cases had received steroid therapy and 7cases had combined steroid pulse therapy. 7cases have had recurrence, and the average time to recurrence was 58.2 months. Kidney biopsy(KBx) was done 23 cases, each classes was as followed; II1, III6, IV9, III+V2, IV+V1 and V4. KBx classes of recurrence cases were III1, IV2, III+V1, IV+V1 and V1. Compared the group of class III or IV with class V, decline of complement, immune-complex(CIC) positive and high SLEDAI showed significant difference, although no difference for the therapy. The patients of recurrence showed significant low platelet counts and complement. We had confirmed no hemodialysis case, the death was 1 case on LN recurrence. [Conclusion] Our data indicated that low complement, CIC positive and high SLEDAI suggest class III or IV in pathologically, and low platelet count or complement may lead recurrence.

P1-172

Efficacy of induction therapy in combination with tacrolimus and mizoribine for steroid resistant lupus nephritis

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Conflict of interest: None

[Objective] We conducted this study to evaluate an efficacy of induction therapy in combination with tacrolimus(TAC) and mizoribine(MZB) for steroid-resistant lupus nephritis(LN). [Methods] Combination of TAC and MZB was used against 5 patients who did not response with steroid therapy alone. The 5 patients are all female. The 3 patients revealed the LN at the disease onset, the remaining 2 patients were recurrence. The dosage of TAC was adjusted according to the serum levels. MZB was administered at 150mg/day in all patients. [Results] After the therapy,4 patients revealed a significant improvement of proteinuria, serum albumin, and pitting edema. Among the 4 patients,2 patients achieved a remission state. Only 1 patient did not show the amelioration. Especially, one of patients who achieved the remission, had a LN with class V. Our case indicated that the therapy is effective even in LN with class V. In addition, the all patients exhibited an improvement of titer of anti-DNA antibody and level of complement. Side effects were not observed in all cases. [Conclusion] The present study indicated that the combination of TAC and MZB was effective and safety in LN treatment. This therapy was considered to be a possible alternative therapy of conventional IVCY therapy in treatment of LN.

P1-173

Mycophenolate mofetil versus intravenous cyclophosphamide for induction treatment of proliferative lupus nephritis in Japanese population: a retrospective study

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Conflict of interest: None

[Objectives] Recent studies showed Mycophenolate mofetil (MMF) was at least as effective as intravenous cyclophosphamide (IVC) for the treatment of lupus nephritis (LN), but treatment response may vary by location and race/ethnicity. In addition, no studies compared efficacy of MMF with of IVC in Japanese population. Therefore, we conducted retrospective study to clarify the efficacy and safety of MMF compared with IVC for the induction treatment of active classes III, IV and V LN in Japanese population. [Methods] Twelve and 11 patients received MMF (1.0-3.0 mg/day) and IVC (biweekly or monthly pulses of 0.2 to 1.0 g/m2), retrospectively. Primary endpoint is the proportion of responder defined as patients who met complete or partial response criteria. Secondary endpoints included renal activity component and serological activity. [Results] The primary endpoint was achieved in 10 (83.3%) patients receiving MMF, compared with 5 (45.5%) patients receiving IVC and no significant difference was found between treatment groups (p = 0.089). Secondary endpoints were not also significantly different. MMF group had significantly less frequent hematologic toxic effects than the IVC group. MMF may be an alternative to IVC in inducing renal remission of LN in Japanese population.

P1-174

Preliminary report of prospective, randomized control trial of maintenance therapy for lupus nephritis

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Conflict of interest: None

[Objectives] To evaluate the efficacy and adverse events in maintenance therapy prospectively for lupus nephritis. [Methods] 16 SLE patients who diagnosed of lupus nephritis (ISN/RPS class III and IV) from March 2009 to August 2011 were enrolled. All patients treated for nephritis for the first time and consented in writing. Patients randomized distributed across the three groups (MZB, TAC and AZA). Patients started induction therapy (oral PSL 1mg/kg/day and IVCY 0.4~0.5 g/m^2) and started oral immu-

nosuppressant agent when PSL was tapered to 0.6 mg/kg/day. We evaluated about the persistence rate and relapse rate prospectively. [Results] Pathology of kidney consisted of 8 patients with class III (50%) and 8 class IV (50%). Five patients were treated by MZB, 5 were by TAC, 6 were by AZA. No significant differences were observed in characteristics and clinical parameters at entry among three groups. Median values of follow-up period were 6 months (MZB), 12 months (TAC) and 12 months (AZA). All patient maintained remission and no flare during the observation period. 1 case in MZB (25%), 2 in TAC (50%) and 3 in AZA (50%) discontinued medication after starting maintenance therapy.

P1-175

Long-term outcome of Mizoribine, Tacrolimus and corticosteroids combination therapy for lupus nephritis

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Conflict of interest: None

[Objectives] The conventional cyclophosphamide-based treatment regimens for lupus nephritis (LN) are still not considered optimal treatments. The aim of this study is to evaluate long-term outcome of mizoribine (MZR), tacrolimus and corticosteroids combination therapy for LN. [Methods] We retrospectively evaluated a combination treatment of MZR and tacrolimus with corticosteroids for the induction therapy of 8 newly diagnosed SLE patients with LN. [Results] At baseline, the patients had a mean age of 48.5 years; all 8 patients were female, 8 (100%) had positive anti-double-strand DNA antibody titers, and 4 (50%) were nephrotic. The levels of daily proteinuria were 4.56 g. By month 12, 8 patients (100%) were in complete remission with normalized levels of both proteinuria and serum creatinine, and 5 (62.5%) were in microalbuminuria remission. Our study suggests that MZR and tacrolimus treatment with corticosteroids is well-tolerated and may prove to be an optimal remission-inducing regimen for LN.

P1-176

Multitarget therapy for remission induction of Lupus Nephritis (LN) in our hospital

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Conflict of interest: None

Multitarget therapy, predonisolon (PSL) + mycofenolate mofetil (MMF) + tacrolimus (TAC), is effective induction therapy for LN IV+V. Mizoribine (MZR) resembles to MMF pharmacologically. Therefore PSL + TAC + MZR is also reported its effectiveness in Japan. Five cases treated with PSL + TAC + MMF or MZR in our hospital, from September 2010. We report efficacy and safety of the each therapies. Three men and two women, 31.6±12.1 years old, developed LN for the first time. Urine protein/urine Cr ratio was 1.36±1.4 g/gCr, and anti-DNA-antibody titer was 94.7±65 IU/ml at the onset. Four cases underwent renal biopsy. According to ISN/RPS classification, one with IV+V, one with IV, two with III. Two were administered MMF, three were MZR. At 12 weeks (n=4), urine protein/urine Cr ratio was 0.13±0.14 g/gCr, anti-DNA-antibody titer was 6.9±6.7 IU/ml. Complements were normalized in all cases. TAC dosage was 3.20±0.64mg/day, MMF dosage was 1000mg/day, MZR dosages were 300mg alternative days in two cases, 450mg twice a week in one case. No one had significant adverse effects. Our data suggest efficacy and safety of multitarget therapy. MZR seems to be as effective as MMF, if its plasma concentration is sufficient.

P1-177

a case of elderly onset lupus nephritis, presenting renal failure and nephrotic syndrome

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Conflict of interest: None

[Objectives] We present a case of lupus nephritis presenting progressive renal failure and nephrotic syndrome by the progress for about six weeks. [Methods] The case is 73 year-old man who has a history of hypertension and angina pectoris. He has never been pointed out elevation of serum creatinine level or proteinuria before one year, but 6 weeks before admission he found malaise, anorexia, and generalized edema. He was referred to our hospital from his primary physician for increased serum creatinine and proteinuria. On admission, he has marked generalized edema, increased serum creatinine, nephrotic range proteinuria, hypocomplementemia, and positive antinuclear antibody and anti-DNA antibody. But he didn't have other symptoms such as photosensitivity, cytepenia, serositis, or skin rash. On 7th day, we performed renal biopsy, which showed proliferative glomerulonephritis with wire-loop like lesion. On the fluorescent staining, IgG, C3, and C1q were positive. So we diagnosed lupus nephritis. [Results] Lupus nephritis is known for secondary glomerulopathy which is common among young women. This case didn't have typical presentation for SLE. The case shows that when we see progressive renal failure or nephrotic syndrome, even if elderly, we must consider lupus nephritis.

P1-178

Lupus nephritis with positive MPO/PR3-ANCA developed after propylthiouracil therapy for 17 years

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Conflict of interest: None

A 51 years old man presented with thrombocytopenia and hyperthyroidism was refered to our hospital. The patient had Graves' disease and had been treated with propylthiouracil (PTU) for about 17 years. In August 2010, He was pointed out thrombocytopenia and PTU treatment had been discontinued. However, thrombocytopenia and hyperthyroidism was progressed, he admitted to our hospital. Laboratory examinations showed pancytopenia, high titer of ANA, positive MPO/PR3 ANCA, proteinuria and hematuria. We performed bone marrow puncture and there were no evidence of hemophagocytic syndrome. Renal biopsy showed Lupus nephritis (Class II) and acute tubular necrosis, and we finally diagnosed ANCA-positive Lupus nepritis. He was effectively treated with plasmapheresis combined with a puls of cyclophosphamide (i.v.), 3 pulses of methylprednisolone (i.v.) and IVIg therapy. After 3 months, thrombocytopenia and proteinuria were improved, and MPO/PR3 ANCA titer was markedly reduced. We report this rare case of Lupus nephritis with positive MPO/PR3-ANCA developed

after propylthiouracil therapy for 18 years. Clinicians should comfirm Anti-DNA-Ab and MPO/PR3-ANCA titer in PTU-treated patients at fixed intervals.

P1-179

Globally enlarged glomerular capillaries in a patient with thrombotic microangiopathy and systemic lupus erythematosus

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Conflict of interest: None

A 40 year-old woman was admitted to our hospital for restlessness and rapidly progressive kidney injury. She had headache, fever, and painful palmer erythema 2 weeks prior to admission. She had an episode of Grave's diease without requirement of treatment at age 14. Laboratory findings showed thrombocytopenia (6.3×10^4 /μl) and serum creatinine level of 2.4 mg/dl. Serologic evaluation showed positive antinuclear antibody, anti-double stranded DNA antibody, IgG anti-cardiolipin antibody, and elevated lupus anticoagulant. Magnetic resonance imaging of the brain showed lacunar infarctions. She was diagnosed as systemic lupus erythematosus (SLE) with secondary antiphospholipid syndrome (APS). Although pulse methylpredonisolone and anticoagulation was started, platelet progressively decreased. Because development of thrombotic thrombocytopenic purpura (TTP) was suspected, plasma exchange was initiated with improvement of general condition. Renal biopsy revealed some glomeruli exhibited segmental endocapillary proliferation and other glomeruli had cellular crescents. Furthermore a glomerulus exhibited its capillary globally enlarged and the arteriole near the glomeruli showed luminal obliteration by thrombi.

P1-180

Radiographic outcome of DMARDs-treated RA patients in daily practice: A large-scale prospective longitudinal cohort study (the 1st report of Apple Survey)

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Conflict of interest: None

[Objective] In 20 related-centers of the Nagasaki University and Tohoku University we are conducting a large-scale prospective study (Apple Survey) to investigate extent of radiographic progression. We have tried to assess the extent of rapid radiographic progression (RRP) defined as mTSS >3.0 in synthetic DMARDs-treated RA patients. [Patients and Methods] Ninety-three out of the 579 patients registered between May 09 and Jul 11 had evaluable data for 1 year. DAS28-CRP was assessed every 3 months. Radiographs of the hands and feet were taken every 6 months. The images were scored by trained readers. Based on the DAS28-CRP at 6 months, patients were stratified into two groups; remission/low (L) or moderate (M)/high (H) for the assessment of ΔmTSS at1 year. [Results] Mean age was 61.6±11.9 yrs at baseline. At 6 months, sixty-six patients attained remission or LDAS, while 27 remained at MDAS or HDAS. RRP occurred in 8 out of the total 93 patients; 2/66 in remission/LDAS (3%) and 6/27 in MDAS/HDAS (22.2%). When compared to patients in remission or LDAS, significantly more patients exhibited RRP in MDAS or HDAS ($p<0.01$). [Conclusions] Our data have suggested that radiographic progression in patients with RA in daily practice is associated with the time-integrated disease activity.

P1-181

Survey on continuation rates of biologics in Akita cohort

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Conflict of interest: None

[Objectives] We assessed continuation rates of biologics, reasons for discontinuation and switching, and adverse events in rheumatoid arthritis (RA) patients in Akita. [Methods] Biographical data on RA patients treated by 30 physicians at 25 institutions affiliated with Akita Orthopedic Group on RA were registered. Continuation rates of biologics (1st-BIO; 2nd-BIO), reasons for discontinuation and switching, and adverse events were assessed. [Results] Of 1,533 RA patients registered, 301 were men and 1,232 women. 1st-BIOs were used by 321 (21%), 60 men and 261 women. The 24-month continuation rates were 65% for infliximab (IFX: 114 patients), 79% for etanercept (ETN: 162), 71% for adalimumab (ADA: 21), and 96% for tocilizumab (TCZ: 24). The reason for discontinuation and switching was reduced effects in 41 patients. Adverse events were interstitial pneumonitis in 4 patients, malignant tumor in 4. Of 321 patients using 1st-BIO, 67 (21%), 18 men and 49 (73%) women, switched to 2nd-BIO. The 12-month continuation rates were 100% for IFX (3 patients), 73% for ETN (22), 86% for ADA (8), and 79% for TCZ (18). Discontinuation was due to reduced effects in 4 patients. Adverse events were malignant tumors in 2 patients.

P1-182

Orthopedic surgery for RA in NinJa report 2010

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Conflict of interest: None

Aim Analyze/report RA-related orthopedic surgeries performed in '10 using NinJa. **Method** Presence or absence, type, frequency, etc. of surgeries examined in 7254 patients registered in '10(♀5921, ♂1333) & compared with '03 to '09. **Results/Discussion** Of 7254 patients in '10, 304 patients/352events (4.2%/4.9%) underwent RA surgeries. The number of RA surgery cases in '03,

'04, '05, '06, '07, '08 and '09 was 8.5%, 7.3%, 7.2%, 7.1%, 6.4%, 4.7% and 4.9% respectively: a decrease. In '10, RA surgeries to total patient number ratios were (per type) 2.5% (artificial joint), 0.3% (synovectomy), 1.03% (arthroplasty), 0.4% (arthrodesis) & 0.1% (tendon repair). Medication: 58%, 19% and 11% of patients received total MTXs, total biologicals & total immunosuppressants, respectively: an increase. The number of surgery cases was influenced by an increase in the development of new drugs to decrease. Follow up planned.

P1-183

Medical cost in patients with rheumatic disease: a consideration of subsidy for the intractable disease.

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Conflict of interest: None

[Objective] To estimate and compare the direct and indirect costs of illness in rheumatic disease. [Method] Our study included 727 patients with rheumatoid arthritis: RA (n=360), systemic lupus erythematosus: SLE (n=112), systemic scleroderma: SSc (n=60), Sjögren syndrome: SjS (n=36), polymyositis / dermatomyositis: PM/DM (n=28), polymyalgia rheumatic: PMR (n=27), mixed connective tissue disease: MCTD (n=22), vasculitis syndrome (n=22), Behçet's disease (n=16), and other connective tissue disease (n=44) who visited our department in November and December 2009. The blineded questionnaires were collected from the patients. [Result] Mean direct medical cost in all patients were 15,900 JPY/month. Mean direct medical cost were the highest 21,000 JPY/month in RA patients compared with those of other disease ($P<0.05$). It is suggested that these differences were caused by use of biological agents in RA and medical subsidy in other disease. Next, we investigated 234 patients received medical subsidy for the intractable diseases. Thirty two patients paid medical cost more than a burden limit (11,500 JPY/month). The visit number to the hospital and/or department were increased in thse 32 patients. [Conclusion] Medical subsidy for RA and some of other rheumatic disease should be considered.

P1-184

Death analysis of 144 rheumatoid arthritis patients at our institute for these 24 years

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Conflict of interest: None

[Objectives] To investigate life expectancy in RA patients, reviewing records for 144 patients who died over the past 24 years. [Methods] Of all RA 899 patient cases at our institute, we enrolled 144 cases who have died over the past 24 years, and divided them into two groups by median. We estimated gender, age, RA duration and causes of death. [Results] The averages of 73 patients of former group (before 2003) and that of 71 patients of latter group (after 2003) were follows. Male ratio were 23.6%, 36.6%, age at death 72.0±10.5 years old, 77.0±9.01 years old, RA duration (from RA onset to death) 15.7±10.9 years, 20.7±12.7 years, and death of infections rate 24.7%, 39.4%. The latter group was significantly higher than the former group in them. In 2003 when divided by median into two groups, IFX, which is the first biologics for RA in Japan, was approved in July. Because RA durations to the death and the age at death of the RA patient were equally prolonged for five years after 2003 compared to before 2003, we can say that life expectancies of RA patients from onset of RA might be improved by progress of the RA medical treatment like biologics agents. However, the first cause of death was infection in both groups and all causes of three cases of ETN were infections.

P1-185

Measuring quality of care in rheumatoid arthritis using American College of Rheumatology quality indicators

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Conflict of interest: None

[Objectives] To measure the percentage of Quality Indicators (QIs) met in patients with rheumatoid arthritis (RA) in out-patient clinic, and to evaluate the association between QIs and the hospital and clinic cooperation (HACC). [Methods] American College of Rheumatology (ACR) QIs, 7 measures for Rheumatoid Arthritisand 6 for Drug Safety (DS), were applied to 98 RA patients with the first visits from April 2008 to March 2010, who attended regularly for one year or more. Further we analyzed the association of QIs and HACC. [Results] The percentage met for QIs was 100% in 8 measures, however, it was low in periodic assessment of disease activity (26.5%), functional status assessment (44.9%), DS: informing patients about risks (0%), DS: prophylaxis for patients about risk for gastrointestinal (GI) bleeding (53.7%), MTX baseline/follow-up monitoring (92.5%/97.1%), Glucocorticoid (GC) baseline monitoring (53.7%). The enrollment of the RA patients into HACC was independently and negatively associated with the prophylaxis for GI and GC baseline monitoring, adjusted for the confounding factors such as age, sex, duration of disease, disease activity at first visit, and biologicals usage.

P1-186

Change of RA activity during the year

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Conflict of interest: None

[Objectives] Change of RA activity during the year was assessed. [Methods] This study consisted of 348 patients with RA including 140 patients treated with biologics. The average age was 62.1 years old and the average period of RA was 10.8 years. Since September 1st 2009 to August 31st 2011, all parameters for RA activity were assessed in total 3811 cases including 2174 cases treated with biologics. The results were compared among the months. [Results] In all cases, the average CRP value was 0.65mg/dl since October to December and was 0.53mg/dl since July to September. The difference was statistically significant. In cases with biologics, the average CRP value was 0.67mg/dl since October to December and was 0.50mg/dl since January to March. The difference was statistically significant. The CRP value of 0.70mg/dl since April to June was also significantly higher than that since January to March. No significant difference was found among other parameters. However, ESR and MMP-3 values were also higher since October to December and since April to May. CRP was significantly higher in autumn to early winter and in spring even in the patients treated with biologics. It is clear that the change of season influ-

enced the RA activity.

P1-187

Clinical study of organizing pneumonia associated with rheumatoid arthritis

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Conflict of interest: None

[Objectives] Clinical features of organizing pneumonia (OP) associated with rheumatoid arthritis (RA) were examined. [Methods] We investigated 17 cases of OP in 578 RA patients who were admitted to our department from January 2001 to August 2011. [Results] Five males and 12 females, whose average age was 63.3 years old, were diagnosed with OP based on histological examination and/or radiological and clinical findings. Out of the 17 cases, 4 showed the simultaneous onset of RA and OP. When OP developed, an antirheumatic drug was used in 12 cases: MTX monotherapy in 3 cases, combination with MTX and biologics in 5 cases (four Infliximab and one Tocilizumab), combination with MTX and Bucillamine in 2 cases, combination with MTX and Tacrolimus in one case, and Bucillamine monotherapy in one case. One case resolved spontaneously, and the other 16 cases were administrated corticosteroid. All cases of OP resolved, but three cases relapsed later. [Conclusions] Since OP developed without medication, it was suggested that medication played no role in the development of OP associated with RA.

P1-188

A case of successful treatment of rapidly progressive interstitial pneumonia in an amyopathic dermatomyositis patient with multiple immunosuppressive treatment and high-dose of intravenous immune globulin infusions (IVIG)

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Conflict of interest: None

We report a 49 year-old woman who was treated successfully with multiple immunosuppressive treatment and IVIG because of rapidly progressive interstitial pneumonia in a clinically amyopathic dermatomyositis (CADM) patient. Her erythema was appeared in the circumference of her both eyes and the administration of prednisolone (PSL) of 10mg/day was started. However, her erythema spread around her both hands and cervical lesion. Although she had no muscle weakness, myalgia and abnormal creatine kinase levels, she had Gottron's papule, heliotrope rash and interstitial pneumonia. Therefore she was diagnosed as having CADM. She was treated with high-dose of methylPSL (1g/day intravenously for 3 days) followed by oral PSL (60mg/day), and added CyA simultaneously. But interstitial pneumonia and her respiratory failure were rapidly exacerbated. High-dose of methylPSL, CyA, intravenous cyclophosphamide (IVCY) and IVIG (400mg/kg/day for 5 days) were administered repeatedly. Her respiratory failure and her chest radiography were gradually improved, and the dose of PSL was decreased. It is known that the patients in CADM with interstitial lung disease (ILD) have poor prognoses in spite of various treatments. Our case might provide useful treatment of the patients with CADM-ILD.

P1-189

Clinical features of Systemic Sclerosis (SSc) patients associated with interstitial pneumonia (IP) of our institute

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Conflict of interest: None

[Background] We aim to know autoantibodies and treatment of SSc patients with IP. [Methods] On October 31, 2011, we reviewed clinical data of SSc patients with IP of our institute including complications, autoantibodies and treatment. [Results] Total SSc patients with IP were 110 with 15 males. Among them, patients complicated with other collagen vascular diseases were 23. Autoantibodies of SSc patients with IP were as follows. 20 patients were anti-topoisomerase antibody positive, 20 anti-centromere antibody, 30 anti-RNP antibody, 33 anti-nuclear antibody with nucleolar pattern. Patients received anti-IP therapy were 41. Among them, 37 patients were prescribed corticosteroids. 24 patients azathioprine. 6 patients cyclosporine. 5 patients tacrolimus. [Conclusions] There were no predominant autoantibody of our SSc patients with IP. Our favorite treatment of SSc patients with IP were azathioprine with corticosteroids.

P1-190

Exacerbation of interstitial lung disease (ILD) in patients with pre-existing ILD treated with biologics

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Conflict of interest: None

One of the problems on using biologics (BIO) is development/exacerbation of interstitial lung disease (ILD). According to the PMS, the incidence of development/exacerbation of ILD was 0.5 %, while our data was 4 %. We thought the reason of the difference to be high incidence of pre-existing ILD in our patients. We aimed to know the incidence of exacerbation of ILD in RA patients with pre-existing ILD treated with BIO including TCZ. Subjects were 53 patients with RA (male/female = 24/29) with mean age of 67 years (range 44-84). The numbers of patients treated with ETN, IFX, ADA and TCZ were 36, 9, 2 and 6, respectively. Only patients observed for 12 months were analyzed with the exception that patients who discontinued BIO because of ILD exacerbation were included. Exacerbation of ILD was recognized in 13 (24.5 %) patients; the BIOs used were ETN in 7, IFX in 5, ADA in 1, and TCZ in 0, respectively. There was no difference in the incidence of ILD exacerbation between TNF-blockers and TCZ, however IFX induced ILD exacerbation more frequently than TCZ (56 % vs. 0 %, $p < 0.05$). In conclusion, although the number of patients should be added, TCZ may induce ILD exacerbation less frequently.

P1-191

Exacerbation of interstitial lung disease with RA caused by streptococcus pneumoniae infection

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Conflict of interest: Yes

Seventy one year-old male has been diagnosed as rheumatoid arthritis (RA) because of morning stiffness, joint swelling and tender in Nov, 2008. He was also pointed out interstitial lung disease (ILD) related with RA and prescribed daily 5mg of prednisolone and daily 1000mg of salazosulfapyridine. He developed cough and sputum in Oct 2010, and was admitted to our hospital Dec 2010. Laboratory data showed WBC14,100/μl, CRP10.14mg/dl, ESR80mm/hr, SP-D183ng/ml and KL-6 1120U/ml. Chest CT examination revealed honey-comb, traction bronchiectasis and ground glass opacity in lung fields. Streptococcus pneumoniae was identified in bacterial culture from sputum. Administration of antibiotics was started, although ground glass opacity in chest CT was getting worse immediately. Exacerbation of ILD may be one of the most critical problems during the management of ILD with RA. In this case, Streptococcus pneumoniae infection was the leading cause of exacerbation of ILD, suggesting the critical significance of infection control in management of ILD with RA. As for serum markers of ILD, SP-D and KL-6 simultaneously changed during the clinical course of this case.

P1-192

The utility of Ga scintigraphy in evaluation of the activity of interstitial pneumonia in rheumatoid arthritis

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Conflict of interest: None

[Objective] To clarify the characteristics of Ga scintigraphy to interstitial pneumonia(IP) in patients with rheumatoid arthritis(RA). [Patients and Methods] Ga scintigraphy was performed between March 2008 and August 2011 in 24 RA patients with IP, and we evaluated the findings of Ga scintigraphy to lung fields, background of patients, hematological examination, the pattern of IP by Computed Tomography(CT), treatment to IP, and the outcome retrospectively. [Result] Eleven patients showed accumulation of Ga in the lung fields(Ga+ group), and 13 patients showed no accumulatin(Ga-group). There was no significant difference of background of patients, hematological examination, the pattern of IP by CT. But the disease duration of RA in Ga+ group was shorter than that in Ga- group (average 4.7 vs 14.0 years). In Ga+ group 4 patients died of IP, and in Ga- group, 3 patients died, one died of IP, two of other diseases. Patients in Ga+ group were treated with corticosteroid and immunosuppressive drug include of cyclophosphamide. On the other hand, no immunosuppressive drugs were administerated in Ga- group. [Conclusion] It was suggested that a possible benefit of Ga scintigraphy to evaluate of the activity of IP getting worse rapidly.

P1-193

The clinical effects of Tacrolimus for the patients with interstitial lungdisease associated with connective tissue diseases

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Conflict of interest: None

[Background] Interstitial lung disease is a serious complication in patients with connective tissue diseases. Activated T lymphocytes may contribute to the pathogenesis of interstitial lung disease associated with connective tissue diseases (ILD-CTD) due to the increase in lymphocyte number in the BALF obtained from patients with ILD-CTD. Therefore, we have employed tacrolimus, a potent T cell inhibitor, for the treatment for ILD-CTD and evaluated the efficacy and safety of it. [Methods] ANCA-associated vasculitis (n=2) and PM/DM (n=4) patients were enrolled. Combined prednisolone (PSL) and tacrolimus therapy was initiated. HRCT and pulmonary functional test were performed and serum KL-6 was measured for the evaluation of its clinical effects. [Results] The early administration of tacrolimus in combination with PSL prevented ILD exacerbation and contributed to taper the PSL dosage. Tacrolimus was well-tolerated in all patients without any adverse effects including an opportunistic infection under monitoring of the blood levels of this immunosuppressant. Further experiences and clinical studies are required to evaluate the long-term efficacy and safety of it in ILD-CTD patients.

P1-194

The changes in expression levels of ADAMTS-4 and ADAMTS-5 in response to connective tissue growth factor treatment in fibroblast-like synoviocytes from rheumatoid arthritis patients.

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Conflict of interest: None

[Objectives] The aim of this study is to clarify the effect of connective tissue growth factor (CTGF) on the expression levels of the ADAMTS-4 and ADAMTS-5 in rheumatoid arthritis (RA) fibroblast-like synoviocytes (FLS). [Methods] FLS were prepared from the synovial tissues of RA patients, who had undergone total knee replacement surgery. The amount of ADAMTS-4 and ADAMTS-5 mRNA in FLS treated with CTGF at various doses and times were quantified using real-time PCR. [Results] ADAMTS-4 was increased by CTGF, while ADAMTS-5 was not. The peak time of expression of ADAMTS-4 mRNA was 4 h after stimulation with FLS. [Conclusions] Our data suggests that CTGF increases the expression of ADAMTS-4, one of the most efficient enzymes of aggrecan degradation in synovial tissues of RA patients.

P1-195

Potential of cartilage repair by human autologous synovial fluid cells of 26 patients with osteoarthritis knee

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Conflict of interest: None

【Objective】 To investigate the possibility of chondrogenic differentiation and cartilage repair of synovial fluid cells of osteoarthritis (OA) knee. 【Methods】 Synovial fluids from 26 patients with OA knee were aspirated from each knee joint and cultured *in vitro*. The morphology of cultured synovial fluid cells, cell proliferation rate, the phenotype, and chondrogenic differentiation were analyzed in *in vitro*. Also, human autologous synovial fluid cells were transplanted to OA cartilage, and the cells were traced in *ex vivo*. 【Results】 In 19 of 26 materials, the cells proliferated satisfactorily. The cell proliferation in six materials was very slow and one material contaminated. Culture-expanded synovial fluid cells had a fibroblastic morphology and the phenotype was negative for CD10, CD14, and CD45, and positive for CD13, CD44, and CD105. Pel-

let culture of synovial fluid cells showed chondrogenic differentiation. In the *ex vivo* study, autologous transplanted synovial fluid cells were observed in repaired or enhanced regenerative cartilage areas and showed a tendency to infiltrate the original degenerative cartilage of OA.

P1-196

Do RA biologics inhibit human osteoclast formation and bone resorption directly?A preliminary report

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Conflict of interest: None

[Objectives] In this study, we sought to clarify whether biologics (Bio) have direct effect on human monocyte-osteoclast differentiation and resorption pit formation *in vitro*. [Methods] Monocytes were cultured with RANKL and M-CSF on cover slips and dentine slices. Infliximab, adalimumab, etarnercept, tocilizumab, and abatacept, were added to culture medium, respectively. 14 and 21 days cultures were assessed for cytochemical and functional evidence of osteoclast differentiation. [Results] After 14 days incubation, numerous TRAP+ multinucleated giant cells were seen in control culture. TRAP+ multinucleated cells were also seen in the culture with added Bio, and significant difference was not found. After 21 days incubation, resorption pit on dentine slices were seen. Addition of Bio did not make any differences on resorption pit formation. [Conclusion] All Bio did not show direct effect on human osteoclast formation in this study. This result suggests that in the presence of enough RANKL and M-CSF, Bio do not inhibit bone resorption. It is known that some cytokines stimulate osteoclast formation. Thus, extinguishment of inflammation and decreasing of proinflammatory cytokines caused by Bio may result in inhibition of osteoclast formation and bone resorption in RA.

P1-197

Clinical Features of Pseudogout: Chart Review of 180 Cases

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Conflict of interest: None

[Objectives] To study the clinical features of pseudogout [Methods] Retrospective chart review of the patients (pts) with pseudogout from Jan 2006 to Apr 2010 was performed. We included pts with positive calcium pyrophosphate (CPP) and co-existing monosodium urate (MSU) crystals or bacteria in synovial fluid (SF). [Results] We enrolled 180 pts with positive CPP crystals. Six pts with septic arthritis and 9 pts positive both with MSU and CPP crystals were found. Of 174 pts without septic arthritis, 65.9% were female and the mean age was 80.5 years. 78.8% had monoarthritis. The involved joints were the knee (87.9%), ankle (14.9%), followed by shoulder, elbow, wrist, hand and foot. Fever was seen in 42%. Preceding events included infection (14.9%), cerebrovascular accident (11.5%) and surgery (10.9%). The mean value of laboratory tests were; WBC 9,217/μl, CRP 10.9mg/dl, SF WBC 6,057/μl and SF neutrophil 52.5%. Hypomagnesemia and hypophosphatemia were seen. We found chondrocalcinosis in knee (89.6%), wrist (51.4%), pubic symphysis (40.5%), hip (35.1%) and periodontoid space (61.9%). As treatment, NSAIDs and intraarticular corticosteroids were used the most. 92.5% achieved remission by 1 month. Maintenance therapy was needed in 10.3% and 19.5% had recurrent attacks during the period.

P1-198

IL-6 negatively regulates osteoblast differentiation through ERK pathway *in vitro*

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Conflict of interest: None

[Objectives] Since RA patients treated with anti-IL-6 R Ab show increase of serum P1NP, a bone formation marker, IL-6 is thought to have negative effect on osteoblast differentiation. However, previous reports regarding the effects of IL-6 on the differentiation *in vitro* are not consistent. The purpose of this study was to clarify the effect of IL-6 on the differentiation *in vitro*, with consideration of signal pathways. [Methods] The differentiation was induced in MC3T3-E1 cells with or without addition of IL-6 and soluble IL-6 R. The differentiation was assessed by ALP activity, mineralization and expression of Runx2 and osteocalcin(OC). We examined which signal pathways were activated by IL-6 and their effects on the differentiation were assessed by using each specific inhibitor. [Results] IL-6 significantly reduced ALP activity and mineralization, and expression of Runx2 and OC, which indicates negative effect on the differentiation. IL-6 activated ERK and STAT3. The negative effect on ALP activity was restored by inhibition of ERK. On the other hand, the negative effect was enhanced by inhibition of STAT3. These results indicate ERK has negative effect, whereas STAT3 has positive one. Predominant activation of ERK signal compared to STAT3 signal may result in inhibiting osteoblast differentiation.

P1-199

Effects of BMP-3b on BMP-induced osteoblast differentiation

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Conflict of interest: None

[Objective] Involvement of BMP-3b/GDF-10 in the physiological process of osteogenesis, embryogenesis and adipogenesis has been reported. However, details of functional receptors and intracellular signaling of BMP-3b have yet to be elucidated. Here we investigated biological role and cellular mechanism of BMP-3b in osteoblast differentiation. [Methods] C2C12 cells were treated with BMP-3b in combination with BMP-2, -4, -6 and -7. Real-time PCR, Western immunoblot analysis and promoter assay were performed. [Results] BMP-3b stimulated activin/TGF-responsive promoter activities, Smad2/3 phosphorylation and activin/TGF target gene PAI-1 mRNA expression. These actions of BMP-3b were suppressed by co-treatment with BMP-2. BMP-3b suppressed the expression of BMP-induced osteoblastic markers and BMP-2-induced Smad1/5/8 phosphorylation. Reciprocal antagonism between BMP-3b and BMP-2 was not observed in cells overexpressing Smad4. BMP-3b-induced PAI-1 expression was suppressed by ALK-4/ActIIA receptor inhibition. [Conclusion] BMP-3b plays an inhibitory role in the process of osteoblast differentiation through activating Smad2/3 via ALK-4/ActRII, in which BMP-3b and BMP-2 are mutually antagonistic possibly by competing Smad4

availability.

P1-200

Blockade of IL-20 suppressed ovariectomy-induced bone loss

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Conflict of interest: Yes

[Objectives] IL-20 is a member of IL-10 family of cytokine. It is expressed in monocytes, epithelial cells and endothelial cell. It has been reported that IL-20 is involved in the pathogenesis of psoriasis, rheumatoid arthritis and athelosclerosis. It was reported that blockade of IL-20 reduced the severity of arthritis and prevented bone loss in murine arthritis model. However, mechanisms to control bone metabolism by IL-20 has not yet fully understood. In this study we investigated the effects of anti IL-20 antibody on ovariectomy-induced osteoporosis model. [Methods] Twelve-week old female mice were subjected to ovariectomy to induce bone loss. Anti IL-20 antibody or control antibody was administered weekly for 4 weeks. Three dimensional micro CT analysis of the distal femora was conducted to analyze bone volume/tissue volume (BV/TV) and trabecular number (Tb.N). [Results] Three-dimensional micro CT analysis revealed that treatment of anti IL-20 antibody suppressed ovariectomy induced reduction of BV/TV and Tb.N. These results indicate that IL-20 is involved in the regulation of bone mass. IL-20 could be the new therapeutic target of osteoporosis. This work is a collaborative study with Novo Nordisk.

P1-201

Determination of Procollagen I N-Terminal peptide and Osteopontin in postmenopausal women with vertebral osteoporotic fractures

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Conflict of interest: Yes

[Objectives] To evaluate the levels of procollagen I N terminal peptide(P1NP) and osteopontin(OPN) in postmenopausal women with vertebral osteoporotic fractures and its role in the osteoporosis. [Methods] 80 postmenopausal women were included in this study with age range50-77years. Subjects were divided in to two groups: group A:44 of them were women with vertebral fractures and group B: 36 of them without vertebral fracture (serve as controls). Lateral X- ray of the thoracic & lumber spine were taken for all women of both groups. All women in group A were diagnosed as osteoporosis with DXA(GE/lunar DPX-NT13.6). [Results] Serum P1NP levels of 44 patients were in the upper limit of normal values which range from 48.8 to 63.6 ng/ml, whiles all the control group levels in the lower limit which range from 34.5 to 48.9 ng/ml. Serum OPN levels of both groups were increased more than normal values (<14.7ng/ml), the range of group A was between 17.6 to 38.4 ng/ml (mean 25.17±5.41 ng/ml), while the range of group B was between 14.9 to 17 ng/ml (mean 15.9±0.65 ng/ml) Serum P1NP and OPN levels in the postmenopausal women with vertebral osteoporotic fractures were significantly higher than control group(P=0.001).

P1-202

The effects of teriparatide against osteoporosis in rheumatoid arthritis patients

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Conflict of interest: None

Background: Since 2010, teriparatide, a bone formation stimulator, has been available in Japan. However, there are few reports about the effects of teriparatide in RA patients. Aim and Methods: We investigated the following effects of teriparatide: tolerance, dynamics of serum bone formation markers, Activities of Daily Living (ADL), and bone strength. We collected data from 26 RA patients who started taking teriparatide. Their mean age and duration of RA was 74±9.5 years old and 23±13 years, respectively. Results: The 6 months adherence was 96%. One case stopped treated due to facial flushing. After 6 months of treatment, the means of the intact P1NP, ucOC and bone mineral density were elevated by 127%, 239% and 3%. The bone mineral densities of the femoral neck decreased in 70% of the cases, however, a DXA-based hip structural analysis revealed an enlargement of the cortex thickness in some cases. 64% and 56% of cases had improvements in their modified Health Assessment Questionnaire and Visual Analogue Pain Scale after 2 months of treatment. Conclusions: The characteristics of teriparatide in RA patients were good tolerance, elevation of lumbar bone mineral density and improvement of the ADL. The agent is therefore thought to be useful to treat osteoporosis in RA patients.

P1-203

Impediment at the outset of the treatment with daily self - injection of teriparatide

Kazumasa Kimura, Kunihiko Konishi, Tetsuya Torii
Kyohritsu General Hospital

Conflict of interest: None

[Objectives] We evaluated the impediment at the treatment with daily self - injection of teriparatide. [Methods] I recommended daily self - injection of teriparatide as an additional therapy to patients who have a contraindication to or are intolerant of alendronate and risedronate, or who have had an unsatisfactory response to treatment with alendronate, or risedronate and who are 65 years or older and have a T - score of – 4.0 SD or below, or a T - score of – 3.5 SD or below plus more than two fractures, or who are aged 55 – 64 years and have a T – score of – 4 SD or below plus more than two fractures. In addition, interviews were conducted directed to patients who did not consent to the treatment. [Results] The greatest obstacle faced at the outset of the treatment were most of them do not consent as they have fear of self - puncture with a needle or they have no confidence and insecurity for medical procedure.

P1-204

The effects of teriparatide on bone mineral density and ucOC in postmenopausal women with osteoporosis previously treated with bisphosphonates

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Conflict of interest: None

[Objectives] We evaluated the effects of teriparatide on bone mineral density and ucOC in postmenopausal women with osteoporosis previously treated with bisphosphonates. [Methods] A total of 13 postmenopausal women with low bone mineral density at the hip or spine (a T score of less than – 4.0, or a T score of less than – 3.5 with an additional risk factor for osteoporosis), 63 – 88 years of age (77.6 ±6.92), who had previously received either bisphosphonates therapy for 7 – 100 months (40.3 ±29.6), were assigned to daily treatment with teriparatide, and were followed for 5 months. [Results] With teriparatide, ucOC (ng /ml) increased from baseline (2.10 ± 0.88) at 5 month (13.7 ± 5.93) significantly ($P < 0.001$). BMD was not increased from baseline (0.527 ±0.078) at 5 month (0.553 ±0.103) with teriparatide treatment ($P = 0.059$). The results suggest that serum ucOC levels are affected by anabolic effects of teriparatide, and the need for review of requirement for vitamin K and standard level in ucOC of postmenopausal women who are treated with teriparatide.

P1-205

Combination therapy with bisphosphonates and statin in rheumatoid arthritis patients during an 18 month follow-up: Effects on bone mineral density and bone metabolism

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Conflict of interest: None

[Objectives] To investigate the effects of a combination therapy with bisphosphonates (Bis) and statin on the BMD and bone metabolism of rheumatoid arthritis (RA) patients. [Methods] Seventy-seven RA patients receiving prednisolone and Bis for over 4 years were divided into 2 groups: Bis and Bis+statin (n=42 and35; average age, 66.4 and 65.3 years, respectively). During an 18 month treatment and follow-up, we measured the serum levels of NTx, TRACP-5b, PICP, and RANKL. BMD levels of the 2 groups at the radius, lumber spine, and femoral neck were compared using DXA. [Results] A significant decrease in BMD of the radius was observed in the Bis group, but in the Bis+statin group, BMD was maintained at the basal line. A significant increase in BMD of the lumbar spine was observed in the Bis+statin group. A significant decrease in serum NTx was obsereved at 18 months in the Bis group, but serum NTx was up-regulated after 6 months in the Bis+statin group. Serum PICP tended to decrease after 6 months in the Bis group. [Conclusion] Bone remodeling was maintained in the Bis+statin group, because osteogenesis was up-regulated with the up-regulation of bone resorption. These results indicate that the combination with statin is preferred to Bis alone in osteogenesis or bone formation.

P1-206

Fracture Assessment Tool (FRAX) does not improve persistence with bisphosphonate therapy

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Conflict of interest: None

[Objectives] The effectiveness of bisphosphonate is compromised by poor persistence to treatment. FRAX was developed to identify persons at high risk of bone fracture requiring medical intervention by calculation of individual 10-year probability (%) of fracture. Our objective was to determine the effect of reporting FRAX results and treatment recommendations on persistence with bisphosphonate therapy. **[Methods]** Patients were randomized to receive either FRAX results and treatment recommendations (FRAX group) or only treatment recommendations (control group). All patients were complicated with rheumatic disease and newly prescribed with bisphosphonate. **[Results]** Eighty-two patients were included in FRAX group, and sixty-eight patients were in control group. The persistence at 1-year was high and not different between the two groups (88.6% in FRAX and 87.8% in control, $P=0.567$). In FRAX group, there was no difference on 1-year persistence between high ten year probability of major osteoporotic fracture (≧30%, 11 patients) and low probability (<30%, 71patients) (100% versus 86.9%, $P=0.126$). **[Conclusion]** This study failed to demonstrate that reporting FRAX results and treatment recommendations could improve persistence with bisphosphonate therapy in rheumatic disease patients.

P1-207

The frequency of severely suppressed bone turnover detected in X-ray (SSBT-Xp) among patients with rheumatic diseases using bisphosphonates

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Conflict of interest: None

[Objectives] To clarify the incidence of severely suppressed bone turnover in X-ray(SSBT-Xp) among patients with rheumatic diseases(RD) treated under bisphosphonates(BP). [Methods] Ninety-six patients with RD taking BP were included. The mean age was 55.6 years old(19-84), 87(90.6%) were females, the mean disease duration was 13.8 years(1.2-43.7) and all of them were taking prednisolone(PSL); the mean dose was 9.8mg daily(0.5-25). The mean duration of BP usage was 5.0 years(0.5-12). The X-ray of hips and femurs were examined and those who beaking was detected in cortices were defined as SSBT-Xp. [Results] SSBT-Xp was detected in 17 patients, 24 femurs(17.7%); 11 in lateral cortex(7 in subtrochanteric, 3 in diaphysis, and 1 in supracondylar) and 15 in medial cortex(14 in subtrochanteric, 1 in diaphysis), bilateral SSBT-Xp was observed in 7 patients(41%), prodromal pain was detected in 2 patients(1%). All cases were treated with alendronate. The mean age, duration of BP therapy, PSL dose and duration of PSL usage of SSBT-Xp showed no significant difference compared to those of SSBT-Xp-negative patients. [Conclusion] The incidence of SSBT-Xp in patients with RD under BP treatment has been little reported so our study is significant to clarify risk factors and prevention for SSBT.

P1-208

Subchondral insufficiency fracture of the femoral head in males

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Conflict of interest: None

INTRODUCTION: Subchondral insufficiency fracture of the femoral head (SIF) is a recently proposed concept, which has been reported to be observed mainly in the elderly osteoporotic females. The purpose of this study is to document the clinical characteristics of SIF in male. MATERIALS AND METHODS: Between 2001 to 2011, we had 38 consecutive SIF hips in our department. Among them, 14 hips (35%) were males. We reviewed their clinico-radiological characteristics. RESULTS: The age range was 16 to 62 (Ave. 44years). The affected side was right in 3 and left in 11. Twelve hips were healed by the conservative treatment, while 2 hips underwent surgical treatments. DISCUSSION: SIF in male is seen in 40 to 50, and the prognosis seems to be good as compared with females.

P1-209

Patients treated with vitamin K2 show significantly lower serum CRP and MMP-3 levels compared to non-treated patients in Rheumatoid Arthritis

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Conflict of interest: None

[Objectives] Vitamin K2 (VitK2) is used for osteoporosis treatment, while recent study have demonstrated that VitK2 induces apoptosis of RA synovial cells and inhibits development of collagen-induced arthritis of rats. The aim of this study is to assess the effect of VitK2 on RA disease activity. [Methods] 129 female RA patients without biologics (mean age 62.4 years old, mean disease duration 14.7 years, mean DAS28-CRP 2.7, 65.9% taking methotrexate (MTX), 65.1% taking prednisolone (PSL)) were enrolled. Cross-sectional study was conducted by measuring CRP, MMP-3, IL-6, Bone mineral density (BMD) of lumbar spine and hip, and bone metabolism markers. [Results] Serum CRP levels were significantly low in VitK2-treated group compared to VitK2-naïve group (0.5±0.7 mg/dl v.s. 1.7±2.0 mg/dl; $P<0.001$) as well as serum MMP-3 levels (127.6±127.6 ng/ml v.s. 220.4±205.7 ng/ml; $P<0.01$). Among variables which showed significant correlation with CRP and MMP-3 (VitK2 dosage, PSL dosage, IL-6, and DAS28-CRP), VitK2 dosage and PSL dosage showed significant correlation ($R=-0.28$ $P<0.05$). After adjustment with PSL dosage by two-way analysis of variance, VitK2 dosage still showed significant correlation with CRP and MMP-3. VitK2 showed no significant correlation with IL-6, BMD, and bone metabolism markers.

P1-210

Characteristics of lumbar scoliosis in patients with rheumatoid arthritis

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Conflict of interest: None

[Objectives] To elucidate the characteristics of lumbar scoliosis in patients with rheumatoid arthritis (RA). [Methods] 23 RA patients were studied. The factors that will possibly contribute to the progression of scoliosis were analyzed. [Results] The average of Cobb angle increased from 15.3 to 23.3. The average increase of Cobb angle per year was 1.88. Apical vertebral rotation, lateral listhesis, the height of intercostal lines, which are reported to be related to the progression of degenerative scoliosis, were not significantly correlated with the progression of scoliosis in our subjects. Most of the patients were receiving glucocorticoid in addition to antirheumatic drugs. Patients who were receiving bisphosphonates showed slower progression of scoliosis compared with those who were not receiving any treatment of osteoporosis.

P1-211

Clinical investigation of osteoporosis in patients with collagen disease

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Conflict of interest: None

[Objectives] To investigate osteoporosis(OP), especially glucocorticoid-induced OP in patients(pts.) with collagen disease(CD) in our department. [Methods] We examined CD pts. who had been treated with glucocorticoids(GC) and whose BMD was measured during from Nov., 2010 to Jan., 2011. The name of a disease, drugs for OP, the GC dosage, the existing fracture(FR), a change of BMD and a new FR onset etc. were investigated. [Results/Comments] 117 pts.(M:F 18:99), the median age 62(M 69.5, F 61). T score(Tsc) was -1.370(M -0.660, F -1.630), significantly low in F and negatively correlated with age ($p<0.05$). The average GC dosage was 6.5mg daily. No correlation was seen between the dosage and Tsc. Bisphosphonate(BIS) was used in 69 pts., Tsc in pts. treated with and without BIS(BIS+ and BIS- group) was -1.850 and -0.830, respectively and the former was significantly low($p<0.001$). Tsc and serum NTx were significantly negatively correlated ($p<0.05$). In BIS+ group NTx was significantly low($p<0.05$) and it is considered that bone absorption should be suppressed by BIS. Serum cystatin C significantly correlated with age($p<0.0001$) but no correlation with Tsc or NTx. The GC dosage and the existing FR were investigated and BMD change and a new FR onset will be investigated prospectively.

P1-212

Risk factors of traumatic fractures in rheumatoid arthritis

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Conflict of interest: None

The aim of this retrospective study was to investigate the risk factors of fracture for patients with rheumatoid arthritis (RA). There were 1282 patients with RA followed at our hospital during 2001 to 2010. We evaluated the data of their age, time of RA, and use of steroid and bisphosphonate medication. Total of 125 patients, 14 males and 111 females, were developed fractures, which were most frequently found in vertebrae for 26% of them. At the time of injury, mean age of patients with fracture was 66±10 years old. The risk of fracture was significantly increased in the patients with vertebral fractures who were treated with steroid. Also RA patients treated with steroid and bisphosphonate had the significantly lower risk of fracture compared to patients with steroid only. Therefore we suggested that it could be the prevention factor of fractures for RA patients to taper steroid and use of bisphosphonate.

P1-213

Relationships with undercarboxylated osteocalcin and insulin in rheumatoid arthritis and volunteers from TOMORROW study

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Conflict of interest: None

[Objectives] The insulin signaling in osteoblast was a regulator of bone and glucose metabolism. The undercarboxylated osteocalcin (ucOC) promotes insulin sensitivity and stimulates insulin secretion by the β cells of pancreas. The relationships with bone and lipid metabolism attracted attention in rheumatoid arthritis (RA). We evaluated the relationships with ucOC, insulin and lipid metabolism in RA and volunteers. [Methods] We analyzed the data derived from TOMORROW study, which is prospective cohort study for RA and volunteers. We investigated the correlation between ucOC and bone, glucose, lipid metabolism, to reveal the factors influenced by ucOC. 341 female (171RA, 170volunteers) and 63 male (31RA, 32volunteers) were included in this study. [Results] The mean ucOC is 5.02ng/ml in RA and 4.35 in volunteers (N.S). There was no correlation between ucOC and insulin in RA (r=-0.041, p=0.5663) and volunteers (r=-0.037, p=0.6008). Only bone metabolic markers (osteocalcin, BAP, NTx) showed a strong correlation with ucOC. Glucose and lipid metabolic markers didn't correlate each other. [Discussion] There was no correlation between ucOC and insulin. Various factors are concerned in insulin secretion. So, we need to reveal the degree of ucOC influence for insulin homeostasis in human.

P1-214

The effect of adalimumab (ADA) on the serum levels of ucOC in the patients with rheumatoid arthritis.

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Conflict of interest: None

[Objective] Several previous studies have indicated that the higher serum level of ucOC could be a risk factor for osteoporotic fracture. On the other hand, RA becomes one of the risk factor of osteoporotic fracture. TNF blocker make the progression for RA treatment, however, the effect of TNF blocker on bone metabolism is still unknown. In this study, we investigated the effect of adalimumab (ADA) on the serum levels of ucOC. [Methods] 11 patients with RA who were administrated ADA were enrolled in this study. We compared the serum levels of ucOC before the administration of ADA, 3 months and 6 months after the administration of ADA. [Results] The administration of ADA significantly increased in the serum level of ucOC time-dependently (before administration was 3.09±2.04ng/ml, 3 months after administration was 3.75±2.50ng/ml and 6 month after administration was 4.14±2.54ng/ml.) On the other hand, the serum levels of BAP and NTx were no significant change before and after the administration of ADA. [Conclusion] ADA increased the serum levels of ucOC time-dependently. It might indicate that TNF blocker increased the OC production in the bone, which caused decrease the vitamin K sufficiency in the bone.

P1-215

Detection of regulatry T cells in the salivary glands of patiens with Sjogren's syndrome and Mikulicz's disease.

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Conflict of interest: None

[Objectives] Recently, it has been reported that the regulatory T cells play an important role in autoimmune diseases, that CD4+CD25+Foxp3 regulatory T cells did not detect in the salivary gland in the patients with Sjogren's syndrome. We studies the expression of FoxP3 in the salivary gland of patients with Sjogren's syndrome and Mikulicz's disease. [Methods] 5 cases of Sjogren's syndrome, one case of Mikulicz's disease. We studies the expression of FoxP3 immunohistochemically. [Results] Foxp3 was positive in 3 cases of Sjogren's syndrome and a Mikulicz's disease.

P1-216

Anti-centromere protein B antibodies are associated with sicca syndrome, but not the titer is correlated with salivary production rate

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Conflict of interest: None

[Objectives] To clarify whether or not SPR is associated with titer of Anti-centromere protein B antibodies (anti-CENP-B). [Background and Methods] We previously described that salivary production rates (SPRs, measured by the Saxon test) in subjects with anti-CENP-B mildly decreased with age, and that titers of anti-Ro, anti-La, and anti-U1RNP antibodies are negatively correlated with SPR with age correction. [Results] Forty-nine female subjects, who had anti-CENP-B but not have anti-Ro, anti-La, or anti-U1RNP were enrolled. Demographic features of the subjects are as follows; the age was 60 ± 10 years old (mean ± SD); anti-CENP-B level, 158.4 ± 59.5 index; SPR, 1.62 ± 1.31 g/2 minutes. SPR significantly decreased with age [simple linear regression: $y = -0.0426x + 4.1703$, where y = SPR (g/2 minutes), x = age (years old), $r = -0.329$, $P < 0.05$]. Anti-CENP-B level was not correlated with SPR with age correction (calculating formula: SPR + 0.0426 × age; $y = 0.0019x + 3.8635$, $r = 0.092$, $P = 0.530$). [Conclusion] Anti-CENP-B antibodies are associated with sicca syndrome, but not the titer is correlated with SPR.

P1-217

MR imaging of the parotid glands in Sjögren's syndrome

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Conflict of interest: None

<Objective> To assess the correlation of MR imaging (MRI) of parotid glands with X-ray sialography (X-sialo), pathology in labial salivary glands (LSG) biopsy, and salivary secretion in patients with Sjögren's syndrome (SS). **<Methods>** We performed MRI of parotid glands on 10 patients with SS satisfied revised Jap-

anese diagnostic criteria (1999). We classified the MRI findings according to the degree of high intensity area in T1WI and T2WI, into Grade0 (T1-, T2-), Grade1 (T1+, T2-), Grade2 (T1+, T2+), Grade3 (T1++, T2+), and Grade4 (T1+++, T2-). We compared the MRI grading with Rubin and Holt staging in X-sialo (0~4), Greenspan grading in LSG biopsy (0~4), and salivary secretion by Gum test (ml/10min). **<Results>** 1) All 10 patients were female, the age was 50.3±14.0 years old. 2) In the MRI grading, 4 patients were Grade 1, 4 were Grade2, and 2 were Grade 3. X-sialo staging was 1.3±0.8, Greenspan grading was 2.1±1.0, Gum test was 9.1±6.4ml. 3) There was significant positive correlation between the MRI grading and X-sialo staging, Greenspan grading ($P<0.05$), whereas slightly negative correlation between the MRI grading and Gum test. **<Conclusion>** This study showed MRI of parotid glands might be the useful noninvasive tool for evaluation of destruction and inflammation in salivary glands.

P1-218

Sicca symptoms were associated with the development of common cold in patients with rheumatoid arthritis.

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Conflict of interest: None

Objective: To investigate the relationship between sicca symptoms and common cold in patients with rheumatoid arthritis (RA). Method: The subjects of the study were participants of IORRA Study in October 2010. Dry eye and dry mouth were assessed using scoring methods by MaCarty and Fujibayashi, respectively. Diagnosis of common cold was based on patient's self report, assessment by physicians, and modified Jackson criteria. The development of common cold was investigated for a month before IORRA study. The association between sicca symptoms and development of common cold was investigated. Results: In this study, 5545 RA patients (female 84%, age 59.9 years, disease duration 13.7 years) were included. Dry eye and dry mouth were observed in 67.4% and 48.5% of patients, respectively. Diagnosis of Sjögren Syndrome was made in 6.4% of patients. The proportions of patients with common cold based on patient's report, physician's diagnosis and Jackson criteria were 24.2%, 10% and 1.8%, respectively. Univariate analysis revealed that scores of dry eye and dry mouth were significantly higher in patients with common cold than those in patients without common cold. Conclusion: It was suggested that the sicca symptoms were associated with the development of common cold in patients with RA.

P1-219

Hematological emergency associated with primary Sjögren syndrome.

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Conflict of interest: None

[Introduction] Severe cytopenia is rare in primary Sjögren syndrome (SS). [Case] Case1: A 62-year-old woman with primary SS presented with anemia and thrombocytopenia. On admission, her hemoglobin was 6.4g/dl, and her platelet count was 33,000/μl. Direct-Coombs test and anti-platelet antibody was positive. Autoimmune hemolytic anemia and immune mediated thrombocytopenia were diagnosed and successfully treated by steroids and transfusion. Case2: A 38-year-old woman with primary SS presented with purpura in the lower extremities. On admission, her hemoglobin was 7.4g/dl, and her platelet count was 14,000/μl. ADAMTS13 activity was undetectable and ADAMTS13 inhibitor was positive. Thrombotic thrombocytopenic purpura was diagnosed and successfully treated with steroids. Two cases didn't fulfill the ACR classification criteria of systemic lupus erythematosus (SLE). [Conclusion] Hematological emergency is rare but life-threatening complication of primary SS.

P1-220

The usefulness of the salivation stimulation examination using the capsaicin

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Conflict of interest: None

[Objectives] With a new filter paper including the capsaicin, we examined salivary flow of the patients with collagen diseases. Sixteen patients diagnosed as hyposalivation were recruited Of these, patients with SjS or patients complicated with SjS were nine cases (SjS group), other patients were seven cases (non-SjS group). [Methods] A new filter paper including the capsaicin was used. It was inserted into oral cavity for two minutes and measured salivary flow. In addition, we evaluated the subjective dry mouth symptom using visual analog scale (VAS). [Result] There was not the significant difference of the age and VAS between SjS group and non-SjS group. The spot counts by the saliva test using the filter paper which did not include capsaicin were 3.9±0.2 in both groups. In SjS group, the spot counts were 3.9±0.2 by the new filter paper including the capsaicin. In non-SjS group, the spot counts were 2.3±1.7. There was the significant difference in the spot counts between SjS group and non-SjS group ($p<0.05$). [Conclusion] The possibility that the examination of salivation stimulation using the new filter paper including the capsaicin was useful for a differential diagnosis of SjS in the chair side was suggested.

P1-221

Successful treatment with azathioprine of interstitial pneumonia associated with sjögren syndrome

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Conflict of interest: None

A 70-year-old man was refered to our hospital because of positive for anti-SS-A antibody, and anti-SS-B antibody. High resolution computed tomography (HRCT) demonstrated bilateral ground-glass opacities, implicating complication with interstitial pneumonia (IP). He developed dyspnea in January 2011, concomitantly with worsening of HRCT findings. Video-assisted thoracopicsurgery (VATS) was performed, and lung biopsy specimens revealed UIP and OP. The saxon test revealed a hyposecretion of saliva. He was diagnosed as having sjögren syndrome (SjS) with IP. The laboratory findings showed KL-6 5752 U/ml, arterial blood gas measurement showed PO_2 64.3 Torr, PCO_2 32.0 Torr. Oral

prednisolone(PDN, 40 mg/day) and azathioprine(AZP, 50 mg/day) were started. Pulmonary function tests and HRCT were improved 1 month after the treatment. IP associated with SjS has various pathological findings with different prognosis. Although, UIP is known to be refractory to PDN, we reported a case of SjS associated with UIP successfully treated with AZP in addition to PDN.

P1-222

A case of pulmonary arterial hypertension with Sjögren's syndrome for which an immunosuppressive therapy is effective

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Conflict of interest: None

【Background】There are many reports that showed availabilities of the immunosuppressive therapies for pulmonary arterial hypertension(PAH) followed by connective tissue diseases(CTD), but most of those reports targeted PAH with systemic lupus erythematosus or systemic sclerosis. There is no established therapy for PAH with Sjögren's syndrome(SS).【Case】A 66-Year-Old women. Her eyesight was getting dim, and she had dry symptoms. Her interstitial pneumonia(IP) was pointed out on the computed tomography scan image of the chest by chance. She was progressively becoming unable to breathe. She had autoantibodies against SS-A and SS-B antigens, and her salivary function declined on gum test and salivary scintigraphy, so she was diagnosed as primary SS. Her IP was getting worse and her pulmonary arterial pressure(PAP) was increasing, so she was admitted to our hospital.【Course】She started taking prednisolone(PSL) 1mg/kg. Her symptoms of IP and PH got better. However, her PAP did not be normalized only by PSL, then ambrisentan was added.【Conclusion】We experienced a case of PAP with SS for which an immunosuppressive therapy is effective, so will report it with bibliographical considerations.

P1-223

A case of Sjogren's syndrome complicted by pulmonary MALT lymphoma

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Conflict of interest: None

The patient was a 46-year-old woman. She was aware of dryness in the mouth around 2004, diagnosised thrombocytopenic purpura in a nearby clinic to receive a nose bleed in 2009, when the rise of anti-SS antibody A and anti-SS antibody B, the dry mouth symptoms, dry eye symptoms, Sjögren's syndrome was suspected. In addition, elevated IgG, M-protein is also recognized, diagnosed with Stage I in multiple myeloma bone marrow aspirate examination. Chemotherapy was started because of elevated levels of IgG further. But the effect did not last. High IgG merger would Sjogren's syndrome symptoms, treatment was continued for preventive purposes PSL15mg/day over viscous syndrome. Since May 2011 she had cough and sputum appeared.. Chest CT images proved interstitial pneumonia with a focus on lower lung field. She did not improve were treated with antibiotics and antifungal. So she was admitted to our hospital was introduced at the purpose of medical treatment and examination of a malignant tumor interstitial pneumonia with collagen disease. She is attempting a lung biopsy in VATS, was diagnosed with pulmonary MALT lymphoma. Malignant lymphomas can be associated with Sjögren's syndrome with those of primary lung are reported in addition to the literature because it is rarely discussed.

P1-224

Evaluation of quality of life in patients with primary Sjogren's syndrome when they select the drugs such as cevimeline and pilocarpine

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Conflict of interest: None

[Objectives] The aim of study was to evaluate health-related quality of life (QOL) in patients with primary Sjogren's syndrome when they selected the two drugs such as cevimeline and pilocarpine. [Methods] Eleven patients with newly diagnosed Sjogren's syndrome was evaluated by using self-rating depression scale (SDS) and WHO QOL 26 before and after the treatment with cevimeline and pilocarpine. Nonparametric test and logistic regression analysis were used (significance was determined as $p<0.05$ and $p<0.2$) [Results] Before the treatments, there was no difference of SDS scores between in patients with Sjogren's syndrome and in previously reported normal control. The selection of two drugs was influenced by SDS score ($p=0.2$), social functioning score in WHO QOL score ($p=0.18$) and the decreased feeling of water intake in the patients with Sjogren's syndrome. These results suggest that the analysis of QOL in patients with Sjogren's syndrome might be useful in managing them.

P1-225

The clinical picture of patients with chronic pain syndrome and fibromyalgia – A report of a retrospective survey

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Conflict of interest: None

The latest criteria for the diagnosis of fibromyalgia (FM) proposed by the ACR2011 covers more patients than those defined with the criteria in 1990, which included pain in 18 specified tender points. We conducted a retrospective study of 29 patients (4 males and 25 females, mean age 50.5 years) with chronic pain syndrome who visited our rheumatology clinic during the 2-year period from April 1999 to March 2010. Most patients did not meet the criteria for pain in the 18 tender points, and had generalized pain. Intravenous or oral Neurotropin was used in 9 patients (31.0%) and oral Pregabalin was used in 13 patients (44.8%). Patients had a history of teeth extraction, trauma, divorce, separation, domestic violence, and/or other negative social background factors. Some patients had gain from illness and did not respond to drug treatment. Physicians in rheumatology clinics tend to see patients with FM longer than those with rheumatoid arthritis and other rheumatic diseases, and 11 patients (37.9%) also visited Dept. of Psychosomatic Medicine or Psychiatry. FM may be best approached through collaboration by rheumatologists and psychosomatic/mental specialists.

P1-226

Psychosomatic manifestations of the Depression type Fibromyalgia: the FM subcategory associated with type 2 bipolar disorder or panic disorder other than major depression episode ?

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Conflict of interest: None

[Objectives] The purpose is to investigate the psychosomatic characteristics of the fibromyalgia(FM) due to analyze and assess the clinical features of the depression type fibromyalgia (FM) after classifying them into 3 subcategories by the way recomended by Nishioka et al. [Methods] At first, all the FM patients are divided into myotonic, enthesitis and depression type due to symptomatological manifestations **on our outpatient clinic basis.** Then each subgroupes are performed Cornel medical index(CMI), Patients corresponding to area III or IV of the CMI are also done **Mini-**International Neuropsychiatric Interview. [Results] The 60 FMs were divided into myotonic 15, enthesitis 5 or depressive 15 as well as overlapping type 35 cases which consisted of myotonic and depressive type. The distribution of the participants according the CMI test:area I(3), II(12), III(20) and IV(25). The 45 patients undergone MINI and diagnosed as follows:type 2 bipolar disorder (25), panic disorders with/without agoraphobia (9) in addition to major depression episode (11), [Discussions] Clinical guideline for the fibromyalgia 2011(Japan College of Fibromyalgia Investigation) does not refer directly to the comorbidity such as bipolar disorder (type 2), panic disorder and other mental disorders.

P1-227

Comparison of lymphocyte subpopulations between fibromyalgia and rheumatoid arthritis

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Conflict of interest: None

Purpose: To examine the lymphocyte subpopulations in FM patients. Materials and Methods: Nineteen patients with FM attending our hospital were studied. The mean age was 49 years. Rheumatoid arthritis (RA) patients who were diagnosed untreated newly, served as control group. The control subjects consisted of 48 RA patients, with mean age 53 years. Flow cytometry was used to measure lymphocyte subpopulations, CD3, CD19, CD4, and CD8. White blood cells (WBC) counts, immunoglobulin (IgG, IgA, and IgM) were also measured at the same time. Results: The mean of percentage of lymphocyte subpopulations between FM group and RA group were (mean +/- SD); CD3(%): 67.7 +/- 9.5, 65.4 +/- 9.4, CD19(%): 13.6 +/- 6.9, 17.8 +/- 6.9, CD4(%): 40.1 +/- 8.4, 41.6 +/- 8.0, CD8(%): 33.5 +/- 11.1, 30.7 +/- 7.8, respectively. CD19 in FM patients were significantly lower than those in RA patients ($p<0.05$). On the other hand, we found no differences in the percentage of CD3, CD4, and CD8. The WBC counts (/mL) were 6306 +/- 1900, 6331 +/- 2376, IgG (mg/dL): 1213 +/- 369, 1409 +/- 360, IgA (mg/mL): 229 +/- 130, 240 +/- 95, IgM (mg/mL): 101 +/- 42, 136 +/- 132, respectively. Conclusion: From our results, it was suggested that lymphocyte subpopulations in these two diseases were different, especially in CD19.

P1-228

Evaluation of serotonin, tryptophan and GABA in serum of fibromyalgia patients (FM)

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Conflict of interest: None

[Objectives] The role of serotonin and tryptophan and GABA in FM [Results] Serotonin, tryptophan and GABA in blood was evaluated. In light of serotonin, the process of the accounts in FM patients, in processing course were evaluated. The relations, between serotonin, tryptophan and pain index are evaluated. The number of the patients and their blood samples to have been examined, in serotonin, was 7 male cases with 13 blood samples, and female FM 31csaes with 45 blood samples. About tryptophan, 16 cases were examined among them. The average account of serotonin of FM cases in blood showed 73.8ng/ml. Healthy subjects of that is 145ng/ml. Trtryptophan value of FM cases showed 47nmol/ml, that account was almost equal to normal subjects. The interval change process of blood serotonin in FM cases was reviewed. Among cases of FM with wide soaring of blood serotonin account, we could win distinctly improved cases, in 6 cases. There was no relation between serotonin ad tryptophan. GABA in blood of FM cases, were evaluated. The account GABA in FM cases showed tendency of tiny lower value from healthy subjects account. The relation between pain index of FM cases and GABA account was evaluated. The relation between serotonin and GABA was reviewed. The pain indexes detection was conducted.

P1-229

Effectiveness of K Point block for ophthalmological symptome of fibromyalgia patients

Naoki Shiraishi
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Conflict of interest: None

[Objectives] [Methods] [Results] (FMS)

P1-230

Effect of epidural block with K Point block for fibromyalgia

Naoki Shiraishi
Kanagawa Dental College

Conflict of interest: None

P1-231

The steroid early reducing method for ANCA associated vasculitis

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Conflict of interest: None

[Objectives] We examined the steroid-early-reducing-method based on the BSR/BHPR guideline for ANCA associated vasculitis. [Method] We retrospectively examined 9 patients of ANCA associated vasculitis who was hospitalized in our department from April 2010 to November 2011, and remission introduction was performed. [Result] We examined 3 Granulomatosis with polyangiitis(GPA) cases, 5 microscopic polyangiitis(MPA) cases and one Churg-Strauss syndrome(CSS) case. The range of age was from 25 to 88 years old (an average of 64.1 years old, 4 men and 5 women at the time of development of symptoms). 4 cases adopted the steroid-early-reducing-method, in which 3 cases were able to carry out remission introduction but 1 case was not. Critical infection occured in 1 case within steroid-early-reducing group. Another five cases using the usual steroid reducing method were able to carry out remission introduction. There were no difference about

the duration of hospitalization between steroid-early-reducing group and a usually-reducing-group. [Consideration] It is uncertain that the steroid-early-reducing-method contributes to the reduction in infection risk and shortening of duration of hospitalization, and further examination will be required for the method.

P1-232

A case report of eary onset Giant cell aortitis/Temporal aortitis diagnosed by not contrast CT but FDG-PET-CT

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Conflict of interest: None

A 80-year-old Japanese woman was admitted to our hospital because of prolonged fever and weight loss in December 6th. The slight fever started from September 19th and 3kg weight loss was observed. Laboratory data showed high CRP(11.0mg/dL) and ESR(103mm/hr). But physical examination showed no abnormality. The other laboratory data and chest X-ray, abdominal echography, computed tomography(CT) scan from neck to abdomen showed no infectious disease or malignant disease. About connective tissue disease, immune globulin W.N.L., ANA 40(Speckled pattern), MPO-ANCA negative, PR3-ANCA negative. Contrast CT scan showed no aortitis. So we implemented FDG PET/CT which showed high accumulation of FDG along by the aorta and bilateral subclavian arteries. Echography showed the thickness and the stricture of lumen of bilateral temporal arteries and vertebral arteries. We performed biopsy of the right temporal artery in which the tissue image was compatible with the giant cell aortitis / temporal arteritis. This case showed the usefulness of FDG PET/CT for diagnosis of early onset aortitis.

P1-233

A case of antineutrophil cytoplasmic antibody (ANCA) negative Churg Strauss syndrome (CSS), complicated with aphagia, showed a good response to low dose glucocorticoid (GC)

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Conflict of interest: None

[Objectives] In ANCA negative CSS cases, active vasculitis process is less frequently than ANCA positive cases, and an additional immunosuppressant is less required. We evaluated the response of lower dose of GC for earlier clinical phase of ANCA negative CSS patient. [Methods] A 65-year-old man, who was diagnosed as asthma twelve years ago, had been treated with inhaled steroid. In January 2011, he was referred to our hospital because of dyspnea and speech disturbance. MRI of the brain revealed multiple small infarctions, and he was diagnosed as motor aphagia caused by cardiogenic infarctions. Intravenous anticoagulant therapy was initiated. Prominent eosinophilia, bilateral pulmonary opacities and pericardial effusion shown by chest CT were revealed. Eosinophilic infiltration was observed histologically in the sigmoid colon biopsies, but sural nerve biopsies did not demonstrate eosinophilic infiltration nor vasculitis. Considering these findings, the patient was diagnosed as CSS, and started to treat with oral prednisolone 20mg/day. He achieved a remission with GC therapy alone. [Results] This case was recognized to be suited for eosinophilic phase, vasculitis was not apparent in biopsies. It is supposed that earlier phase of ANCA negative CSS can be controlled with lower dose of GC.

P1-234

A case of successful long-term tacrolimus therapy in patient with recurrent episodes of microscopic polyangiitis (MPA)

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Conflict of interest: None

72 year-old woman, suffered from interstitial pneumonia since May in 2005, was admitted to our hospital because of jaw claudication, pain and numbness on lower extremities. Hematuria, elevation of MPO-ANCA (74EU) and CRP(3.4mg/dl) were seen. Renal biopsy showed interstitial nephritis. Microscopic polyangiitis (MPA) was diagnosed, then 20mg/day of prednisolone (PSL) and methotrexate (MTX) were started as the remission induction and maintenance therapy. However, steroid dependent relapses occurred, then MTX was changed to tacrolimus (TAC). After the start of TAC therapy(1~3mg/day), she had been in remission without relapse for 5 years with low dose PSL (5mg/day). Adverse effect of TAC, such as renal disturbance and infection, were not seen. It was suggested that TAC was effective drug for maintenance therapy and had redused steroid-dose –effect for MPA treatment.

P1-235

A case of recurrent Wegener granulomatosis which was controllable via combination of many kinds of immunosuppressant therapy

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Conflict of interest: None

A 22-year-old man was admitted to the hospital for the appearance of purpura on his lower legs, multiple lung nodules, acute kidney dysfunction, proteinuria, and hematuria in March 2010. Because of the increase of PR3-ANCA (140U/ml), and leukocytoclastic vasculitis by skin biopsy and crescentic glomerulonephritis by kidney biopsy, he was diagnosed as Wegener granulomatosis. He was treated with intravenous steroid pulse therapy (mPSL 1000mg ×3days) and oral PSL60mg/day, but the disease activity was scarcely controlled. Then IVCY therapy was introduced (cyclophosphamide 750mg/ m^2 /4 weeks). After 2 times of IVCY therapy, his clinical symptoms became improved. When the dose of PSL was reduced to 8 mg/day in July 2011, the disease activities relapsed in spite of the added PSL and mizoribine. After then, IVCY therapy was required again for the control of his condition. In August 2011, he was treated with one time of intravenous infusion of low-dose rituximab (200mg/day) and oral azathioprine, resulting in the disappearance of CD20 positive cells, normalization of serum level of PR3-ANCA and the attenuation of the disease activities. We report the case of recurrent Wegener granulomatosis, which was controllable via combination of many kinds of immunosuppressant therapy.

P1-236

Long-term outcome and cyclophosphamide effect on Japanese patients with microscopic polyangiitis associated with antineutrophil cytoplasmic antibody

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Conflict of interest: None

[Objectives] The aim of this study is to clarify cyclophosphamide (CY) effect on Japanese patients with ANCA positive microscopic polyangiitis (MPA). [Methods] Sixty four patients, who were newly diagnosed as ANCA positive MPA between 2000 and 2010, were included in this retrospective study. Patients were divided into two groups based on whether they received combination therapy of CY and corticosteroid (CS) or CS alone for remission induction. The primary outcome was defined as death from all causes. [Results] Among 64 patients, 29 received CY and 35 did not. Oral CY dosages were between 12.5 and 50 mg daily. Between the two groups, there were no differences in confounding factors except higher proportion of men in CY group. Nine patients reached the primary outcome in CY group and 13 in CS group. The survival rate in CY group was slightly higher than in CS group, but there was no statistical significance (0.86 vs. 0.77 at one year and 0.73 vs. 0.64 at 5 years, p=0.648). CY hazard ratio fully adjusted by age, sex, Birmingham vasculitis activity score, serum albumin and C-reactive protein was 0.657 (95%CI, 0.254-1.699; P=0.386). [Conclusion] We could not find CY effect on Japanese patients with ANCA positive MPA. CY effect may be limited in Japanese patients with ANCA positive MPA.

P1-237

A patient with cryoglobulinemia who was effectively treated with combination of double filtration plasmapheresis and plasma exchange therapy.

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Conflict of interest: None

A 46-year-old woman suffered from leg purpura was diagnosed as cryoglobulinemia (CG) from positive serum cryoglobulin and skin biopsy findings (leukocytoclastic vasculitis) in 2009. In November 2010, she started to have fever and a leg ulcer. She was administrated in our hospital at December 19, because of exertional dyspnea and lower leg edema due to congestive heart failure with acute renal failure (ARF). Mixed CG type2 was diagnosed from patterns of immune-electric findings, high level of immunoglobulin, low complement and the pathologic finding from leg ulcer. Acute renal failure with CG was diagnosed from cylindruria, poikilocyte and rapid Ccr deterioration. Double filtration plasmapheresis (DFPP) and plasma exchange (PE) therapy were performed immediately. Dyspnea, lower leg edema and the urinary findings were improved immediately. Level of immunoglobulin was also decreased. After that, high dose predonisolon therapy was started and her leg ulcer was improved. The case which mixed CG associate with ARF is rare (approximately one of 2 million people). We suggest that when a patient with mixed CG develops ARF, DFPP and PE combination therapy with predonisolon might be considered.

P1-238

A case of refractory cutaneous polyarteritis nodosa with HBV carrier status successfully treated with etanercept

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Conflict of interest: None

We report a patient with refractory cutaneous polyarteritis nodosa, who was a hepatitis B virus carrier, effectively and safely treated with etanercept. The patient was a 60-year-old woman. She was diagnosed with hepatitis B carrier status [HBsAg(+), HBsAb(-), HBeAg(-), and HBeAb(+)] at the age of 30. Seven years before, she presented with fever, purpura, livedo reticularis, subcutaneous nodes, and dysesthesia in dorsum of feet and ankle arthritis. Skin biopsy disclosed cutaneous polyarteritis nodosa. No other organ damage was noted. Diagnosis of cutaneous polyarteritis nodosa was made. She was treated with prednisolone, cyclophosphamide, tacrolimus, azathioprine, colchicine, methotrexate, and plasma exchange one after the other; however, the efficacy of the treatments was limited. During the treatment, HBV-DNA levels increased, and lamivudine and adefovir were administered. From July 2011, administration of etanercept (25mg per week) was started and it improved the clinical symptoms and data promptly. No adverse events have been noted.

P1-239

A case of Cryoglobulinemia with Sjogren syndrome effectively treated with IVCY

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Conflict of interest: None

In 1996, dryness of mouth and eye in addition to anti-SS-A antibody positive appeared, and then she was diagnosed as Sjogren syndrome. In 2007, the numbness of bilateral lower limb appeared, and then perpheral neuropathy was diagnosed. On May, treatment with PSL 40mg/day (alternate days) was started. As symptom improved gradually, PSL was reduced gradually to 25mg/day. On March 2008 neurologic symptom got worse and rash in lower limb appeared. Laboratory findings showed decrease of complement (CH50 23, C3 67 and C4 5) and elevated IgM. Because of these findings, we measured cryoglobulin, which showed high titer(5~10%). And then skin biopsy was performed, which showed thrombosis formation and the deposition of IgM, so we diagnosed as leukocytoclastic vasculitis associated with cryoglobulinemia. At the same time, multiple organizing pneumonia was pointed out. We treated with PSL 30mg/day (alternate days) after pulse steroid therapy and immunoadsorption plasmapheresis, but the effect of these therapy was not sufficient. IVCY(pulse CPA therapy) was started, which improved symptoms of cryoglobulinemia and decrease cryocrobulin (<1%), so PSL was gradually decreased. We suggest that IVCY is one therapeutic option for cryoglobulinemia not effectively treated with other treatment.

P1-240

A case of microscopic polyangitis (MPA) which test positively for anti-glomerular basement membrane (GBM) antibody while treatment with adalimumab (ADA)

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Conflict of interest: None

A 69-year-old woman was diagnosed as rheumatoid arthritis (RA), suffering from bilateral arthritis of fingers and toes 16 months ago. She did not respond to both methotrexate (MTX), which was stopped because of emerging interstitial pneumonia, and bucillamin. ADA was administered 4 month before admission, but edema and purpura on legs were noted a month before. She was admitted to our hospital, since her renal function showed rapidly worsening. She was diagnosed as MPA with concurrence of MPO-ANCA and anti-GBM antibody. Methylprednisone pulse therapy followed by oral prednisone 1mg/kg/day, plasma exchange and oral cyclophosphamide (CYC) 1mg/kg/day were started. ANCA and anti-GBM antibody got normalized soon, whereas renal function did not recover enough to come off dialysis. Examination of the serum bebore starting ADA showed negative for anti-GBM antibody, which assumed the possibility of ADA inducing anti-GBM antibody.

P1-241

A case of ANCA-negative renal-limited vasculitis treated with cyclophosphamide pulse therapy.

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Conflict of interest: None

Pauci-immune renal-limited vasculitis (RLV) is generally associated with ANCA, but ANCA is undetectable in up to 10% of cases, which constitutes a rarely studied variant of RLV. We report a 54-year-old female patient with rapidly progressive glomerulonephritis and nephrotic syndrome who was negative for ANCA but showed pauci-immune focal glomerular necrosis and crescent formation in histology. A skin biopsy of purpuric plaque showed a leukocytoclastic vasculitis with no deposition of IgA in dermal vessels. These findings are unlikely compatible with those of Schonlein-Henoch purpura. The patient was classified as RLV, a subset of microscopic polyangiitis, according to the European Medicines Agency (EMEA) algorism, and responded well to the treatment of high-dose prednisolone plus cyclophosphamide pulse therapy, resulting in early improvement of proteinuria and renal dysfunction. The significance of the exact diagnosis in an active vasculitic disease process even in the absence of ANCA should be underlined.

P1-242

Polyarteritis nodosa diagnosed by nerve biopsy in a 34-year-old woman, showing peripheral nerve involvement and central retinal artery e while being treated as multiple sclerosis

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Conflict of interest: None

A 12-year-old woman became aware of numbness in feet and hands. At age 22 she was diagnosed as having multiple sclerosis (MS) based on abnormal signals in the cervical cord on MRI. Interferon-βwas started because of frequent fluctuation of clinical symptoms, such as numbness in limbs and auditory disturbance, ascribable to MS. These symptoms were successfully treated with methylprednisolone pulse therapy, but reworsened in a short interval. When she was admitted to our hospital at age 34, an electrophysiological study revealed peripheral nerve involvement. Sural nerve biopsy showed extensive loss of myelinated nerve fibers with fibrinoid necrosis and perivascular infiltration of inflammatory cells, leading to the diagnosis of polyarteritis nodos (PN). During stay in our hospital, she developed central retinal artery occlusion, which was also considered as a symptom due to vasculitis. In the present patient, visceral organ involvement and cutaneous manifestations typical of PN were absent, and nerve biopsy was highly useful for the precise diagnosis.

P1-243

Steroid sparing effect of methotrexate in two cases of refractory aortitis syndrome

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Conflict of interest: None

Case report 1: A 35-year old woman with Takayasu's aortitis (TA) has been treated by corticosteroid (CS) and inflammatory disease activity was controlled by CS. However, decreased dose of prednisolone (PSL) to less than 10mg/day was associated with the relapse of disease activity. Methotrexate (10mg/week) resulted in the control of the disease and reduction of PSL. Case report 2: A 31-year old man with TA treted by CS repeated the relapse of the disease when the PSL dose was decreased to less than 20mg/day. Cyclophospamide was not effective and methotrexate (15mg/day) resulted in the control of disease and PSL was decreased to 13mg/day. Although CS should be given as first-line therapy, low doses of methotrexate may facilitate the disease's control and weaning from the CS.

P1-244

A case of miliary tuberculosis with dermatomyositis and institial pneumonia

Nao Tatsukawa, Koji Nagai, Yuri Hiramatsu, Yuko Kimura, Tohru Takeuchi, Shigeki Makino, Toshiaki Hanafusa
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Conflict of interest: None

A 63-year-old woman was treated with prednisolone (20mg/day) and cyclosporine (180mg/day) for dermatomyositis and interstitial pneumonia since 2009. She felt general fatigue and loss of appetite in November 2011. Her laboratory findings showed the increased levels of liver and biliary enzymes, and CRP. Ultrasonography and computed tomography of the abdomen had normal findings, and all drugs except steroids were discontinued without the reduction of liver enzymes and CRP. Therapeutic trials of antibiotics did not result in favorable response. In January 2011, computed tomography of the chest and abdomen were performed, and showed thicking of the gall bladder wall and diffuse nodular shadow at the bilateral lung. Cultures of the sputum, gastric fluid and urine yielded *mycobacteria tuberculosis*. Miliary tuberculosis has an insidious clinical course and is difficult to its diagnosis like this case.

P1-245

A case of miliary tuberculosis revealed by significant elevation of neutrophil CD64 expression in a patient with rheumatoid arthritis on treating inveterate cellulitis in crus

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Conflict of interest: None

A 73-year-old woman with rheumatoid arthritis (RA) receiving adalimumab(ADA) together with isoniazid for tuberculosis (TB) prevention during 9 months. Refractory cellulitis on the both legs had appeared since February 2010, which needed intravenous treatment of antibiotic. On May 2011, oral antibiotics therapy was administered again for 2 months with discontinuation of ADA because of recurrence of cellulitis, but was not effective. Since neutrophil CD64 expression level consistently increased during the therapy, she admitted to our hospital, suspected of atypical infection including tuberculosis (TB). As diffuse particulate shadows were shown in whole lung field at random like miliary TB in chest X-ray and CT scan image, she was transferred to another hospital. Mycobacterium were observed in smear preparation from sputum and gastric juice, where *Mycobacterium tuberculosis* was positive in PCR. In histopathological finding, noncaseating epithelioid granuloma was shown in bronchial and alveolar specimens obtained from bronchoscopy. Biopsy specimens from cellulitis also revealed erythema induratum Bazin. By antituberculous drug her manifestations were gradually improved. Abnormal up-regulation of neutrophil CD64 expression could help to detect the existence of military TB.

P1-246

Tuberculous arthritis of knee joint associated with rheumatoid arthritis treated with etanercept: a case report

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Conflict of interest: None

We present here a 68-year old woman who developed severe tuberculous arthritis in the knee joint following etanercept administration. She was diagnosed as RA 17 years ago. At the beginning, the patient was treated with BUC, AF, SASP and MTX. However, the symptoms remained active. She was administered with 50mg/week of etanercept and the control of RA became good. After 10 months, resistant pain and joint effusion of her right knee was present. Gram staining of the synovial fluid was positive. Open drainage and joint lavage was performed. At that time, culture of synovial fluids was negative. After that, discharge and sinus formation were observed at drainage ports. Therefore, arthroscopic synovectomy were performed again. Nevertheless the portals were not healed and discharge existed. Finally, acid-fast stains of the pus and synovial fluids were performed and tuberculous/PCR were positive. Treatment with isoniazid, rifampin, ethambutol and pyrazinamid were started. In addition, open synovectomy and debridement was performed. The wound healed and knee swelling decreased significantly. Tuberculosis infection is one of the most important complaints for the RA patients treated with biologics, while tuberculous arthritis is rare. We should keep in mind about the condition.

P1-247

Two cases of extrapulmonary nontubercular mycobacterial infection complicated with rheumatic diseases

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Conflict of interest: None

The first case was a 74-year-old female. She was diagnosed as seronegative microscopic polyangiitis because of fingertip ulceration, rapidly progressive glomerulonephritis, and enterocolitis in 2008, and treated with betamethasone (0.5 mg/day) and mizoribine pulse therapy (1,200 mg/week). She complained of swelling of the right palm in May 2010. Drainage of the cutaneous lesion was performed. Polymerase chain reaction (PCR) and a culture of the aspirated fluid were positive for *Mycobacterium intracellulare*. The second case was a 49-year-old female, who was diagnosed as mixed connective-tissue disease in 1986 and treated with methylprednisolone (4 mg/day). She suffered from rheumatoid arthritis in November 2009 and methotrexate (8 mg/week) was initiated. Painful swelling of the right wrist was developed and not relieved despite the additional treatment of infliximab. MRI of the right wrist showed the fluid and rice body of the flexor tendon synovium. Tenosynovectomy was performed. PCR and a culture of the washing fluid were positive for *Mycobacterium intracellulare*. Both patients were treated with ethambutol, rifampicin, and clarithromycin. We review these cases with reference to the previous literature.

P1-248

A case considered with not ANCA-associated vasculitis but non-tuberculous mycobacterial pulmonary infection

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Conflict of interest: None

A 57-year-old woman presented with high fever, polyarthralgia, pulmonary nodular infiltrates. MPO-ANCA test was positive and culture of sputum revealed the growth of Mycobacterium avium. After treatment with CAM, RFP and EB, the symptoms disappeared, pulmonary shadows improved, and MPO-ANCA became negative. The cause of pulmonary lesions was considered not ANCA-associated vasculitis but non-tuberculous mycobacterial pulmonary infection.

P1-249

Pneumocystis pneumonia study of seven patients in our department

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Conflict of interest: None

Pneumocystis pneumonia (PCP) is opportunistic infection with Pneumocystis jiroveci. I have studied retrospectively the clinical data of 7 cases experienced in our department. Mean age 60.1 years 50-76 years, male: female ratio was 1:6. The underlying disease in three patients with RA, four patients had other collagen diseases. Steroid pulse therapy has been performed in three of four patients previously treated as collagen disease, immunosuppressive agents were using in 6 cases. β-D-glucan was average at 48.7 ~

1857.9pg/ml 11360pg/ml. Treatment was started at the ST combination in all cases, was changed to pentamidine for the side effects in 3 of 7. Steroid assistance has been made in four for hypoxemia. Outcome was 1 death, six patients were cured. Risk of developing RA patients in the elderly, patients with collagen diseases and risk factors were impressive administration of immunosuppressants or more of steroid pulse therapy. This case is an example of a failed or not been any prophylaxis, reaffirmed the importance of prophylaxis.

P1-250

Analysis of poor prognostic factors in rheumatoid arthritis patients complicated with Pneumocystis pneumonia.

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Conflict of interest: None

[Objectives] To examine poor prognostic factors in RA patients complicated with PCP. [Methods] Fourteen patients with PCP were treated from April 2010 to August 2011. By dividing those patients into two groups according to final outcome of hospitalization, the dead group and alive group. [Results] All 14 patients were once recovered from PCP, however, five patients were died during the hospitalization due to acute interstitial pneumonitis (IP) in 3, renal insufficiency due to amyloidosis in 1 and intestinal tract perforation in 1. Compared to the alive group, patients in dead group were older age (75.0 vs 62.5 years), had higher prevalence rate of IP (51.7 vs 9.1 %), lower levels of β-D-glucan (44.7 vs 398 pg/ml), and lower usage of biologics (14.3 vs 36.4 %). No difference was detected in sex, complication of diabetes, methotrexate use, corticosteroid use, p/f ratio at the time of hospitalization, white blood cell count, lymphocyte count, IgG, positivity of Pneumocystis DNA, detection of the Pneumocystis antigen, dosage of steroid pulses and dosage of ST agent. [Conclusion] Patients with RA complicated by PCP had poor prognosis in case of older age, preexisting IP and lower level of β-D-glucan.

P1-251

Clinical Characteristics of Pneumocystis jiroveci Pneumonia in patients with Collagen diseases

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Conflict of interest: None

【Objective】 Recently, *Pneumocystis jiroveci Pneumonia* (PCP) has been reported that the use MTX and biological agents for patients with RA are high incidence of PCP. We examined retrospectively PCP in patients with collagen disease.【Methods】 We examined background, treatments, prognosis of 7 PCP patients with collagen disease who visited our hospital between September 2006 and September 2010. A diagnosis of PCP was baced on satisfaction of all of the following criteria; a) symptoms such as fever, cough, and progressive dyspnea, b) detection of P. *jirovecii* by traditional staining or PCR in respiratory specimens, c) sigmificantly elevated plasma (1,3)-β-D-glucan level.【Results】 We examined retrospectively 7 cases (5 patients with RA, 1 patient with Polymyositis,1 patient with Microscopic polyangiitis. All RA-PCR are outpatients. All patients were receiving steroids or immunosuppressant or MTX, but had not been received biological agents. The peripheral blood lymphocyte count at the onset of PCP were <500μ/ml. The mean age of the patients was 69 years (range 59-81). 4 patients had interstitial pneumonia. 4 patients had diabetes mellitus. 1 patient had malignancy. All patients were not given trimethoprim/sulfamethoxazol(TMP/SMX).

P1-252

A case of *Legionella pneumophila* pneumonia complicated in a patient with rheumatoid arthritis under tocilizumab therapy

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Conflict of interest: None

A 64-year-old male with rheumatoid arthritis (RA), receiving tocilizumab (TCZ) therapy for RA and its complications, was admitted on emergency because of appetite loss and progressive dyspnea without fever on July 28, 2011. Hypoxia and hypotension were so severe that emergent intubation was performed in intensive care unit. Because the *Legionella pneumophilia* antigen was detected in a urinary specimen with bilateral infiltrative shadows in chest X-ray and CT scan images, he was diagnosed as *Legionella pneumophila* pneumonia. Immediately administration of pazufloxacin and erythromycin was carried out in addition to steroid pulse therapy, sivelestat sodium hydrate and catecholamin, but respiratory failure was gradually advanced. Five days after admission, high grade fever suddenly appeared when methicillin resistant *Staphylococcus aureus* (MRSA) were also detected in cultures from blood. Although teicoplanin against MRSA sepsis and rifampicin as well as endotoxin adsorption therapy were made as additional therapies, he unfortunately died 12 days after onset of the disease. Physicians should assume *Legionella* infection when we see the severe pneumonia, and are needed to make an optimal evaluation of the disease, considering the distinctive function of this agent.

P1-253

Clinical characteristics of nocardiosis in patients with rheumatic diseases

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Conflict of interest: None

[Objectives] Nocardiosis is a critical complication in patients with rheumatic diseases, due to its high fatality and strong tendency to recur. To clarify the clinical characteristics of nocardiosis in patients with rheumatic diseases. [Methods] We reviewed medical records of nine patients who suffered from nocardiosis in our hospital. [Results] The underlying diseases were SLE (n=2), ANCA-associated vasculitis (n=4), Behecet's disease (n=1), adult onset Still's disease (n=1), and Sjogren's syndrome (n=1). Seven of the nine were accompanied by type 2 diabetes. All patients had a history of high dose prednisolone treatment (mean 50mg/day), and six were taking more than 20mg/day (mean 20.6mg/day) of prednisolone at the time of diagnosis. Four patients were taking another immunosuppressant at the time of diagnosis, and the other two had a history of immunosuppressant therapy. Importantly, five of the nine already had disseminated nocardiosis, when pulmonary lesions were identified. These data suggest that high dose steroid therapy with another immunosuppressant and diabetes may be risk

factors for nocardiosis in patients with rheumatic diseases, and we need to pay attention to disseminated nocardiosis when pulmonary lesions were identified.

P1-254

Clinical experience of three cases of pulmonary nocardiosis with rheumatic diseases.

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Conflict of interest: None

[Objectives] It has been recognized that pulmonary nocardiosis is often found in the patients with rheumatic diseases who were treated with predonisolone and immunosuppressants. This time we experienced three cases of pulomonary nocardiosis, Here we have investigated the clinical course of pulmonary nocardiosis in our department. [Methods] We report 3 patients of pulmonary nocardiosis in our department who were diagnosed and treated in our department in these 6 years. [Results] (Case 1/2/3) Age and sex. 77F/65M/80F; Underlying diseases, temporal arteritis/SLE/AOSD, Dose of predonisolone at onset, 40mg/20mg/25mg, Immunosuppressants, -/-/Ctclospoirne A. Diabetis mellitus, -/+/+. Samples for diagnose of nocardiosis, sputum/specimens from lung biopsy/samples from cutaneous abscess. Treatment, MINO+salfametxazole-trimethoprin/salfametxazole-trimethoprin/MINO+salfametxazole-trimethoprin. Conclusion: Early diagnosis and precise treatment such as minocyclin and salfametxazole-trimethoprin prevented patients with pulmonary nocardiosis from serious condition.

P1-255

Disseminated Cryptococcosis on ANCA-associated vasculitis

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Conflict of interest: None

85 year old woman came to our hospital because of loss of appetite and decreased mental status. She had a previous diagnosis of ANCA related vasculitis before and take orally prednisolone 13mg/day. As we suspect steroid withdrawal, we put her prednisolone 20mg. After that, she got better soon, but she appealed suicide feeling and depressive mood and had cognitive dysfunction. After few days, her left arm had swelling, and she got a fever. Despite of taking antibiotics, there is no improvement, so we did skin biopsy. We found noncaseating granuloma. After that, we diagnosed cryptococcosis from blood culture and positive cryptococcal antigen. On chest CT scan, there is multiple nodular density. We added Grocott's variation on her skin, so we found spore of Cryptococcus. If you find noncaseating granuloma in histopasological sample of skin in the immunocompromised host, you should suspect cryptococcosis and do Grocott's variation and Periodic acid-Schiff stain.

P1-256

Pulmonary cryptococcosis is not a rare complication in patients receiving biologics

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Conflict of interest: None

Pulmonary cryptococcosis (P-crypt) has been reported to be rather rare disease. Specifically, a group from Nagasaki University reported that the annual incidence is approximately 1/100,000. Wallis reported that the annual incidence of P-crypt were between 4.3 – 7.1/100,000 in patients receiving IFX or TEN, but we have felt that the incidence is higher. Here we picked up patients with P-crypt among patients receiving biologics (BIOs) and analyzed. The diagnosis of P-crypt was made based on the chest CT findings compatible with P-crypt and positive serum Cryptococcus antigen. We found 3 patients with P-crypt out of 36 IFX users (8.3 %). The underlying rheumatic diseases were RA in 2 and psoriatic arthritis in 1, respectively. The interval between introduction of IFX and the development of P-crypt were 2, 18, and 24 months, respectively. The incidence was 0.38/100 patients month. P-crypt did not develop in other BIOs and the incidence was significantly higher in IFX ($p < 0.000\%$). All the patients were successfully treated with fluconazole. The reason of higher incidence in IFX users is thought to be its strong suppression against granuloma formation. In conclusion, P-crypt is not a rare complication in BIOs users and we have to be aware not only of TB but also of P-crypt.

P1-257

A Case of pseudomembranous and ulcerative invasive pulmonary Aspergillosis in a patient with SLE

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Conflict of interest: None

A 54-year-old women diagnosed as SLE on 1979 received 10mg dose of prednisolone once daily. She developed non-Hodgkin lymphoma in February 2010. She was gave R-CHOP therapy and achieved a complete remission. But she had diarrhea and abdominal pain from the beginning of February 2011, and had massive melena in mid-March, so she was admitted to our hospital. She was stopped bleeding by non-eating and rest, but high-resolution Chest CT scan showed multiple cetrilobular nodules with focal cavities. Bronchoscopy showed white multiple pseudomembranes and ulcers in the left second carina and left superior lobar branch. Bronchial washing and biopsies were performed, and they revealed Aspergillus. The patient was started antifungal drugs and made improvement. A Case of pseudomembranous and ulcerative invasive pulmonary Aspergillosis is rare, and we think that Bronchoscopy is helpful as a diagnostic tool in airway invasive pulmonary Aspergillosis.

P1-258

A case that developed during progress of SLE and was difficulted in diagnosis of pulmonary aspergillosis

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Conflict of interest: None

We reported a 39-year-old woman who was diagnosd as having SLE because of butterfly rush, disk-like erythema, photodermato-

sis, and positive of anti-Sm and antinuclear antibody on January 2011. The administration of prednisolone was started and then, betamethasone was followed by dermatology. On May 24, her temperature rose to 38 degrees. Ganciclovir was administered for treatment of hemophagocytic syndrome which was caused by CMV, because of decreases of WBC and platelets, elevation of LDH and ferritin, and positive of CMVpp65 antigen. Later, her temperature falled, but dyspnea and the consolidation at the both lower lobes in her chest X-ray were presented. Although β-D glucan, aspergillus antigen and CMVpp65 antigen were negative, we suspected some kinds of infectious diseases. After that, the new nodular shadows in the apex of the right lung and the both lower lobes were presented. And then, the right pneumothorax was demonstrated. On July 1, she was operated VATS. There were diffuse white nodules which indicated infections. The bulla was dissociated, and aspergillus druse was demonstrated as pathological finding. The nodular shadows of both lobes were improved tendency by the antifunga use. We experienced a case that was difficulted in diagnosis of pulmonary aspergillosis.

P1-259

A case of Cytomegalovirus related hemophagocytic syndrome with SLE

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Conflict of interest: None

A 62-year-old femail was diagnosed as systematic lupus erythematosus (SLE) because of malar erythema, stomatitis, leukocytepenia, and positivity for ANA and anti-ds-DNA antibody in August 2009. She was initiated with prednisolone (PSL40 mg/day) and azathioprine (AZP50mg/day) with favorable response. In June 2011, when PSL was tapered to 9mg/day with 75mg/day of AZP, she had high fever, general fatigue and poor appetite. Laboratory findings showed pancytopenia, elevated levels of LDH and ferritin, and positivity for cytomegalovirus (CMV) antigen. Chest CT scan revealed grand-glass shadows and nodular shadows in bilateral lung fields, suspecting CMV pneumonia. Bone marrow aspiration showed hemophagocytosis. Serum complement and anti-ds-DNA antibody levels were stable. She was assessed CMV-related hemophagocytic syndrome with SLE. Her clinical and laboratory findings were gradually improved after intravenous steroid pulse therapy and anti-vial agents.

P1-260

Reserch of CMV antigenemia in patients with collagen disease during immunosuppressive therapy.

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Conflict of interest: None

[Objectives] CMV reactivation is often problematic in patients with collagen disease in immunosuppressive therapy. CMV antigen pp65 (C7-HRP) measurements are useful for early detection of CMV antigenemia. Considering the background and clinical course of patients with CMV antigenemia in the immunosuppressive therapy. [Methods] From October 2008 to February 2011, 152 cases of patients with collagen disease and related disorders were measured C7-HRP in our department, made retrospectively studied. [Results] 30 patients were positive for CMV antigen more than once, include 10 SLE, 8 RA, 4 MPA, 3 AOSD, 2 MCTD, 2 SjS, and 1 PM case. Steroids have been administered in all patients. 14 patients ware treated with steroid pulse(>mPSL250mg). Time to develop CMV antigenemia from the treatment was 22 ± 15.3 days. 3 patients treated with CPA, 10 with immunosuppressive drugs such as CsA, 2 with biologic agents. Cases in many antigen-positive cells were treated with GCV, and Death from CMV infection was not observed. [Conclusion] Steroid pulse therapy and immunosuppressive drugs are the risk of CMV antigenemia. Find them early and start treatment, leading to a good outcome.

P1-261

Three cases of Parvovirus B19 infection closely resembles to SLE.

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Conflict of interest: None

Since the patients of parvovirus B19 infection sometimes fulfill the diagnostic criteria of SLE, it can be difficult to distinguish parvovirus B19 infection patients from SLE. We reports the three patients of parvovirus infection with SLE like symptoms. Three patients with SLE like symptoms came to our hospital from 2010 to 2011. [Result] We wonder these cases SLE or parvovirus infection because these patients presented arthritis and facial erythema at the first visit. Anti-parvovirus B19 IgM antibodies were positive in all three patients. However, they all also had one of SLE like symptoms such as arthritis, leukocytopenia or thrombocytopenia. Moreover, emergence of an anti-nuclear antibody (FANA) was appeared in all cases. Their arthritis and facial erythema disappeared without treatment. [Discussion] It has previously been reported that the patients of parvovirus B19 infection present with the symptoms identical to SLE. Another report showed that SLE like symptoms occurred after parvovirus B19 infection persists longer duration in high titer FANA positive group compared with a weakly positive group. In our three cases, two had low titer FANA and one had high titer FANA. We would like to report three cases above with the bibliographic discussion.

P1-262

Septic multiple abscesses in an immunoconpromised host with rheumatoid arthritis on methotrexate and corticosteroid

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Conflict of interest: None

[Introduction] Patients with rheumatoid arthritis (RA) are susceptible to pyogenic infections because of the immunosuppressive treatment with methotrexate (MTX), corticosteroid (PSL), or biologics. **[Case report]** A 61-year-old female with a 10-year history of RA (Steinbrocker stage III class2), on 8mg/week of MTX and 5mg/day of PSL, presented with high fever, general malaise, and polyarthritis. On laboratory studies disclosed the following values: white blood cells, 18750/mm^3; C-reactive protein 37.27 mg/dl. Three blood culture yielded gram-positive cocci (MSSA). Therapy with cefazolin, ampicillin, or penicillin G was given for 4 weeks. CT of the chest and abdomen revealed bilateral iliopsoas muscle abscesses and lumbar discitises. On hospital day 2, percutaneous abscess drainage was performed and in place for 2 weeks. MRI revealed the plantar abscesses of bilateral feet and sternoclavicular arthritis. On hospital day 8, surgical drainage and amputation of the right forth toe was performed. On hospital day 21, surgical drainage and arthrodesis of the left first toe was performed, as the pyogenic arthritis of the first toe was relapsed. On hospital day 26, the infection was under control and the patient could walk with

lumbar hard corset.

P1-263

Analysis of Pyothorax complicated with Rheumatic diseases

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Conflict of interest: None

[Objectives] Pyothorax is a rare but severe disease, especially in patients with rheumatic diseases. It is very important to know the clinical backgrounds in these patients. [Methods] We examined the clinical background, complications, medication before onset, therapy for pyothorax in 26 pyothorax patients who admitted in our hospital from 2000 to now. [Results] Eleven patients were diagnosed as tuberculous pyothorax out of 26 patients. Three patients were complicated with malignant diseases. Four patients had rheumatic diseases including rheumatoid arthritis (2 patients), systemic lupus erythematosus, and Behcet's disease. Further examination about 4 pyothorax patients complicated with rheumatic diseases demonstrated that 1) Pneumococcus, Nocardia, or aerobic gram-negative bacteria were detected as infecting organism in 3 patients, 2) Two patients received steroid therapy, 3) All patients were intensively treated by antibiotics for 3 to 4 weeks and used thoracic cavity drainage. 4) Two patients underwent on thoracoscopic operation for curettage and windowing. When rheumatologist would encounter the pyothorax patients as compromised host, they should examine infecting organism at first in these patients, then provide them with medical treatment such as effective antibiotics

P1-264

Lemierre's syndrome: A case difficult to be differentially diagonosed from granulomatosis with polyangiitis.

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Conflict of interest: None

A 69-year-old Japanese female was treated for her periodontal disease in April, 2011. In mid-June, she suffered from fever and sore throat. After treatment with an antibiotic, labial edema, labial bulla, and palpebral edema newly occurred. Stevens-Johnson syndrome was suspected, and she was admitted to dermatologic department. Although she was treated with high dose glucocorticoids, the fever and the palpebral edema were deteriorated, and exophthalmoses and rapid visual impairment further appeared. CT scan revealed multiple orbital tumors, and multiple lung cavities. Then, granulomatous polyangiitis (GPA) was suspected, and she was introduced to a rheumatologist. Biopsy from the orbital tumors showed anaerobic bacterial infection, and thromboses in cavernous sinus and internal jugular veins were found in her head MRI results. Thus, jugular vein thrombophlebitis was considered, which followed sepsis from periodontitis. Taken together, this case was diagonosed as Lemierre7s syndrome. In Lemierre's syndrome, lung septic microemboli with cavities and orbital tumors have been reported, which should be carefully discriminated from similar manifestations in GPA.

P1-265

Inflammatory cytokines act on mesenchymal stem cells resulting in altered osteoblast differentiation

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Conflict of interest: None

[Objectives] Mesenchymal stem cells (MSCs) have been reported to be effective on autoimmune diseases due to their immunosuppressive effects and multipotency. Therefore, MSCs possess a potential to be applied for treatment of rheumatoid arthritis (RA) aiming not only disease improvement but also repair of destructed joints. We herein investigated the effects of inflammatory cytokines on osteoblast differentiation from human MSCs (hMSCs). [Methods] hMSCs were cultured in osteobalstogenic condition in the presence of inflammatory cytokines (TNF-α, IL-1β, IL-6 or IL-17). [Results] Among the tested cytokines, IL-1β strongly enhanced osteoblast differentiation evaluated by RUNX2, alkaline phosphates staining, expression of osteoblastic genes and mineralization. Mineralization was almost completely inhibited by siRNA of Wnt5a or Ror2, the receptor for Wnt5a. IL-6 and IL-17 were less effective compared to IL-1β, whereas TNF-α inhibited this process. [Conclusions] hMSCs are able to differentiate into osteoblasts through activation of Wnt5a-Ror2 pathway under some adequate inflammatory condition in vitro, suggesting its usefulness for RA treatment aiming joint repair.

P1-266

Evaluation of the risk factors of relapse in patients with Adult onset Still's disease

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Conflict of interest: None

[Objectives] We evaluated the clinical characteristic in relapsed cases of Adult onset Still's disease (AOSD). [Methods] A total of 31 patients with AOSD were retrospectively divided into relapsed group and not-relapsed group, and their symptoms, laboratory data and doses of steroid at administration were statistically compared. [Results] The number of relapsed group was 11 and that of not-relapsed was 20. No significant differences in frequency of high fever, arthralgia, eruption, pharyngalgia, and lymphadenopathy were observed between the groups. Frequency of pleural effusion was significantly higher in relapsed group than that in not-relapsed group ($p=0.038$). Serum ferritin levels were significantly higher in relapsed group (17357±8781) (ng/ml) than not-relapsed group (14552±3845) (ng/ml) ($p=0.030$). No significant difference in proportion of patients who received steroid pulse therapy was observed between the groups, but doses of oral prednisolon were significantly higher in relapsed group (48.1±16.0) (mg/day) than that in not-relapsed group (36.0±11.3) (mg/day) ($p=0.042$). [Conclusion] Pleural effusion, high levels of serum ferritin and high dose of oral prednisolon may be the risk factors of relapse in patients with AOSD.

P1-267

A case of adult onset Still's disease (AOSD)-like manifestations concomitant with metastatic thyroid papillary carcinoma

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Conflict of interest: None

A 68-year-old Japanese man was suffering from abrupt onset of high-fever accompanied by arthralgia, myalgia, sore throat, macular eruption and liver dysfunction. Six-month before the onset, ^{18}F-FDG PET/CT had detected unexpectedly three calcified thyroid lesions without ^{18}F-FDG uptake. Two-month before the onset, US-guided fine needle aspiration made a diagnosis of papillary thyroid carcinoma (PTC). Soon after occurrence of the rheumatic manifestations, the subsequent ^{18}F-FDG PET/CT showed not only the three thyroid lesions same as previous one, but also 18F-FDG uptake in the thyroid lesion. A diagnosis of adult-onset Still's disease (AOSD)-like manifestations associated with PTC was made, and treatment with 40 mg/day of prednisolone (PSL) resolved the symptoms and liver dysfunction promptly. Dosage of PSL was gradually tapered without recurrence. Five-month later, total thyroidectomy followed by ^{131}I thyroid ablation treatment was performed at PSL dosage of 18 mg/day. Seven-month after the thyroidectomy, dosage of PSL was tapered to 2 mg/day, and both AOSD-like manifestations and PTC had not relapsed. Making a diagnosis of AOSD, it may be necessary to consider the presence of associated malignancy including solid tumor such as PTC.

P1-268

Adult onset Still disease-like clinical condition developed from gouty arthritis

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Conflict of interest: None

A 54-year-old man who had repeated gout attack developed swelling and redness from light knee to lower leg. He was diagnosed and treated as cellulitis, but failed therapy with antibiotics. Suspected gout attack, he was given colchicine and NSAIDs, but failed. Since he additionally developed high grade fever, elevated serum ferritin and transaminases, we diagnosed him with Adult Onset Still Disease(AOSD)-like clinical state. Medication of prednisolone (1mg/kg) and tacrolimus was started, but it was not enough. Medication of infliximab with MTX was started, his symptom was disappeared.

P1-269

A case of adult-onset Still's disease with large vessel vasculitis

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Conflict of interest: None

A 19-year-old woman was admitted to our hospital becase of a week history of high fever, pharynralgia, and myalgia. She had high fever, sore throat, cervical lymphnode swelling, splenomegaly and her data showed leucocytosis, high CRP level, high liver enzyme, high ferritin level (6247 ng/ml), RF negative, antinuclear antibody negative. So she was considered as adult onset Still's disease (AOSD). But enhancement chest magnetic resonance imaging (MRI) revealed thickened wall of aortic arch and branch artery with enhanced. Administration of 55 mg/day (1 mg/kg/day) of prednisolone (PSL) was started and physical symptoms, laboratory data and imaging significantly improved. The dose of PSL was decreased without suffering a relapse. This is the first case report of adult onset Still's disease with large vessel vasculitis.

P1-270

Four cases of steroid-resistant adult onset Still's disease

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Conflict of interest: None

Adult onset Still's disease (AOSD) is systemic inflammatory disorder of unknown etiology and pathogenesis. Steroid therapy is effective in most cases, but some are resistant and need combined use of other drugs such as methotrexate, cyclosporin A (CsA) and tocilizumab. We summarized 4 cases of AOSD, who needed hospitalization and received immunosuppressants, and assessed the efficacy of the agents, especially CsA. All cases were female. Three were new-onset, and one was recurrent. About the former, the flares were observed when taking high dosage of steroid after steroid pulse therapy, and CsA was added. CsA trough level was controlled to 150-200 ng/ml. Though CsA was effective in 2 cases, one case was also refractory to CsA. Instead of CsA, tacrolimus (TAC) was instituted at the trough level of 5-10 ng/ml, which leads to remission. About the latter, the recurrence was occurred when using 5mg/day of prednisolone (PSL). PSL was increased to 40mg/day, but it was ineffective. CsA was appended, and which resolved the disease. Observed side effects were renal dysfunction and opportunistic infection, and both were mild. Our cases suggest that the prompt use of immunosuppressants, such as CsA, is effective for steroid-resistant AOSD, and it also may be useful for reducing steroid dosage.

P1-271

A case of Adult-onset Still`s disease with severe liver dysfunction successfully treated by plasma exchange.

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Conflict of interest: None

41-year-old male developed polyarthritis May 2011. He had high grade fever and skin eruption. Laboratory data revealed elevated CRP(10.8mg/dL), liver dysfunction(GOT146IU/L, GPT112IU/L, ALP474IU/L,γGTP127IU/L), and elevated serum ferritin(6410ng/mL). Bone marrow examination showed hemophagocytic syndrome. A diagnosis of Adult-onset Still`s disease was made, and methyprednisolone pulse therapy, subsequent administration of prednisolone 60mg/day and cyclosporin(100mg/day) was done. However, his liver dysfunction got worse (GOT5884IU/L, GPT3528IU/L, ALP832IU/L,γGTP577IU/L) and serum ferritin level was markedly elevated(197117ng/mL). The patient was transferred to our hospital Sep 2011. In addition to mPSL pulse and cyclosporine(200mg/day), plasm exchange was performed. Liver dysfunction and hemophagocytic syndrome were recovered. We report a case of life-threatening Adult-onsent Still`s disease with severe liver dysfunction and hemophagocytic syndrome, successfully treated by mPSL pulse therapy, cyclosporine and plasma exchange.

P1-272

Adult-onset Still's disease in a patient over 80 years old successfully treated with cyclosporin A and methotrexate added to predonisolone.

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Conflict of interest: None

We report an 82-year old Japanese woman with adult onset Still's disease(AOSD). This patient was admitted to our hospital for evaluation of high fever, arthralgia, cough and sore throat, which had not responded to antibiotics. After exclusion of infectious diseases, ANCA-associated vasculitis and lymphoma, the diagnosis of AOSD was made, based on high fever, sore throat, arthralgia, leukocytosis, abnormal hepatic function and a remarkable elevated level of serum ferritin. The AOSD was diagnosed according to the Yamaguchi criteria of 1992. She was treated with steroid pulse therapy(methyl predonisolone 1000mg/day for consecutive 3days) followed by intravenous prednisolone(100mg/day). This therapy, however, was not effective for clinical symptoms and laboratory data. Then cyclosporin A (100mg/day) and methotrexate(7.5mg/week) were added. After this additional treatment, her fever and polyarthralgia subsided with improvement of serological parameters, such as CRP and ferritin. Then, the dose of predonisolone was successfully tapered to 7mg/day. As far as we examined, the onset of AOSD over 80 years been extremely rare. Our patient suggest that AOSD should be included in the differential diagnosis of fever of unknown origin, when ANCA-associated vasculitis is ruled out.

P1-273

A case of a refractory adult still disease (ASD) that tocilizumab was successful and the joint echo was useful to the disease evaluation

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Conflict of interest: None

Case report: A 54 years-old woman. Which was diagnoses as ASD. Although the steroid medical treatment including a pulse therapy was started, the reaction was poor, hemophagocytic syndrome was also concurred with, and remission was obtained at last by CyA addition medication. However, since an arthritic pain and generation of heat were revived in process of steroid gradual decrease, combined use of low-dose MTX was also carried out, but disease became more serious conversely by MTX medication. Then, since IL-6 in serum was a high price (49.8 pg/ml), tocilizumab (8mg/(kg)) was started the two whole weeks. As a result, condition and a blood test view have been improved, and loss in quantity of CyA and steroid was also attained. Furthermore, the echo finding improved the thickness of disease joint synovial membrane or the unusual blood-flow signal which were accepted before medical treatment. Tocilizumab experienced this time one example of ASD which carried out excellent. Until now, together with the report currently accumulated, it is thought to the ASD of intractable case also by CyA or MTX by steroid resistance that tocilizumab is effective. Moreover, this case is one precious example which could point out the change on a joint echo before and after medical treatment.

P1-274

Two cases of chroic arthritis type adult onset Still's disease treated with biologics

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Conflict of interest: None

The benefit of biologics for Adult Onset Still's Disease is being discussed. We used biologics for chronic arthritis type AOSD and closely followed the courses this time, therefore we will report on that. [Case 1] 48 years old, female. In 2006 when she was at the age of 42, the symptom appeared. The treatment was started with PSL45mg, and December of the same year since she was making satisfactory progress. Although it was increased to 7.5mg/week, PSL couldn't be reduced to or below 15mg. Therefore, we changed it to infliximab in March 2011, then DAS28-ESR was decreased to 1.0 after 6 months and she achieved complete remission. Serum IL6 was significantly decreased after the administration of infliximab, rather than tocilizumab. [Case 2] 49 years old, female. In 1986 when she was at the age of 24, the symptom appeared with fever and polyarticular pain, which were improved with PSL40mg, though repeatedly reappeared as the amount was decreased. It was poorly controlled even with the concurrent use of MTX, azathioprine, etc. Therefore, in March 2004, we used infliximab, by which she had less disease activity and has had no obvious reappearance since then, up until now. [Discussion] There is a possibility that infliximab is highly beneficial for chronic arthritis type AOSD.

P1-275

Functional change of Mesenchymal Stem Cell through Adipogenesis: An *In Vitro* Model of Bone Edema

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Conflict of interest: None

[Objectives] Bone edema is a pathological change in rheumatoid arthritis (RA) that is detectable by magnetic resonance imaging (MRI). The recent histological analyses revealed that bone edema is the result from the replacement of adipose tissue with inflammatory cells. Here we demonstrate the possible roles of mesenchymal stem cell (MSC) in bone edema formation and the pathogenic potential of the cell. [Methods] Adipogenesis of bone marrow-derived MSC were induced by standard adipogenic induction medium in the presence or absence of cytokines. The cytokine productions were screened by antibody array system and confirmed by ELISA. The migration assay was performed to determine the locomotive abilities of MSC. [Results] The TNFa, interleukin (IL)-1b, IL-6 and TGFb inhibit the adipogenesis of MSC. Production of IL-6 was remarkably reduced in MSC after adipogenesis. Conversely, the IL-8 secretion was augmented after adipogenesis. The mobility of MSC after adipogenesis is reduced in migration assay compared to that of undifferentiated MSC. Our data suggest that the inflammatory milieu promotes the appearance of bone edema by blocking adipogenesis of MSC in bone marrow.In the bone edema, the enhanced IL-6 production and the increased mobility of MSC may contribute to the progression of RA.

P1-276

Poly-lactic-co-glycollic acid scaffold enhances osteoblastogenesis of mesenchymal stem cells

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Conflict of interest: None

[Objectives] Although treatment of rheumatoid arthritis (RA) has evolved, it is still a challenge to aim bone repair. Mesenchymal stem cells (MSCs) possess the property to differentiate into osteoblasts and chondrocytes with immunosuppressive effect. [Methods] Therefore we have evaluated the effect of poly-lactic-co-glycollic acid (PLGA) sheet as a scaffold on mineralization of MSCs under inflammatory conditions. [Results] When MSCs was seeded on PLGA sheet and simply cultured in growth media for 7 days, enhance mineralization was observed compared to MSCs alone. Culture in osteogenic induction medium further enhanced this effect. In order to evaluate the efficacy *in vivo* MSCs were directly injected intra-articularly or PLGA sheet seeded with MSCs (PL-MS) was implanted into ankle joints of collagen induced arthritis (CIA) rats. Implantation of PL-MS to bilateral ankles significantly suppressed arthritis score with less bone destruction analyzed by X-ray, micro CT and histology while intra-articular injection had less effect. In conclusion, PLGA sheet possess the nature of enhancing mineralization of MSCs and simultaneously suppressed arthritis and bone destruction. Our results highly implicate that MSCs is an useful tool for RA treatment aiming joint repair.

P1-277

Toward understanding the pathophysiology of Progressive Pseudorheumatoid Dysplasia and the roles of WISP3 in cartilage

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Conflict of interest: None

[Objectives]WISP3 mutations cause Progressive Pseudorheumatoid Dysplasia (PPD). The clinical pathophysiology of PPD resembles osteoarthritis (OA), however, there has been few reports revealing the molecular pathobiology of PPD and the roles of WISP3 in cartilage. **[Methods] and [Results]**We first obtained hip cartilage from PPD and primary hip OA patients, knee cartilage from healthy people and created primary chondrocyte cultures. We then examined the expression of type II collagen, MMP13, and ADMTS5. The both PPD and OA groups showed low expression of type II collagen and highly expression of MMP13 and ADMTS5. Also, the MMP13 or ADAMTS5 expression decreased in PPD and OA groups after we added WISP3 conditioned medium (CM). Next, we added WISP3 CM onto ATCC cell line. The cell proliferation significantly increased in WISP3 CM group, but not in WISP3 (-) group. The expression of type II and X collagen increased in WISP3 CM group, but not in WISP3 (-) group. Taken together, these results indicate that the molecular pathobiology of PPD might resemble OA, WISP3 can decrease the inflammatory cytokines in both PPD and OA patients, and WISP3 could increase normal chondrocyte proliferation and differentiation. Further studies will be needed to better understand the pathophysiology of PPD.

P1-278

Analysis of the expression of tryptophan hydroxylase 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 levels. TPH has the two isoforms; TPH1 expressed in the peripheral and CNS tissues expressing serotonin, such as skin, intestine and the pineal gland, and TPH2 expressed exclusively and dominantly in CNS. We previously reported that decoy receptor 3 (DcR3) overexpressed in rheumatoid synovial fibroblasts (RA-FLS) stimulated with TNFα inhibits Fas-induced apoptosis and that DcR3-Fc inhibited cell proliferation induced by TNFα or IL-1β via TL1A expressed on RA-FLS. Further, we found that TPH1 mRNA is expressed in RA-FLS and suppressed by DcR3 by using comprehensive genetic analysis using microarrays. We investigated the expression of TPH in RA-FLS and the effects of TNFα, IL-1β and DcR3 on the expression of TPH. [Methods] After RA-FLS were incubated with TNFα(1ng/ml) or IL-1β(1ng/ml) for 24h, or DcR3(1μg/ml) for 12h, the relative expression levels of mRNA of TPH1 and TPH2 in RA-FLS were quantified by real-time PCR. [Results] The mRNA expression of TPH1 and TPH2 in RA-FLS was identified. TPH1 mRNA expression was decreased by DcR3 in RA-FLS. Meanwhile, TPH1 mRNA expression was also decreased by TNFα or IL-1β in RA-FLS.

P1-279

Abundance of Calpain and Aggrecan-Cleavage Products of Calpain in Degenerated Human Intervertebral Discs

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Conflict of interest: None

[Objectives] There are some reports of relation between calpain and cartilage tissue degeneration. Though it is not strictly part of the usual joints, the structure of the intervertebral discs (IVD) is shortly presented as its pathology is very common. We focused on proteinase; calpain that catalyze the limited proteolysis of proteins. Aim of this study is to assess the expression of calpains and calpain-induced aggrecan fragmentation in early and advanced stages of degeneration of human IVD. [Methods] Disc tissue samples of 55 patients were divided into two groups. Protein levels of two types of calpain, m-, μ- and their inhibitor calpastatin were assayed, and immunohistochemical techniques were used. We also assayed purified aggrecan fragmentation by Western blotting and immunohistochemistry with VPGVA antibody, which recognizes the m-calpain generated neo-epitope GVA. [Results] Discs at degenerated stages expressed significantly high levels of calpains and calpastatin, and cells expressed degenerative enzymes. Further finding showed that antiGVA-reactive aggrecan fragments was significantly higher in discs at advanced compared with early stages of degeneration. These findings suggest that calpains may be involved in human IVD degeneration via proteoglycan (PG) cleavage.

P1-280

Histone Deacetylase Inhibitor Suppresses mechanical stress-induced cartilage matrix Degradation

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Conflict of interest: None

[Objectives] Catabolic mechanical stress causes degradation of articular cartilage via activation of RUNX-2, and up-regulation of MMPs, and aggrecanases expression. We previously showed that histone deacetylase inhibitor (HDACi) can repress the cartilage destruction in an animal arthritis model. However, the precise mechanisms of HDACi in prevention of matrix degradation are not fully understood. [Methods] In the current study, cyclic tensile strain (CTS, 0.5 Hz, 10% elongation) was applied for 30 minutes in SW1353 cell and human chondrocytes. The amplitude and the frequency of stretch were controlled by ST-140 (STREX, Osaka, Japan). Cells were incubated with or without HDACi (TSA: 10nM, MS-275: 100nM) for 12 hours before CTS. The expressions of RUNX-2, ADAMTS-5, MMP-3, and type II collagen (COL2A1) were examined by real-time PCR. [Results] HDACi suppressed CTS-induced expressions of RUNX-2, ADAMTS-5, and MMP-3, but up-regulated COL2A1 expresssion. The protein expressions of RUNX-2 and ADAMTS-5 evaluated by immunocytochemistry were also enhanced by CTS, but inhibited by HDACi. Our results suggested the inhibitory effect of HDACi on mechanical stress-induced RUNX-2, ADAMTS-5, and MMP-3 expression, that supported the effects of HDACi on cartilage destruction *in vivo*.

P1-281

The effects of hinokitiol on human cells revealed by a proteomic approach

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Conflict of interest: None

[Objectives] Hinokitiol, a natural substance extracted from plants like Chamaecyparis obtusa var. formosana, is known to have various functions such as anti-bacterial activities. However, the effects of hinokitiol on human cells have not been fully understood. Thereby, we here comprehensively analyzed the effects of hinokitiol on human peripheral blood mononuclear cells (PBMCs) by proteomic approach. [Methods] PBMCs were cultured with or without hinokitiol for 24 hours, then the protein profiles of the PBMC samples were compared by 2-dimensional fluorescence difference gel electrophoresis. The protein spots whose intensity was altered by the stimulation with hinokitiol were subjected to protein identification by mass spectrometric analysis and the subsequent protein data base searching. [Results] The intensity of 63 protein spots was increased to more than 1.5 folds or decreased to less than 1/1.5 folds by the hinokitiol stimulation($p<0.05$). We identified 22 out of the 63 proteins, which are involved in cytoskeleton structure, polypeptide synthesis, homeostasis, and apoptosis. [Conclusion] This study identified multiple proteins that are significantly influenced the hinokitiol in PBMCs. Our data would be of great help to use hinokitiol more effectively and safely in daily life.

P1-282

Meaning of intervention in the treatment for rheumatoid arthritis by medical social worker

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Conflict of interest: None

[Objective] to examine the meaning of intervention in the treatment by medical social worker (MSW) when rheumatoid arthritis (RA) patients start and continue biologic treatment. **[Methods]** We looked into 107 cases which we gave advice to outpatients as MSW between January 2005 and October 2011. **[Results]** Counseling about biologic agents was 58.9% of all cases, about nursing-care insurance was 23.4% and about other social security system was 17.7%. On counseling about biologic agents, we enhanced their understanding and appreciation of clinical condition and treatment about RA. We further guided patients to the use of social security system after its explanation. In addition, we gave them information about medical service and nursing-care system in our hospital, and supplemented informed consents by doctor. In the result, 76.2% of cases consented to the introduction of biological therapy. **[Conclusion]** Most RA patients have psychological and economic worry about advanced therapy. MSW support RA patients with the use of medical knowledge and social-work technique while exploring aspects of individual life. This multilateral support helps patient's decision about the introduction and continuation of biological therapy. More practical intervention is expected in the future.

P1-283

The tendency of inquiries by telephone from out patients in this hospital and the answers to them

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Conflict of interest: None

【Objective】 The tendency of inquiries from out patients and answers to them were analyzed in order to obtain the basic data for improvement of the adherence【Method】 About 1400 outpatients in this hospital under observation were taken as a population of this analysis. The inquiries accepted in this hospital between August 1, 2011 and October 15, 2011 were recorded. They were analyzed by considering the sex, age, medicine taken, date, name of the disease, subject of query, and answer from this hospital【Results】 The total inquiries were 107 times (male: 13, female: 94, 53.7±17.1 years old); biologics:23.4%, steroidal: 63.6%, MTX: 30.8%; RA:50.5% and SLE:12.1%) Time: in the morning 66.3%, Monday and Tuesday: 21.5%, Friday: 23.3%. Subject: wishing interview: 62.6%, medication: 22.4%. Answered after confirmed by the Doctor: 44%, by telephone: 27.1%【Summary】 There was not a significant difference in this analysis of the inquiries between the disease and biologics. In the case of medication with the significant side effects, it is surmised that a informed consent is well carried out than other normal medicines. It is supposed that inquiries about the medicines will be decreased, if the education of the patients is completely carried out, because the 22.4% inquiries was about medicines.

P1-284

For RA patients to improve their self management ability.

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Conflict of interest: None

[Objectives] Recently, the therapy of rheumatoid arthritis (RA) has advanced considerably. In our hospital ward, however, there is no support tool for patients' self-management, and intervention of nurse is inadequate. To examine the efficacy of instruction with the pamphlet made with literatures, expert opinions and patients' demands. [Methods] This was a baseline–controlled study of 16 RA inpatients of our ward. Instruction, which was based on the pamphlet, was held 3 times per one patient. Data was collected with self-administered questionnaire before and after instruction, and 1 week after discharge. Survey items were attribute, knowledge, self-efficacy and free writing about the pamphlet. [Results] Improvement of patients' knowledge about RA and self-efficacy were recognized after the instruction, compare to before it ($p<0.01$). However, after discharge, its knowledge and self-efficacy were declined, compare to just after the instruction. It was estimated that the instruction with the pamphlet was effective for improvement of patients' knowledge and self-efficacy. After the discharge, their knowledge and self-efficacy were declined, and patients had a tendency to have a stress or anxiety. Thus, it was thought that the continuous instruction for outpatients was needed.

P1-285

Relationship among social support, QOL, and disease activity in RA patients.

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Conflict of interest: None

[Background] The quality of life (QOL) in RA patients is generally low, due to disease-associated physical dysfunction as well as psychological and social problems. It is reported that the social support (mainly from family and friends) promotes positive health behavior and decrease psychological stress, leading to the improvement of QOL. However, few reports as to the associations between social support, disease activity and QOL in RA patients have been performed previously. [Objectives] To clarify the relationship among social support, QOL, and disease activity in RA patients. [Methods] SF-8 for the measure of QOL and social support scale (Iwasa, 2007) were used, and their association with DAS28 was analyzed. [Results & Discussion] Although SF-8 scores showed strong association with DAS28 scores, social support scores showed significant association only with mental QOL and did not showing association with DAS28 scores. Multiple regression analysis showed that DAS28 scores were significantly related to physical QOL, and also that DAS28 and social support scores (especially from friends) were significantly associated with mental QOL. The results suggest that encouraging social support particularly from friends as well as reducing disease activity may be important for QOL in RA patients.

P1-286

The differences of patients' background and therapies among hospitals (First analysis with data from NinJa 2010)

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Conflict of interest: None

[Objectives] To know the differences of clinical background and therapies among hospitals. [Methods] Data from RA patients registered in the large cohort database (NinJa; National database of rheumatic diseases by iR-net in Japan) in 2010 was analyzed. The clinical factors bellow were compared among 9 hospitals which registered more than 300 patients ; average age, duration of disease, Stage, DAS28, SDAI, remission rate, mHAQ, and usage of steroids, MTX and biologics. [Results] 7254 patents data were registered to NinJa in 2010. The hospitals varied in average age from 60.8 to 8.5, in average duration of disease from 9.2 to 19.9 years, in rate of Stage I from 1.3% to 37.9%, in average DAS28 from 2.9 to 4.1, in average SDAI from 7.4 to 12.2, in rate of remission from 14.1% to 30.8%(SDAI), 8.0% to 24.0%(Boolean), in mHAQ from 0.2 to 08, in average dose of steroids from 3.7 to 4.7, in average dose of MTX from 6.6 to 8.5 mg and in rate of usage of biologics from 9.7% to 35.9%. [Conclusion] The great differences were found in background of patients among hospitals. The differences of therapies, especially usage of biologics, might have resulted from those differences. Then it is important to consider the background of patients on the comparison of the treatment outcome among hospitals.

P1-287

Effective use of RA database in our hospitalfrom the standpoint of health information management

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Conflict of interest: None

【Purpose】Developing a database to help improve outcomes in patients with RA, we have been achieved conjunction with physicians. But it is inadequate to cooperate with other medical staff. In order to promote effective use and maturation of the RA database in the medical team, we tried to reconstruct RA database.【Methods】Non-physician medical staff involved in RA (nurses, physiotherapists, speech therapists, social workers) rased medical problems of RA in the current work and offered solutions. In addition, we stored and integrated the medical information in the database.【Results】Integrated information with the ex-data enabled us to analyze information chronologically in a cross-data manner. In addition to clinical information, it is possible to manage information such as mental anxiety for biologics. Although RA database - system rebuilding in the medical team matured, co-medical staff are not able to make the most of information in the database. Utilizing RA database system, we would like to support the medical team so the patient can receive the final benefit.

P1-288

Relation between an affected region of joints and functional disability in patients with rheumatoid arthritis in Japan: a nationwide study based on the *NinJa* database 2010

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Conflict of interest: None

Objective: To identify a region of joints that affects functional disability in patients with RA. **Methods:** Data were extracted from *Ninja* database 2010. Total Joint indices (TJI) of upper/large, upper/small, lower/large, and lower/small regions were calculated as described previously (1). Multiple comparisons of mHAQ were performed between TJI=0 in all 4 regions and TJI=0 except for one region. **Results:** Mean (SE) of mHAQ was 0.312 (0.014) for TJI=0 in all regions (n=1651), 0.565 (0.023) for TJI positive only in upper/large region (n=844), 0.330 (0.020) for TJI positive only in upper/small region (n=665), 0.532 (0.028) for TJI positive only in lower/large region (n=488), and 0.256(0.046) for TJI positive only in lower/small region (n=79). Groups of TJI positive in upper/large and lower/large regions had significantly higher mHAQ than other groups. Upper/large region had connection with dressing, eating, hygiene, and grip, whereas lower/large region had relation to arising, walking, reach, and activities. **Conclusion:** Large joint regions predominantly affected functional disability in RA patients. **Reference:** 1. Nishiyama S, et al. Proposing a method of regional assessment and a novel outcome measure in rheumatoid arthritis. Rheumatol Int. DOI 10.1007/s00296-011-2058-9, 2011

P2-001

Acetyl-Proteomics for the Investigation of Pathological Molecules In Rheumatoid Arthritis

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Conflict of interest: None

[Background/Objective] To investigate roles of acetylation in the pathogenesis of RA, we here applied acetyl-proteomics to peripheral blood mononuclear cells (PBMCs) between RA and healthy. One of the proteins predominantly acetylated in RA was identified to be alpha-enolase (ENO1). We tried to investigate acetylation of ENO1 affect the function, for example A) Localization B) Activity and C) Antigenecity of ENO1. [Methods/results] A) We prepared the cytosol and nuclear fraction of the PBMC. Next, we detected the acetylated and total ENO1 of each fraction samples. As a result, the localization of ENO1 wasn't changed by the acetylation. B) We prepared acetylated ENO1 by *in vitro* acetylation. We measured the enzyme activity of acetylated and non-acetylated ENO1. As a result, acetylation of ENO1 up-regulated the enzyme activity. C) Acetylated and non-acetylated ENO1 were subject to WB using some sera of patients with RA. [Conclusion] As a result, the antigenecity of ENO1 wasn't changed by the acetylation. We found that acetylation of ENO1 up-regulated the enzyme activity. This data indicate that the activation of ENO1 by acetylation may participate in the pathogenesis of RA.

P2-002

The induction of human tolerogenic dendritic cells by protein kinase C inhibitor, bisindolylmaleimide I

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Conflict of interest: None

[Objectives] Tolerogenic dendritic cells (tDCs) play a critical role in immune tolerance and regulation of autoimmune disease such as rheumatoid arthritis. Recently, the bioactive molecules and drugs that enhanced induction of tDCs have been reported and applied to the therapy. Therefore, we screened these molecules and analyzed the mechanism of these molecules in induction of tDCs. [Methods] From the libraries of lipids, nuclear receptor ligands, and kinase inhibitors, we screened the molecules that showed lower expressions of CD80, CD83, and CD86 and that produced higher concentration of IL-10, compared with mature DCs. [Results] The former is 24 kinds and the latter is 10 kinds. Of these, protein kinase C inhibitor, bisindolylmaleimide I showed high production of IL-10 and suppression of allogenic T cell responses. Moreover, bisindolylmaleimide I-treated DCs remained phagocytosis and enhanced the induction of regulatory T cells. Therefore, bisindolylmaleimide I may be potential agent for the induction of human tDCs.

P2-003

Impact of disease activity on lipid metabolism in rheumatoid arthritis patients–TOMORROW study-

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Conflict of interest: None

[Background] Arteriosclerosis is risk factors in Rheumatoid arthritis (RA) patients and is associated with changes in the lipid profile. Therefore, we conducted a prospective cohort study to evaluate risk factors and lipid profile in RA patients associated with disease activity (TOMORROW study). [Method] The participants in the study were consisted 202 consecutive RA patients (109 patients receiving biological agents) and 202 age- and sex-matched healthy volunteer. This study was designed to evaluate lipid profiles and serum adipocytokine (adiponectin and leptin) in relation to disease activity in RA patients prospectively. [Result] RA patients had significantly higher percentage of body fat rate ($p<0.001$) and lower serum level of Total cholesterol, HDL-cholesterol and LDL-cholesterol ($p<0.05$) than control at baseline. Change values of three cholesterol after 1 year were inversely correlated with that of disease activity score (DAS) 28 ($p<0.05$). Serum adiponectin was associated with DAS28 at baseline, but change value of adiponectin was not correlated with that of DAS28 after 1 year. [Conclusion] The results confirm that improvement of disease activity increased the level of lipids, but did not change plasma levels of adiponectin after 1 year in RA patients.

P2-004

Assessment of infertility in patients with rheumatoid arthritis-Analysis in IORRA cohort-

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Conflict of interest: None

[Objectives] To clarify the infertility in patients with rheumatoid arthritis (RA). [Methods] By using the IORRA survey in October 2009, patients who wanted to become pregnant were recruited. Infertility was defined who could not become pregnant within two years or had treatment for infertility. The factors associated to infertility were analyzed between patients who became naturally pregnant and patients who were infertile and nulliparity. [Results] Among 179 recruited patients, 84 (47 %) patients became pregnant naturally, 73 (40 %) patients were infertile and 22 (13 %) patients gave up getting pregnant because of RA treatment. The average duration until pregnancy in patients with natural pregnancy was 0.8 years. Among patients with infertility, 32 patients became pregnant within 2.4 years and 41 patients was stayed nulliparity during 4.2 years. The age at expectation for pregnancy was younger in patients with natural pregnancy than that in patients with nulliparity (33.2 vs 35.8 years). The dose of prednisolone (3.2 vs 4.9 mg/day) and the rate of NSAID use (27.6 vs 47.4 %) were lower in patients with natural pregnancy than that in patients with nulliparity, respectively. No difference was observed in CRP, ESR, and past methotrexate use between these two groups.

P2-005

Body mass index and disease activity in patients with rheumatoid arthritis: results from *NinJa* 2010

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Conflict of interest: None

[Objectives] To investigate whether body mass index (BMI) influences on the disease activity of rheumatoid arthritis (RA) using data of *NinJa* (National Database of Rheumatic Diseases by iR-net in Japan) in 2010. [Methods] A total of 3,255 RA patients (2,631 women and 624 men) were included in the analyses. They were categorized by BMI (kg/m^2) (Group A: <18.5, Group B: 18.5-21.9, Group C: 22.0-24.9, Group D: ≧25.0, Group E: ≧30), and their composite disease activity indices (DAS28-ESR, SDAI) and their components (TJC, SJC, PtGA, PtPain, PhGA, mHAQ, CRP, ESR) were compared in a gender-specific manner. [Results] SDAI was highest in Group A in both female and male. Each SDAI (average) and SDAI remission (<3.3) rate (%) were as follows; SDAI: Group A(12.2)>B(9.7)>C(8.2)>D(6.7)>E(4.0) in male and A(11.2)>B(8.7)>C(8.3)<D(8.8)<E(10.6) in female, remission rate: A(20.0)<B(22.6)<C(28.6)<D(33.6)<E(50.0) in male and A(16.3)<B(26.9), C(24.9), D(25.7)>E(20.7) in female. Other components showed similar trends to SDAI. [Conclusion] BMI appears to be negatively associated with RA disease activity, but their trends may be different between female and male patients.

P2-006

Pattern of articular involvement in elderly-onset rheumatoid arthritis

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Conflict of interest: None

<Purpose> To investigate articular involvement in patients with elderly-onset RA. <Methods>In RA patients who participated IORRA at October 2009, we selected 338 patients with EORA, defined as RA with onset at age 65 years or over. Controls were duration-matched RA patients with onset at age <65 years (YORA). <Results> Mean RA duration of both groups was six years. The proportion of patients with tenderness on metatarsophalangeal joints in EORA was significantly lower than that of YORA (YORA 32.1%, EORA 20.7, $p<0.05$). However, the proportion of patients with shoulder, elbow, and knee joint involvement were not significantly different between EORA and YORA. <Discussion> Previously, it has been reported that EORA differs at presentation from YORA by more frequent involvement of large joint such as shoulders, knees. However, the present study showed that pattern of articular involvement of EORA was similar to that of YORA.

P2-007

Assessment of 4 atypical cases of rheumatoid arthritis whose initial symptoms were limited to the legs.

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Conflict of interest: None

[Objectives] We present characteristics of 4 rheumatoid arthritis (RA) patients whose symptoms were limited to the lower extremities. [Methods] Since April 2011, we examined age, RF, anti-CCP antibody, clinical course, and treatment of 4 RA patients whose initial symptoms were limited to the lower extremities. [Results] Patients' ages were ①59, ②68, ③76, ④73 years old. Their RF value (<20 IU) were ①13, ②10, ③4, ④30. Their anti-CCP antibody value (<4.5 U/ml) were ①0.8, ②1.7, ③0.8, ④0.7. Their affected joints were ①bilateral knees, ②bilateral knees, bilateral 2,3,4 MTP joints, ③bilateral knees, bilateral ankle, ④left ankle. Their treatments were intra-articular steroid injection, and ①salazosulfapyridine (SSZ), ②SSZ and bucillamine, ③SSZ, ④methotrexate. In this 4 patients, only 1 patient satisfied the ACR/EULAR 2010 classification criteria (scores:①3, ②5, ③7, ④4). Generally, initial symptoms of RA tend to be bilateral arthritis of small joints of upper extremities. However, there were patients whose first symptoms were large joints of lower extremities. And they had tendency of older age, and negative RF and anti CCP antibody. Because they didn't meet the criteria, we had difficulty in diagnosing. However, they were clinically diagnosed as RA, and our treatment as such were successful.

P2-008

The symptoms of arthritis around feet raise Disease activity score of 28 joints (DAS28)

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Conflict of interest: None

【Background】 Although feet and ankle are not included in component of disease activity score of 28 joints(DAS28) in patient

with rheumatoid arthritis(RA), the disabilities of them are a part of disease. The aim of this study is to investigate whether other joints except for 28 joints influence to DAS28.【Materials & methods】132 out patients (98 female, 34 male) with RA was included in this study. The mean age was 64.1±12.1 years. The mean disease duration was 10.2±9.2 years. The findings of 28 joints, 10 metatarsophalangeal joints, feet ankles and hips are administrated. The patients who have symptoms of other joints except for 28 joints categorize into Group A. The others categorize into Group B. DAS28 and the components of it are compared between Group A and B.【Result】In Group A and B, DAS28-CRP4 were 3.60 and 2.46, respectively. With TJC(5.8 vs 1.3) and SJC (2.9 vs 1.1) and gVAS (42.5 vs 24.9) Group A is significantly greater than Group B. But CRP (0.67 vs 0.66mg/dl) and ESR (30.6 vs 30.9 mm/hr) is not significant difference between Group A and B.【Conclusion】If DAS28or gVAS are high, there may be to exist arthritis around feet and / or ankles. For targeting deep remission with treatment of RA, we must take care for arthritis of other joints except for 28joints.

P2-009

Influence of air pressure changes on the autonomic nervous system in patients with rheumatoid arthritis or fibromyalgia syndrome

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Conflict of interest: None

[Objectives] We measured the urinary levels of catecholamine's in patients with rheumatoid arthritis (RA) or fibromyalgia syndrome (FM), and investigated the influence of air pressure changes on RA and FM. [Methods] The subjects consisted of 9 patients with RA (105 urine samples) and 6 with FM (primary FM: 2 patients, RA-complicated FM: 4 patients)(199 urine samples). Using these samples, we measured the 24-hour urine levels of adrenaline, noradrenaline, dopamine, and VMA. [Results] 1) In the RA patients, the urinary adrenaline and noradrenaline levels at a high air pressure were significantly higher than at a low air pressure. Furthermore, the noradrenaline level at a high air pressure was significantly higher than at an intermediate air pressure. 2) In the FM patients, the urinary adrenaline and noradrenaline levels at a high air pressure were lower than at a low air pressure. There were no marked changes in the urinary dopamine level between high and low air pressures in the RA patients. However, in the FM patients, the urinary dopamine level at a low air pressure was significantly higher than at a high air pressure. Furthermore, this parameter at an intermediate air pressure was significantly higher than at a high air pressure.

P2-010

Two elderly cases of the unidentified acute inflammatory reaction on bone muscular system after 3.11 East Japan earthquake disasters

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Conflict of interest: None

[Objectives] Two elderly persons admitted our hospital because they had acute fever and pain of limb, after 3.11 Japan earthquake. [Methods] Case report [Results] [Case 1] 89 years old man. He evacuated from Ishinomaki. He had fever of 39.2 degrees on March 23. Influenza is negative. Blood examination showed WBC 20300/ml, CRP 23.4mg/dl. TP 5.4mg/dl, Alb 2.4mg/dl. There is no pneumonia image in chest X-ray and no urinary bacteria. He treated with antibiotics as an unidentified infectious disease. However his main complaint changed his left thumb pain on March 26. We started steroid therapy as old onset rheumatoid arthritis. His sharp pain, swelling and local heat of left thumb disappeared on March 30. [Case 2] 94 years old woman. She evacuated from Namie. She had fever of 38.0 degrees on March 25. She felt pain and swelling of her left upper arm. Blood examination showed WBC 5900/ml, CRP 8.0mg/ml, ESR 110mm/1H. TP 6.2mg/ml, Alb 2.8mg/ml. There is no pneumonia image in chest X-ray and no urinary bacteria. We started steroid therapy as untypical RS3PE. Her symptoms disappeared on March 27. We thought that these symptoms were caused for cold, leaving their home town, the insufficient eating habits. These cases support that the theory of environmental factors evoked rheumatic disease.

P2-011

serum lipids among iraqi patients with active rheumatoid arthritis

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Conflict of interest: Yes

[Objectives] To detect the changes in serum lipids among Iraqi patients with active rheumatoid arthritis (RA) and the effects of drug therapy. [Methods] 50 patients with active RA and 50 matched healthy controls were studied with concentration on estimation of fasting serum lipid profile which is repeated after 3 month treatment with different disease modifying anti Rheumatic drugs regimens. Results 50 patients were included in this prospective study 47 female and 3 males. 50 healthy individuals were included in this study as a control group 45 female and 5 male. Our results showed a significant reduction of VLDL, LDL, HDL, serum cholesterol and serum triglyceride in patients with active Rheumatoid arthritis ($p=0.05$, 0.001, 0.001, 0.001 and 0.018 respectively). There was a significant relationship found between ESR and VLDL ($p<0.05$) serum triglyceride ($p<0.04$) and serum cholesterol ($p<0.01$). and there was a significant relationship between serum lipids and articular index VLDL ($p<0.05$), serum cholesterol ($p<0.01$) and serum triglyceride ($p<0.01$). After 3 months treatment with methotrexate or methoterxate+chloroquine ± large dose steroid or chloroquine alone. There was a significant reduction of inflammatory activity and serum lipids return to levels similar to that of control group.

P2-012

The causes of death in deceased patients with RA using NinJa 2010

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Conflict of interest: None

[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 2010. [Methods] 69 deceased patients with RA were registrated in Japanese 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. The mean age at death was 73.8 years old. [Results] The major causes of death of deceased patients

was infection in 17 patients involving in pneumonia in 12 patients. Next was malignancy in 18 patients, cardiovascular disease in 11 patients. The major causes of death were still infection in volving in pneumonia.

P2-013

Chronic kidney disease in patients with RA –a cross-sectional study using IORRA-

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Conflict of interest: None

We have previously shown that eGFR corrected by body surface area was a better indicator than eGFR to predict renal function in RA patients, and the proportion of patients corrected eGFR<60 was unexpectedly high. [Objectives] The aim of study was to characterize RA patients with chronic kidney disease (CKD). [Methods] 4509 RA patients who participated in 2009 IORRA study were included. eGFR was determined using Japanese MDRD equation, and was corrected by body surface area. The associations between corrected eGFR and patients' background as well as patients' characteristics were analyzed. [Results] In the subjects, corrected eGFR was 71.0±18.3 ml/min and the proportion of patients corrected eGFR<60 ml/min were 26.8 % (n=1183). Univariate analysis revealed that DAS28, J-HAQ, proportions of cardiovascular events and hypertension were significantly higher in patients with corrected eGFR<60 ml/min than those in patients with corrected eGFR≧60 ml/min. NSAIDs and glucocorticoid use were not different between groups, but the dose of MTX and use of biologics were significantly lower in patients with corrected eGFR<60 ml/min. [Conclusion] It was suggested that disease activity and cardiovascular comorbidities were associated with CKD in patients with RA.

P2-015

Effect of comorbidity on activity and therapy in patients with rheumatoid arthritis and systemic scleroderma.

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Conflict of interest: None

[Objective] To evaluate the effect of comorbities on the selection of therapy and disease activity, we studied comorbidy index in patients with rheumatoid arthritis (RA) and systemic scleroderma (SSc). [Method] A cohort of 535 with RA and 113 SSc patients who attended Toho University Ohomori hospital Rheumatology center during the period from May 2008 to July 2010. We analyzed relationship between the Charson comorbidity index (CCI) and therapeutic processes of patients with RA and SSc. [Result] RA patients were mean age 61.4, female ratio 78.7%, mean duration 11.0 years, SDAI 7.7, CDAI 7.1 and HAQ score 0.3. Frequency of comorbidity was 61.1%, mean CCI was 0.6 in RA patients. CCI were also correlated with HAQ, SDAI and CDAI in the RA patients. High score CCI patients (<2) administrates PSL. And Low CCI patients (=0) used MTX. On the other hand, SSc patients were average age 62.8, female ratio 89.3% and average duration 11.6 years. The ratios of limited type's scleroderma were 69.2%. However their demographics were almost same as the RA patient, CCI were not also correlated with HAQ in the SSc patients of this cohort. [Conclusion] Therapeutic processes of RA have been affected by several comorbidies. However, the comorbidies did not influence the HAQ index in patients with SSc.

P2-016

The clinical evaluation of the tight control for patients with early rheumatoid arthritis which having a poor prognosis factor

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Conflict of interest: None

[Objective] To evaluate the efficasy of the tight control in patients with early rheumatoid arthritis having positive anti-CCP antibody (>=100 U/ml). [Patients] There were 10 patients who have positive anti-CCP antibody(>=100 U/ml) (male/female:3/7, mean age:55.2, mean disease duration:8 week). DAS28 score at the diagnosis onset was 4.86(tender joint count:7.5, swollen joint count:10.1, ESR:45.2mm, VAS:53.1mm, m-HAQ:0.675). [Method] We used the first DMARDS with MTX 6mg/week, and untill dose up 8mg/week after 2week. We estimete the swollen joint strictly with ultrasound, we used the biologics very early pases for the high activity patients. We did not use steroid. [Result] We estimete the result at the time after 24week. There were 5 patients with MTX (6mg:1,8mg:3,10mg:1), and 5 patients with MTX 8mg and biologics(infliximab 3mg/kg:4, tocilizmab 8mg/kg:1). DAS28 score was 2.24(tender joint count:0.2, swollen joint count:0.6, ESR:16.6mm, VAS:7.2mm, m-HAQ:0.11). There were 6 patients with clinical remission,3 patients with low disease activity. [Discussion] We suggested that it is possible to gain the good result for the early rheumatoid arthritis with poor prognosis factor with MTX and biologics, and it is useful to use the ultrasound for the estimation swollen joint strictly.

P2-017

A case report of vasculo-Behçet disease: treated with infliximab (IFX) and methotrexate.

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Conflict of interest: None

A 30-year-old man was diagnosed with vasculo-Behçet disease at the age of 16. He presented erythema nodosums, polyarthritis, aphthous stomatitis, inadequate blood flow to the left upper limb and numbness of fingers. He was treated with PSL and SASP, but did not respond. After administration of steroid pulse therapy, his symptoms improved. When he was 29 years old, fever and sore throat appeared. He was hospitalized due to numbness of shoulders and fingers caused by inadequate blood flow. The CT showed obscuration of fatty layer around the left subclavian artery. The ASO and ASK titers were high, so we diagnosed relapse of the vasculo-Behçet disease triggered by infection with group A *Streptococci*. After initiation of steroid pulse therapy accompanied by PSL and IVCY, his symptoms improved and CRP dropped. PSL was reduced, but after 3 courses of IVCY, the disease relapsed. After treatment was switched to IFX and MTX, his symptoms improved and PSL were reduced. Standard therapy for vasculo-Behçet disease has not been established, patients are often treated with corticosteroid and immunosuppressant. There is little information about the efficacy of IFX for vasculo-Behçet disease. Our case indicates IFX may be an effective treatment option for IVCY-resistant vasculo-Behçet disease.

P2-018

Investigation of malignant tumors detected by screening CT scan before introducing biologics for rheumatoid arthritis

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Conflict of interest: None

We evaluate all patients in inpatient settings before introducing biologics in order to confirm safety of giving biologics. After that, we decide which agent would be suit for that patient. Among 1107 cases who underwent screening CT scan on admission, we diagnosed 7 malignant tumors: 4 lung cancers, 1 endmetrial cancer, 1 malignant lymphoma, 1 gastrointestinal stromal tumor. Each cases had no symptom and physical abnormality suggesting malignancy and we did not plan to order CT scan before screening tests. We also found 9 cases of possible malignant tumors from the description of CT scan and needed surgical resection. Among 7 cases of malignancies, 6 were in early stage and they does not recur after treatment. We treated 3 patients with biologics after confirming cure of malignancies and no recurrence are seen during followup. If we administer biologics without noticing malignancy and it turn out to be apparent thereafter, this malignant tumor might be thought to be related biologics. Also, we might lost opportunity to start biologics because of advanced malignant tumor. We can perform CT scan noninvasively in a short time and we can also detect chronic pulmonary infections, such as tuberculosis. Hence, it is essential to perform screening test before introducing biologics.

P2-019

Efficacy of combination therapy with methotrexate and gold sodium thiomalate for Felty's syndrome

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Conflict of interest: None

A 67-year-old male was admitted to the hospital for severe leukopenia and arthritis. He was diagnosed as rheumatoid arthritis (RA) about 28 years ago, gold sodium thiomalate (GST) therapy was effective, and then, he quit going to hospital. He was aware of metatarsophalangeal joint pain and pointed leukopenia. According to 2010 ACR/EULAR RA classification criteria, he was diagnosed as RA, with high activity showed by musculoskeletal ultrasonography. Laboratory findings showed leukopenia, mainly neutropenia, (WBC : 1100/μl, neutrocyto : 198/μl), and abdominal ultrasonography showed splenomegaly, so we diagnosed him as Felty's syndrome. He responded insufficiently to the treatment of methotrexate. Then we tried GST therapy, clinical and laboratory findings were improved. We report a rare case of Felty's syndrome treated with methotrexate and GST.

P2-020

A case of MTX associated lymphoproliferative disease complicated with cyptococcus pneumonia.

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Conflict of interest: None

A 72-year old female came to our hospital complaining with lymphadenopathy in the neck on March 2011. She had diagnosed RA in 1990 and received the treatment of MTX and low dose steroids. She received MTX from 2004. (Total MTX 2688mg). Computed tomography showed the lymphadenopathy in the neck, axilla, inguen and multiple pulmonary nodules. She was admitted to our hospital. She had a same episode of multiple pulmonary nodules on April 2010. Clinical findings showed the increased the titer of Cryptococcus antigen, and the QFT was positive. The bronchoscopy revealed the infection of Cryptococcus. (PCR of tuberculosis was negative). Flconazole improved the lung nodules gradually. Lymph node biopsy was also performed. It revealed the hyperplasia of lymphocyte and many EBER positive lymphocyte. The rearrangement of gene was none. The lymphadenopathy was improved after stop MTX. These clinical course and biopsy indicated the MTX associated lymphoproliferative disease (MTX-LPD). This case was difficult to make a diagnosis, because She had not only MTX-LPD but also the infection of Cryptococcus. Clinical course of MTX-LPD has many variation, we report this case with the background of patients with MTX-LPD.

P2-021

Characteristics of MTX-related malignant lymphoma in patients with rheumatoid arthritis

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Conflict of interest: None

We studied retrospectively the clinicopathological characteristics of methotrexate (MTX)-related malignant lymphoma/lymphoproliferative disorder in RA patients. Fourteen RA patients (mean age: 67.7, mean duration from diagnosis of RA: 18.5 years) were developed DLBCL. Mean MTX dose was 6.8 mg/weeks and mean administered duration was 6.0year. Most patients were maintained with low dose RA activity. Mean CRP was high level at 5.2 mg/dl caused by lymphoma. The extra nodal lymphoma lesion was seen 12 (85.7%), and EBER-1 was positive in 4 (28.6%) patients. All patients were withdrawal of MTX. Five (42%) patients were achieved spontaneous regression or complete remission by the discontinued MTX or only rituximab therapy without aggressive combined chemotherapy. Thirteen patients were alive without relapse, although non-germinal center B-cell type (generally poor prognosis cell surface marker) was determined 9 patients (75%). Four patients were flare of RA by discontinued MTX, but they were decreased RA disease activity again by the biologics and tacrolimus. MTX-related malignant lymphoma, even DLBCL was good prognosis and low association of EB virus.

P2-022

Cutaneous lymphoma in rheumatoid arthritis patients treated with methotrexate

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Science

Conflict of interest: None

[Objectives] Rheumatoid arthritis (RA) is linked to an increased risk for non-Hodgkin's lymphomas. This association is credited to the disease activity, but methotrexate (MTX) therapy may also contribute to this risk. We report the cases of cutaneous lymphoma in 2 RA patients treated with MTX. [Methods] Case1. A 67-year-old woman with a 14-year history of RA had receiving (MTX 10mg/wk). She presented with an 8-month history of rubor and ulcers on the left wrist and ankle. Treatment with intravenous antibiotics and debridement was ineffective. Skin biopsy revealed diffuse large B-cell lymphoma. Case2. A 68-year-old woman with a 17-year history of RA had been receiving MTX therapy (8 mg/wk) for 7 years. She presented with ulcers on the buttocks and thighs. Treatment with antibiotics and silver sulfadiazine was ineffective. Skin biopsy revealed cutaneous CD30-positive T-cell lymphoma. CHOP chemotherapy was started because the ulcers persisted after cessation of MTX. [Results] Cutaneous lymphoma complicated with RA is rare and resembles vasculitis and skin infection, thus resulting in delayed diagnosis. Lymphoma should be considered in the differential diagnosis of cutaneous ulceration in RA, and skin biopsy should be performed for early diagnosis.

P2-023

A case of thyroid MALT lymphoma after treatment with methotrexate and infliximab in a patient with rheumatoid arthritis.

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Conflict of interest: None

Thyroid MALT Lymphoma developing during the treatment of rheumatoid arthritis (RA) is rare. We herein report such a case with discussion. The patient was a 79-year-old woman who was diagnosed with RA at the age of 45 (1977). She was treated with bucillamine since 2005. The efficacy of bucillamine was inadequate. Methotrexate (MTX) 4mg per week was administered since 2006. Three months' administration of MTX was also inadequate. She was started on infliximab in November 2008 and the arthritis ameliorated markedly. In September 2009, a right thyroid tumor appeared and grew rapidly. Mucosa-associated lymphoid tissue (MALT) lymphoma was suspected by needle biopsy; however, a definitive diagnosis was not made. MTX was discontinued because of suspicion of lymphoma. After the discontinuation of MTX, the size of the tumor decreased remarkably. On the other hand, arthritis deteriorated gradually and administration of tacrolimus 2mg daily and predonisolone 5 mg daily was started from December 2009. The right thyroid tumor has not relapsed. Instead, a left thyroid tumor developed in November 2010. MALT lymphoma was diagnosed by biopsy of the tumor. Radiation was started.

P2-024

A case of MTX-related lympoproliferative disorders who developed as bulbar tumor

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Conflict of interest: None

A 53-year old woman who has six-year history of rheumatoid arthritis was admitted to our hospital because of gait disturbance and double vision. Brain MRI revealed ring-enhanced tumor which lied dorsal to medulla oblongata. Eviscertion was performed for the purpose of pathological diagnosis because sensory disturbance on facial area appeared and tumor enlarged. Although MTX had been discontinued during perioperative period, new tumor lesion appeared after re-administration of MTX. Tumor had disappeared after cessation of MTX. Although pathological diagnosis of lymphomatoid granulomatosis was made initially, further examination revealed diffuse large B-cell lymphoma with positiveness of EBV-ISH, which was consisitent with MTX-related lymphoprolifeartive disorders.

P2-025

A case of methotrexate related lymphoproliferative disease onset by the tongue tumor

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Conflict of interest: None

The patient is a 67 year-old woman. When she was 37 years old, she was diagnosed rheumatoid arthritis. She started to receive methotrexate(6mg/week) from four years ago. Because of she felt pain on her tongue, she visited the otolaryngologist. MRI revealed tumor on left base of the tongue. And she was admitted to our hospital on suspicion of the cancer of the tongue. The second biopsy revealed that diffuse large T cell lymphoma with EBV infection. Chest CT scan showed multiple lung nodules and PET scan showed increased FDG uptake in the larynx, lung, abdomen, cervical and inguinal lymph node. Methotrexate was discontinued in the diagnosis of methotrexate related lymphoproliferative disease(MTX-LPD). After that, her lymphomas shrank in size and her pain of the tongue was disappeared. Here, we report a rare case of MTX-LPD onset by the tongue tumors.

P2-026

A case report: successful treatment with glucocorticoid for recurrence of rheumatoid arthritis complicated with systemic lymphadenopathy and eosinophilia during MTX therapy

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Conflict of interest: None

We experienced a case of 70-y-old woman with recurrent RA complicated with systemic lymphadenopathy and eosinophilia during MTX therapy. Her polyarthritis was well-controlled with MTX for 10 years, however, polyarthritis was recurrently exacerbated with fever and multiple lymphadenopathy. CRP, MMP-3 and sIL-2R were elevated. Blood EBV-DNA was positive. PET-CT showed systemic lymphadenopathy including abdominal paraaortic lymph nodes with FDG uptake. An inguinal lymph node biopsy revealed reactive hyperplasia with interfollicular plasmacytosis of the lymph node. We suspected MTX-associated lymphoproliferative disorders (MTX-LPD) and discontinued MTX, however, lymphadenopathy, eosinophilia and hyper-sIL-2R was continued and polyarthritis was remarkably exacerbated. Then, we administered 20 mg/d of PSL and polyarthritis, fever, lymphadenopathy and eosinophilia were markedly improved. For a recurrent RA patient with systemic lymphadenopathy during MTX therapy, we should

consider the possibility of MTX-LPD. Cessation of MTX could improve MTX-LPD, however, as this case, did not. Moreover, this case also showed marked exacerbation of RA activity and continued eosinophilia. In such case, we propose that glucocorticoid monotherapy may be a considerable treatment after cessation of MTX.

P2-027

Adaptation and limitation of increasing the dose of Infliximab in the treatment of rheumatoid arthritis.

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Conflict of interest: None

(Objectives) Infliximab (IFX), 1st-generation of biological agent, is useful in the treatment of rheumatoid arthritis (RA). Since the dose over 6mg/kg is approved as one of countermeasures to the primary/secondary failure, the adaptation and limitation were examined. (Method) The treatment progress, DAS28-ESR (4) and changes of inflammatory reaction were investigated for 100 patients who started IFX treatment in the past 6 years. IFX over 6mg/kg was administered to 23 patients who had no marked effects to the rescue treatment (increase to full bottle, add prednisolone/tacrolimus). (Results) The mean DAS28 score of 80 patients, except 20 discontinued INF therapy in a 1 year, was significantly decreased from 6.1 at baseline to 3.6 at 6 month and 3.9 at 12 month, along with the decrease of CRP and MMP-3. The low disease activity was maintained over 1 year for 35 patients who showed the continuous efficacy at 3mg/kg IFX (n=17) and with rescue treatment (n=18). 20 patients were receiving over 6mg/kg IFX and 25 cases have been switched to other biologics. The patients with increased IFX, especially withdrawals after 1 year, had flare at 6 or 12 month after IFX treatment. The efficacy of the increased therapy of IFX would be expected to the 2nd failure but not to the primary failure.

P2-028

Evaluation of dose escalation and/or interval shortening in patients who report a decrease in effectiveness of infliximab infusion

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Conflict of interest: None

Objective: In July 2009, dose escalations and interval shortening of infliximab (IFX) infusion was approved in daily practice. We evaluated the cases that required IFX dose escalation and/or interval shortening. Material and Method: We selected 138 patients (29 men and 109 women; median age, 56 years; age range, 24–81 years) who were treated with IFX for RA. The median of the total number of IFX infusions received was 20 (range, 4–60 times). We evaluated the cases that required dose escalation and/or interval shortening of IFX infusion. Results: Of the 138 cases, 51 cases (36.9%) required dose escalation and/or interval shortening. Of these 51 cases, 15 required dose escalation; 18, interval shortening; and 18, both dose escalation and interval shortening. No serious adverse events were observed in any case. Despite these measures, 18 cases did not respond well. Conclusion: IFX dose escalation and/or interval shortening were carried out in patients in whom IFX treatment was less effective. A recovery of the effectiveness of IFX treatment was observed in 29 of the 51 cases (56.9%). Therefore, dose escalation and/or interval shortening are effective procedures in patients in whom a reduction in the effectiveness of IFX treatment is observed.

P2-029

The effects of an infliximab dose increase in patients with rheumatoid arthritis in a multicenter trial –Second report-

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Conflict of interest: Yes

Objective To evaluate the effect of an infliximab (IFX) dose increase in arthritis patients with insufficient response to IFX. **Patient background** Fifty-five patients (74.5% female) completed the assessment for 12 months. They were an average age of 54.9 years with average disease duration of 12.4 years and average body weight of 57.6 kg. Patients had also received methotrexate 8.2 mg/week on average, and steroids were combined in 77.4% of the patients. **Results** Increasing the average IFX dose from 3.4 to 6.1 mg/kg resulted in a significant improvement in average DAS28 score from 4.7 to 3.52 A good or moderate EULAR response was seen in 63.6% patients and a decrease in DAS score by $^{3}1.2$ were in 45.5% patients. **Conclusion** Dose increase of IFX is useful in arthritis patients with insufficient response to IFX.

P2-030

To investigate the clinical response in patients with rheumatoid arthritis on increasing doses the infliximab.

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Conflict of interest: None

Objective: To evaluate the effect and adverse effects of infliximab dose escalation in incomplete responders in rheumatoid arthritis patients. Methods: 14 rheumatoid arthritis patients treated with incomplete responder with infliximab refractory to methotrexate received 4.5 6, or 9 mg/kg of infliximab every 8 weeks, clinical response (disease activity score in 28) were compared in two patient groups by timing dose up receiving infliximab. Results: The clinical response to different doses of infliximab was comparable, whereas TNF-into patients exhibited a dose-dependent trend. Conclusions: Increasing the infliximab dose in patients with RA was effective significantly associated with the clinical response.

P2-031

fficacy of dose-up and period-shortening therapy with Infliximab in regional circulatory Rheumatoid Arthritis network

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Conflict of interest: None

[Objectives] In regional circulatory rheumatoid arthritis(RA) network as a tool of biologic agents, subcutaneous injection is preferred than intravenous injection. We investigated the dose-up and period-shortening Infliximab(IFX) therapy for RA patients with high disease activity in regional circulatory RA network. [Methods] Five patients with rheumatoid arthritis were treated in regional circulatory RA network. All patients were received dose-up or period –shortening INF therapy. The mean of age was 52.6 years-old, and

disease duration was 2.3 years. The average of methothrexate dose was 8.0 mg per week. Clinical outcomes were evaluated by DAS-28ESR and SDAI. [Results] DAS28ESR was significantly improved from 5.1 to 3.0, and SDAI was remarkablely decreased from 15.1 to 3.5. The average term of reintroduction from the hospital to the clinic was 36.8 weeks. Those results demonstrated that the dose-up and period-shortening IFX therapy for RA patients with high disease activity played an important role in regional circulatory RA network if space and time were permitted in the clinic which introduced the hospital.

P2-032

Usefulness of biweekly 50 mg etanercept in the treatment of rheumatoid arthritis

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Conflict of interest: None

[Objectives] Clinical usefulness of etanercept (ETN) and its inhibitory effect on bone destruction have been established, but some pts are difficult to take usual dose due to various reasons. We studied usefulness of ETN in these pts given 50 mg every 2 weeks (Q2W). [Methods] 9 rheumatoid arthritis (RA) pts who disagreed w/ usual dose (50 mg/w) due to financial reason, difficulty in self-injection or weekly clinic visit, started taking 50 mg Q2W. Changes of DAS28, RF, MMP3 and HAQ in ≧24-week follow-up were analyzed. Patient Background: 8 women and 1 man (mean age 71.9 yrs; disease duration 85.6 months). Concomitant MTX use in 7 pts (77.8%) at mean dose of 8.0 mg/w. Mean DAS28-ESR before ETN was 5.24: high disease activity (DA) 77.8%; moderate DA 22.2%. [Results] Mean DAS28-ESR significantly decreased to 3.04 from 5.24 at week 24: Pts w/ remission (<2.6), low DA (<3.2) and moderate DA were 3 pts each (33.3%). Mean RF and MMP3 also decreased, but statistically significant difference was not seen. HAQ remission rate 37.5%. Change in DAS in these pts was similar to that in our pts on adalimumab (40 mg Q2W). ETN 50 mg Q2W may be clinically useful as a therapeutic option for RA while considering pts' individual conditions in clinical settings.

P2-033

Efforts to realize dose increase of etanercept to 50 mg × 1/week

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Conflict of interest: None

(Objectives):Etanercept (ETN) at 50 mg/w can be highly effective; however many pts actually are on ≤25 mg/w. Explore needs of dose increase to 50 mg/w through survey on pts' treatment satisfaction ongoing w/ ETN ≤25 mg/w. (Methods): Questionnaire in 77 pts on ≤25 mg/w.(Results): 49 pts on 25 mg/w; 8 pts every 10 days; 20 pts every ≥14 days. ETN 50 mg/w had not been given due to financial reason in 9 pts (11.7%); physician's instruction in 54 (70.1%). For treatment satisfaction, 34 (44.2%) was satisfied w/ current treatment, 43 (55.8%) had a higher goal hoping strict control of disease without potential progression of joint destruction and better condition. For needs of dose increase, 22 (28.6%) wanted to try 50 mg/w or consult physician for that occasion. Irrespective of satisfaction, 7 had dose increase to 50 mg/w after physician's review of the appropriateness based on pts' request; 16 maintained their treatment despite of request because of remission after dose reduction or complications. Financial status less interfered w/ ETN introduction than expected. After introduction, many pts improve a treatment goal and overcome financial difficulties. Dose increase to 50 mg/w is effective to maintain QOL for long term with unbiased intervention and care support.

P2-034

Study of the effectiveness and safety in patients switching from etanercept 25 mg twice a week to 50 mg once a week

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Conflict of interest: None

[**Objective**] We studied the effectiveness and safety in patients switching from etanercept (ETN) 25 mg x 2/w to 50 mg x 1/w. [**Methods**] 6 patients with rheumatoid arthritis (RA) who switched ETN 25 mg x 2/w to 50 mg x 1/w at the Department of Rheumatology, Shizuoka Kousei Hospital; for effectiveness and safety evaluation, laboratory parameters and prescribed dose of methotrexate (MTX), steroid, antibiotics and NSAIDs before and within 3 months after ETN treatment were compared. Statistic relevance was affirmed as $p<0.1$. [**Results**] Switch to 50 mg x 1/w resulted in increased Alb ($p=0.052$), MCV ($p=0.023$) and MCH ($p=0.086$), and reduced ALP ($p=0.096$) that showed statistic relevance. DAS-28 (CRP) decreased from 3.56 to 2.57 but was not statistically significant. Prescribed dose of MTX, steroid, antibiotics and NSAIDs was unchanged. Of the 6 patients, 5 continued ETN 50 mg and 1 returned to 25 mg x 2/w. [**Discussion**] Although some patients had a decreased CRP after receiving ETN 50 mg, one returned to 25 mg x 2/w due to pain on administration and elevated liver function levels. Currently, we are evaluating the effectiveness and safety in RA patients who switched treatment as well as conducting a questionnaire survey in patients switching their treatment: we will also report these results.

P2-035

Short-term outcomes of weekly treatment with 50-mg etanercept (ETN) prefilled syringe in patients with moderately active rheumatoid arthritis (RA)

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Conflict of interest: None

Objective: To reveal the effectiveness of ETN in early treatment stage (within 2 months from treatment start) of moderately active RA pts. **Methods:** 14 female pts who started weekly treatment with 50-mg ETN prefilled syringe; mean age was 51.8 years; mean RA duration was 6.6 years. Steroids were used in 73.3% (mean dose: 3.5 mg/day) and MTX in 100% (7.9 mg/week). Mean DAS28CRP and DAS28ESR scores were 3.3 and 3.9, respectively, showing moderate disease activity. In these pts, DAS28CRP and DAS28ESR scores were measured after week 2, 4, and 8. **Results:** Mean DAS28CRP scores after week 2, 4, and 8 were 2.6, 2.4, and 2.6, respectively. Mean DAS28ESR scores were 3.0, 2.7, and 2.8, respectively. In early period of week 2, DAS28CRP score reduced, exhibiting that ETN tended to show effect quickly and its effect was maintained up till week 8. DAS28CRP and DAS28ESR remission rates were 57.1% and 50.0% after week 2, and 50.0% and 50.0% after week 8, respectively. Assessment using EULAR improvement criteria after week 8 revealed good response in 35.7% of the pts, moderate response in 21.4%, and no response in 42.9%. We acknowledged that weekly treatment with 50-mg ETN prefilled syringe can be expected to exhibit high effectiveness and rapid action from week 2 of treatment initiation.

P2-036

Effect of dose escalation in small-dose etanercept administration

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Conflict of interest: None

Objective: Etanercept (ETN) is highly effective at 50 mg weekly dose, but many pts receive smaller dose due to their age, complications, or economic reasons. In the cases where pts experience insufficient effectiveness with small dose ETN administration, clinical effectiveness of dose escalation was examined. **Method:** Eleven pts on <50 mg/week ETN administration were subjected to dose escalation as follows: 25 mg/5 days → 50 mg/week (4 pts), 25 mg/week → 50 mg/week (3 pts), 25 mg/week → 25 mg/5 days (2 pts), 25 mg/10 days ® 25 mg/week (2 pts); (mean weekly dosage: 26.6 mg → 41.8 mg). **Result:** Change in CRP from the baseline was 1.5 → 0.8; tender joint count 4.0 → 3.2; swollen joint count 1.8 → 0.8; and VAS 61.2 → 49.6; (mean observation period: 8.2 weeks), indicating that dose escalation has resulted in marked decrease of disease activity. When the pts were divided into 2 groups, one with dosage increased to 50 mg/week standard dose and the other with dosage increased to less than 50 mg/week dose, CRP change was 1.3 → 0.6 (n=7) and 1.9 → 1.2 (n=4) for each group respectively. **Conclusion:** We consider that dose escalation in pts not responding well to small dose ETN administration is effective, and the larger the dose escalation is, the higher the effectiveness will be.

P2-037

Study of the usage of etanercept for the treatment of rheumatoid arthritis

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Conflict of interest: None

Objective: RA treatment options have broadened including methotrexate (MTX) dose increase to 16 mg/w, & use of 6 different biologicals. Especially ETN + MTX enables pts to select various doses & regimes. Optimal treatment in our pts on ETN classified by ETN & MTX dose was studied. **Subjects & Methods**: 67 RA outpatients (otpts) on ETN were selected & classified to 4 groups by ETN & concomitant MTX maximum dose. Group (Grp) A: ETN >25 mg/w + MTX >8 mg/w; Grp B: ETN >25 mg/w + MTX ≤8 mg/w; Grp C: ETN ≤25 mg/w + MTX >8 mg/w; Grp D: ETN ≤25 mg/w + MTX ≤8 mg/w. Grps were evaluated for disease activity using Boolean index & health assessment questionnaire (HAQ). Pt's satisfaction such as cost-effectiveness was analyzed by questionnaire. **Results**: Grps A, B, C, D consisted 27 pts (40.2%), 19 (28.3%), 8 (11.9%), 13 (19.4%), respectively. ETN-free remission was achieved by 4 pts (5.9%), all in Grp A. Of 21 pts (31.3%) achieving Boolean index remission, 11 (52.3%) were in Grp A, showing that ETN >25 mg/W + MTX >8 mg/w was effective for remission. However no group was superior to others in satisfaction. **Discussion**: We compared Boolean index remission rate & HAQ, treatment satisfaction via questionnaire among our otpt groups defined by ETN & MTX dose & report the optimal treatment in these pts.

P2-038

Steroid dose reduction after Etanercept administration

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Conflict of interest: None

Objective: Steroids are known to have various side effects, but due to the high patient satisfaction attributed to their prompt symptom improvement effect, dose reduction or discontinuation of steroids is difficult. In this study, the effect of Etanercept (ETN) administration in steroid dose reduction was examined. **Method:** 30 patients on concomitant steroid who were able to be monitored for more than 12 weeks after ETN administration were retrospectively examined for the amount of steroid used by prednisolone conversion. **Result:** Mean DAS28-CRP was 3.1 at baseline, and it remained low as 2.2 after 24 weeks and 2.2 after 52 weeks from the start of ETN administration, whereas the mean steroid dosage decreased from 4.6 mg at baseline to 3.0 mg after 24 weeks and 2.0 mg after 52 weeks. There were cases in which quick symptom improvement and high patient satisfaction have hampered the dose reduction of steroid. We consider that when disease activity can be maintained at low score by ETN administration, steroid dose reduction should actively be carried out.

P2-039

A case of ankylosing spondylitis treated by low dose of adalimumab

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Conflict of interest: None

Aged female patient with ankylosing spondylitis was treated by salazosulfapyridine, and then methotrexate. However, these medicines were stopped by side effects. Therefore, low dose of adalimumab was started, and this patient could be maintained in good condition by this treatment.

P2-040

Outcome of combination therapy of tacrolimus and biologics in the treatment of rheumatoid arthritis patients intolerant to methotrexate.

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Conflict of interest: None

[Objectives] The aim of this study was to evaluate the efficacy of combination therapy of tacrolimus (TAC) and biologics (BIO) in rheumatoid arthritis (RA) patients intorelant to methotrexate (MTX) [Methods] Eleven RA patients using TAC (average 2.5mg/day) were treated with BIO from January 2006 to July 2011. All of them received no DMARDs other than TAC. Predonisorone was administrated (average 6.4mg/day) in 6 of them. Seven patients were treated with adalimumab (ADA), 4 with etanercept (ETN). Clinical efficacy and continuation rate of BIO were assessed from their records retrospectively. [Results] At the start of combination therapy, 6 patients were classified in high disease activity and 5 patients in moderate disease activity. Eight patients received BIO over six months. The average DAS28 (3CRP) score improved from 5.35 at initiation of BIO to 3.20 at 6 months, CRP from 3.97

to 2.26. All of them had good or moderate response. By Kaplan-Meier, continuation rate of ADA was 85.7% at 6 months, and the rate of ETN was 100%. Four patients discontinued the treatment with BIO in this study. 3 patients were administrated ADA (2 non responders, 1 adverse event) and one patient ETN (other reason). There was no serious infection resulting from the combination therapy with TAC and BIO.

P2-041

Outcomes of switching Biologics in rheumatoid arthritis.

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Aichi Medical University

Conflict of interest: None

[Objectives] The aim of this study was to assess the outcomes of switching first Biologics(Bio) to another Bio in the treatment of rheumatoid arthritis(RA). [Methods] There were 120 RA patients(Man:23, Women:97) who started bio between 2005 and 2011. 18 paitents of them switch to another Bio were evaluated. The items of first bio were 13 etanercept(ETA), 2infliximab(INF) and 3 adalimumab(ADA). [Results] In the 13 patients treated with ETA were switched to another Bio, 3 patients were switched due to lack of effectiveness (LOE), 7 patients were switched due to secondary LOE, 3 patients were switched due to adverse events(AE). (ETA to INF:3, ETA to ADA:5, ETA to tocilizumab(TOC):1, ETA to abatacept(ABA):4).5 patients of them were switched again to another Bio cause of LOE. Only one patient was switched by 3 times, that is ETA-INF-ADA-TOC, then a good response had been achieved. 2 patients treated with INF were switched due to AE. One was switched to ADA, the other was switched to TOC. These switchings of INF was effective. All of 3 patients treated with ADA were switched to ETA due to AE(2) and LOE(1), These switchings was also effective. The switching from ETA to another bio due to secondary LOE, it seemed to be the problem to control the flare up in initial term of the switching.

P2-042

What is the best second anti-tumor necrosis factor agent in rheumatoid arthritis patients with the first anti-tumornecrosis factor agent failure?

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Conflict of interest: None

[Background] RA patients with an inadequate response to first anti-tumour necrosis factor (f TNF) agent may switch to alternative TNF (alt TNF). It remains unclear what alt TNF is most benefit in etanercept (ETA), higher dosages of infliximab (hd IFX), and Adalimumab (ADA). [Objectives] To analyze the effectiveness of alt TNFs on drug survival rate in RA patients with f TNF failure. [Methods] A retrospective study of RA patients who discontinued f TNF and subsequently received alt TNF was carried out. The primary outcome was drug survival rate. Kaplan-Meier estimates of probability for drug survival were used with the log rank statistic. [Results] Of the 54 RA patients included; 24 received ETA, 12 received hd IFX, and 18 received an alt ADA. At 24month, ETA group had the highest drug survival rate, with significant change. (ETA: 58.3%, hd IFX:50%; $p=0.11$ vs ETA, ADA: 27.7%,; $p<0.01$ vs ETA) [Conclusion] This observational study suggests that ETA is the most effective alt TNF in RA patients with f TNF failure.

P2-043

Remarkable therapeutic response to golimumab in a rheumatoid arthritis patient responding poorly to 5 biological drugs

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Conflict of interest: None

A 46-year-old woman. Rheumatoid arthritis (RA) had been diagnosed in 1996. She had been treated with regimens including a gold salt and bucillamine, but responded poorly, so that methotrexate (MTX) was initiated in 2004. The patient was begun on infliximab (IFX) in June 2006. The treatment was efficacious but, as pneumonia developed, was discontinued in September. Etanercept was started in September 2007, and discontinued in March due to secondary failure. Treatment with IFX was resumed in April 2008, followed by a dose increase, but discontinued in July 2009 due to secondary failure. Tocilizumab was instituted in August 2009, and was discontinued due to secondary failure in March 2010. Adalimumab was then started in April 2010, and was discontinued due to secondary failure in October. In the same month, the patient was begun on abatacept, which was discontinued due to secondary failure in September 2011. Treatment with golimumab (GLM) was started in October 2011. A favorable therapeutic response was obtained soon after the start of GLM treatment and has been maintained, as evidenced by improvement in the DAS 28 using C-reactive protein from 4.91 to 3.27. Thus, GLM has proven effective in this patient who responded poorly to 5 biological drug preparations.

P2-044

Efficacy of Golimumab in Patients with Rheumatoid Arthritis in Clinical Practice: Switching from Other Biologics

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Conflict of interest: None

[Objectives] Golimumab (GLM), a new human anti-TNF antibody from transgenic mice, is effective by subcutaneous injection every 4-week. We participated in the Japanese clinical trial of GLM with 23 biologics (bio) naïve patients (pts). Results of 29 RA pts (both naïve and switching pts) who were administered GLM after its launch in last September, are reported. [Methods] Twenty-nine pts (male 1/female 28) were in this report; mean age (range) was 61.1 yrs (32-72 yrs), mean disease duration (range) was 8.88 yrs (7 mths to 27 yrs). Switching from other bio were in 17 pts (59%); 8 pts from etanercept, 2 from infliximab, 4 from adalimumab, and 3 from tocilizumab. Twelve pts (41%) were bio naïve. All but 2 pts were concomitantly administered with MTX. [Results] DAS28-CRP, SDAI and CDAI were assessed. Both naïve and switching pts achieved or maintained on clinical remission (DAS28>2.6) and the new remission criteria (ACR/EULAR 2011); which suggested GLM was effective in switching pts. GLM sc every 4-week has equivalent efficacy to other bio and ensure delivery at outpatient settings. Therefore, GLM is a biologics which is manageable in clinical practice without compliance issues. Further assessments, including persistence rate, with long-term treatment are required.

P2-046

Efficacy of Golimumab Therapy for Rheumatoid Arthritis Resistant to Infliximab and Adalimumab in Two Patients Previously Suffered from TB.

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Conflict of interest: None

[Objectives] Dr. Smoken showed that Golimumab reduced the signs and symptoms of rheumatoid arthritis in patients with active disease who had previously received one or more TNFα inhibitors. We assess the efficacy and safety of the TNFα inhibitor golimumab in ex-TB patients with active rheumatoid arthritis who had previously received one or more TNFα inhibitors. [Methods] Two active RA patients with ex-TB induced by infliximab, who were administered infliximab followed by adalimumab after TB therapy, had discontinued previous TNFα inhibitors because of lack of effectiveness and then received 100mg golimumab a month. [Results] We confirmed that Golimumab reduced the signs and symptoms of rheumatoid arthritis in ex-TB patients with active RA disease who had previously received TNFα inhibitors: inlfiximab followed by adalimumab.

P2-048

Discontinuation of etanercept therapy in rheumatoid arthritis patients

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Conflict of interest: None

[Objectives] Many reports have reported the high retention rate of etanercept. However, we have experienced the discontinuation of etanercept therapy because of various reasons. The purpose of this study is to investigate the cases of discontinuation in daily clinical practice. [Methods] The study cohort consisted of 883 patients who had undergone first etanercept treatment of 2072 patients registered in the multi-center study (Tsurumai-Biologics-Communication;TBC). Demographic data, including the reasons for which 260 patients had discontinued etanercept treatment were collected. [Results] 37 patients (14.2%) discontinued due to primary failure of etanercept, 78 patients (30.0%) due to secondary failure, 97 patients due to adverse events. Disease duration was 8.3 years, 13.2 years, 13.9 years respectively. The rate of patients who concomitantly received MTX was 70.0%, 60.7%, 45.7%, respectively. [Conclusion] The proportion of patients who discontinued due to adverse events was relatively high. Many of them had long disease duration and could not concomitantly use MTX. It is important to consider how we safely do treatment for such cases in the future.

P2-049

Dose reduction as a therapeutic option of etanercept in rheumatoid arthritis

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Conflict of interest: Yes

[Objectives] Dose and usage of etanercept, especially an option of dose reduction was investigated. [Methods] Medical history of etanercept was investigated retrospectively. [Results] One hundred and seven RA patients were treated with etanercept for more than 6 months and 84 patients were treated 25mgX2/W or 50mg/W of etanercept. Twenty-three patients (21.5%) were treated less than 50mg/W of etanercept; 2 patients, 20 patients and 1 patient were administered once 5 days, 7 days and 10 days, respectively. Ten patients started the treatment with administration of 50mg/W etanercept following reduction of the dose because of excellent response. At the final examination, 6, 2, and 2 patients achieved remission, low disease activity and moderate disease activity. They were responded good evaluated by EULAR criteria. Thirty patients started the treatment with administration of less than 50 mg/W because of complications, low body weight and pregnancy. Serum MMP-3 concentration tended to be low in RA patients treated with less than 50mg/W of etanercept. Other factors such as back ground and disease activity did not show difference. [Discussion and Conclusion] Administration of etanercept once 5 days, 7days and 10days was effective, however predictors of dose reduction have not elucidated.

P2-050

Practical Use of Etanercept (ETN) in Rheumatoid Arthritis of Our Department. -Evaluation of Clinical Result of Dose Reduction after Achievement of Remission and Once-Weekly Dosing of 25mg of ETN-

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Conflict of interest: None

[Objectives] We assessed the clinical results of 34 patients of rheumatoid arthritis (RA) with etanercept (ETN). The patients who had severe complications were injected with 25mg of ETN once weekly. Because of the effectiveness, we also applied once weekly dosing for non- high-risk patients. We tried to reduce the dose of ETN for the patients with long term remission of RA without swollen and tender joints. [Methods] We injvestigated C-reactive protein (CRP), metalloproteinase-3 (MMP-3) concentration and disease activity score including a 28-joint count CRP (DAS28-CRP), immediately before and after 3,6months and every year. [Results] Only 5 in 34 cases got twice-weekly dosing of 25mg of ETN from the beginning. Over the past 4 years, all patients improved with lowering of serum levels of CRP, MMP-3 and DAS28-CRP. Seven of 16 patients withdrew from steroid therapy. Three patients did not improve by ETN therapy, and switched to other biologics. One patients could withdrow from ETN therapy after 3 years and 5 months of the treatment. The most important target to treat RA is to reduce the disease activities in the early stage. ENT remains an expensive drug in Japan, thus dose reduction therapy could be an effective treatment in view of the clinical outcome, safety, and economic account.

P2-051

Study of sustained remission and discontinuation of biologicals after etanercept tapering (follow-up report)

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Conflict of interest: None

Objective: We studied the factors that enabled patients to respond to etanercept (ETN) and then achieve sustained remission and discontinuation of biologicals following the tapering of etanercept. **Methods**: Treatment with ETN was started at a dose of 50 mg/w, followed by dose tapering in patients with DAS28 improvement, resolution of swollen joints and no progression of joint destruction confirmed by X-ray. Patients who had no relapse of swelling or pain of joints with 25 mg every 4 weeks discontinued ETN and were evaluated for the rate of remission and sustained remission, and common factors affecting these rates, using new remission criteria such as simplified disease activity index (SDAI) and clinical disease activity index (CDAI). **Results**: ETN tapering was possible in 16 out of 21 patients, and 2 of them could discontinue biologicals. **Discussion**: Data suggest that ETN-responders who can sustain remission after tapering ETN can have dose reduction up to 25 mg every 4 weeks and further discontinue treatment with biologicals.

P2-052

Progress of 3 cases that became the dosage reopening after Adalimumab treatment cancellation

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Conflict of interest: None

[Objectives] Three of 9 cases that led to cancellation in 46 that started ADA recurred and ADA reopening. About three, I examined after the treatment cancellation situation and the reopening. [Cases]① 63 y.o. man, disease period 0.5 Y. Start time DAS28 4.55, with MTX8mg. Is the third after start; all treatment was interrupted (SDAI 0.5). Revival was coming (DAS28 3.88) 8 Ms later, and it was restarted, but there was no effect. In addition, cancel allergy for MTX was happened. Remission was got by ETN alone therapy afterwards 8 Ms later. (SDAI 0.3)② 62 y.o. woman, a disease period 2 Ys. it was introduced from onset 0.5 Y, and MTX was 4 mg because of hair loss. With folic acid, MTX was gained to 8 mg. Because continued deep remission 0.5 Y in continuous 1 Y 2 Ms; it cancellation (SDAI 0.3). Recur 1.5 Ys later; reopening (DAS28 2.78). Although LDA was got with MTX10mg, the remission cannot be got without improvement of VAS (SDAI 3.5). ③65 y.o. woman, a disease period 15 Ys. MTX was changed to MZR because of a liver disfunction. It was cancelled in SDAI 0.1 (continuous 1 Y 3 Ms). Recur 8 Ms later; reopening (DAS28 3.79). With folic acid MTX8mg restarted. It was gained to 10 mg, and the liver disfunction did not come out, SDAI 0.1 as well as cancellation time

P2-053

Four RA patients who have been in low disease activity for one year after discontinuation of adalimumab

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Conflict of interest: None

[Purpose]: In some patients with RA, disease activity remained low even after discontinuation of adalimumab (ADA). We investigated the background of our 4 patients who could maintain low disease activity (LDA) for more than one year after discontinuation of ADA after achieving LDA. [Subject]: Eighty RA patients who had been started with ADA in our institute from June 2008 to March 2010 were investigated to compare the background of the 4 cases described above and the rest of the 76 patients. [Results]: Duration of illness at baseline ranged 12~504 months. The average DAS28-ESR of the 4 patients decreased from 4.1±0.8 to 2.6±1.0 within one month and was maintained for 12 month (9 month in case1) when ADA was discontinued. The average disease duration of the 4 patients (209 ;12 to 504) months was not different from that of the rest 76 patients (127±126). DAS28-ESR of the rest 76 patients was 5.0±2.0 which was significantly higher than that of the 4 patients. HAQ-DI score of the 4 patients was lower (0.5±0.4) than that of the rest 76 patients (1.0±1.0). [Conclusion]: Some patients who are in low to moderate activity at baseline can maintain long-term LDA even after discontinuation of ADA.

P2-054

Intra-articular steroid injection plus etanercept prevent bone destruction in RApatients with rapidly radiological progressive bone destruction.

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Conflict of interest: None

[Objectives] There are several reports that rapidly radiological progressive cases(RRP) in rheumatoid arthritis exist despite MTX plus etanercept. We evaluate that intra-articular steroid injection into swollen joint prevent the progression of articular destruction in RRP. [Methods] RRP were categorised by CRP>3.0, ACPA>100, and erosion scores>3.0 at the baseline. We treat RRP by MTX plut etanercept. We checked the swollen joints by ultrasound every two weeks. If there are PDUS positive, we give a inintra-articular injection of triamcinolone 20mg under ultrasound guidance. Primary endpoit is ΔSHS (from baseline to 40 weeks) [Results] 40 cases were completed this study. ΔSHS average was 2.54 ± 2.11. [Discussion] In recent days, ΔSHS treated by MTX + etanercept was 4.66 ± 2.44, This is not so head to head study, Intra-articular steroid injection prevent joint damage in RRP.

P2-055

Can rheumatoid cervical lesions be ameliorated by biologicals: a case in which cervical odontoid process osteolysis and atlantoaxial subluxation were reduced by etanercept (ETN)

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Conflict of interest: None

[Objectives] We report an RA spinal lesion reduced by ETN, demonstrating that biologicals can inhibit rheumatoid cervical lesions. [Case] RA developed at age 30, affecting hands, knees, and anklles. Despite DMARDs use, RA relapsed and progressed in 1 yr. The parient refused MTX due to adverse effect on pregnancy. We performed synovectomy 3 times. Stage III RA relapsed. ETN alone 25mg×2/w wqas started 4yrs after onset. [Results] ETN achieved clinical remission in 2 yrs. She returned to work and got married. ETN 25mg every 2 wks maintains complete remission. Before remission, atlantoaxial subluxation found at start progressed, leading to osteolysis and atlantoaxial subluxation of odontoid process. After 3.5-yr ETN use, osteogenesis around the process reduced osteolysis and prevented the subluxation. [Discus-

sion] Atlantoaxial subluxation occurs in 1/3 of RA cases. No report on reduced cervical bone erosion or atlantoaxial subluxation due to RA exists. [Conclusion] In the RA woman desiring marriage and pregnancy, we confirmed that drug survival of ETN alone reduced the cervical lesion and demonstrated that biologicals can reduce rheumatoid cervical lesions. If no treatment goal is achieved, active switching is important. In case of some effects, a drug survival test is important.

P2-056

A case of RA showing plain radiographical restoration with ETN in spite of the continuation of synovitis with MRI

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Conflict of interest: None

(Case) a 44 years old woman. She noticed arthralgia at her right wrist and right ankle joint. She visited our hospital at the same year. There are swelling and tenderness at these joints. CRP and ESR are slightly elevated. We diagnosed her as RA. Because she hoped pregnancy in the future, we prescribed SASP to her. However her symptom and joint swelling did not improved. Plain radiography revealed the progression of joint space narrowing and erosion at the wrist joint. So we prescribed ETN in addition to SASP. Her symptom and swelling were dramatically improved, and disease activity also improved to remission. Although plain radiography revealed restoration of joint space narrowing and erosion, enhanced MRI showed active synovitis. (Discussion) Although some patients with RA were reported to be able to discontinue IFX after achieving DAS remission for six month, patients treated with ETN reported to be difficult to discontinue it. Although this case achieved DAS remission for five years and showed not only no progression with plain radiograph but also restoration of the wrist joints, Gd-enhanced MRI showed active synovitis. This is a valuable case in considering about pathogenesis of synovitis and bone destruction, and the timing of discontinuation of ETN.

P2-057

Repair of bone erosion and joint destruction after adalimumab therapy in patients with rheumatoid arthritis

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Conflict of interest: None

Objective : The bone erosions in patients with rheumatoid arthritis (RA) have been seen frequently, and especially in the advanced patients. Despite of biologics the erosive findings healing on XP images were able to be obtained rarely. We present two cases of RA patients whose damages and/or destructions of the affected joints were repaired after adalimumab (ADA) therapy. Case 1 : A 56-year-old female whose disease duration was 10 years, had received ADA. MTX had been administered 8mg/week concomitantly. After the ADA therapy her disease activities of RA were significantly improved. One year later, joint narrowing and irregularity of joint surface seen in XP were repaired. Case 2 : A 56-year-old female with 1 year disease duration had been administered ADA with MTX at 6mg/week dosage. She had a strong pain in her right foot and ankle. The XP finding revealed that there were joint space narrowing and irregularity of the joint surface in her talo-navicular joint. After the ADA therapy, we could see the bone repair in that joint. There was new bone formation in her talo-navicular joint. Conclusion : These cases suggested that the ADA therapy has an effect of bone repair by blocking the TNF activity, even though in the advanced RA patients.

P2-058

Survey of anxiety in rheumatoid arthritis patients to whom the self-injection of biologic agents are introduced

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Conflict of interest: None

[Objectives] Etanercept and Adalimumab are prescribed for the patient by self-injection. The purpose of this study is to investigate qualitatively and quantitatively anxiety that rheumatoid arthritis (RA) patients feel when the self-injection is introduced. [Methods] The objects are 54 RA patients into whom ETA or ADM is first time introduced. [Results] The quantity of anxiety of the patients before the self-injection introduction was an average of 50.4/100 mm in VAS (Visual analog scale), but significantly decreased with an average of 16.7/100 mm after the introduction. The contents of anxiety were side effects (61%), procedure of injection (48%), curative effects (41%), fear over a needle (37%), and economical burden (37%). Although anxiety decreased by all items after self-injection introduction, uneasiness to an economical load and unexpected side effects still remained. [Conclusion] A continuous psychological support is necessary for RA patients to whom biologic agents are introduced.

P2-059

Nurses' efforts to promote introduction of etanercept (ETN) self-injection at our hospital

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Conflict of interest: None

Objective: ETN self-injection introduction is known to improve pts convenience, but the self-injection rate at our hospital is at low of 30% as of June 2011. To improve this rate and pt instructions, we conducted a questionnaire in pts on self-injection and studied its benefits and their concerns. **Methods:** Questionnaire survey on our 40 pts using ETN self-injection. **Results:** Before switching to self-injection, many pts were concerned about their own ability to use it (23) and to memorize the process (13). After switching, they realized its convenience, stating that it was easier than expected (21) and that they gradually became used to it (15) (multiple answers allowed). Reduced hospital visits and ability to treat themselves according to work or housework seemed to reflect their satisfaction. No inconvenience was associated with self-injection reported 67.5% pts. Our nurses had assumed that many pts were satisfied with ETN injection at hospital and despised self-injection, but questionnaire results revealed high satisfaction with self-injection. We hope to apply these results to pt instructions to improve self-injection rate. Another questionnaire is conducted in pts refusing self-injection. We consider that the result of this questionnaire can also be used for pt instructions.

P2-060

Nursing for distantly located outpatients with rheumatoid arthritis who refuse to self-inject etanercept

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Conflict of interest: None

Objective: To clarify nurses' involvement distantly-living rheumatoid arthritis (RA) outpatients refusing etanercept (ETN) self-injection. **Method:** Three RA outpatients (51 year-old female, 60 year-old female and 49year-old male) living more than 2 hours away, who refuse ETN self-injection are studied here. **Result:** ETN were injected by her spouse, by her son or at the local hospital's outpatient department respectively. **Discussion:** Very few rheumatologists work in Hokkaido, especially in eastern area; thus many patients visit us from far locations. In 2 farmer cases, family members having experience giving injections to livestock became able to inject ETN after 2 training sessions, but to prevent their own style injection, training was repeated thoroughly; the other one was treated at a local hospital. Our hospital has no full-time rheumatologist; therefore the nurses should detect adverse event signals during ETN administration earlier. **Conclusion:** By nurses, both repeated training for injection technique and proactive monitoring of adverse effects are critical for distantly-living RA outpatients under treatment with ETN.

P2-061

Study of QOL using AIMS-2 in patients with rheumatoid arthritis(2)- By injection technique of etanercept -

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Conflict of interest: None

Objective: We studied whether or not the QOL in patients with rheumatoid arthritis (RA) differs among injection techniques of etanercept (ETN) using AIMS-2 (Arthritis Impact Measurement Scales version 2), a scale for assessing QOL. **Methods:** We conducted an AIMS-2 survey in RA patients receiving ETN at our clinic. **Results**: A total of 94 RA patients agreed to cooperate with the survey: 54 treated by self-injection and 40 treated by subcutaneous injection on outpatient basis. For patient's background, the mean age was 53.2 years in self-injection group and 66.2 years in subcutaneous injection on outpatient basis; the later group being significantly higher ($P<0.001$). None of other parameters differed markedly. Of 12 scales of AIMS-2, 11 scales excluding depression were better in the self-injection group, with a significant difference for scales directly correlated to daily living such as mobility, walking, dexterity and household activity. Results from the AIMS-2 survey suggest that self-injection of ETN as an injection technique can achieve higher QOL in RA patients compared with subcutaneous injection on outpatient basis and should be recommended actively; nurses are considered to play an important role in instructing self-injection to the patients.

P2-062

Rheumatoid Arthritis Circulatory Regional Collaboration-Pathway for treatment of RA andElectrical Medical Record Reference System.

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Conflict of interest: None

[Objectives] Since September 2007, we have used the RACRC-Path: Rheumatoid Arthritis Circulatory Regional Collaboration-Pathway. [Methods] We have used RACRC-Path for 43 hospitals and 71 patients as a tool of five biologics in convenience for patients and physicians Collaborating hospitals are situated close to RA patients, after induction phase of biologics, they have tendency to use subcutaneal agents. We have also used electronic medical record reference system which can browse record from collaboration hospitals. [Results] Critical pathway and electrical connection can be useful for rheumatoid arthritis characteristics.

P2-063

Curtailment of medical cost encourages patients to start biologic agents

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Conflict of interest: None

[Background &Objectives]Several biologic agents have been approved for use in treatment of rheumatoid arthritis (RA), revolutionizing it. However, because these agents typically cost in comparison with other drug therapies, many patients are hesitating to start them. To avoid losing the period, in which biologics should be used, we have started etanercept (ETN) treatment once every other week for some patients, and increased the frequency of injection if current treatment might not be enough. We evaluated this method. **[Results & Discussion]**Twelve patients were evaluated at 48 weeks. Two patients were treated with ETN once every other week, and the others were injected ETN weekly. Average DAS28 ESR score improved from 5.08 to 3.53 and average CRP also decreased from 2.3 to 0.6 mg/dL. Not all patients have agreed dose escalation and reached low disease activity or remission statas, but 90% patients expressed their satisfaction with this protocol, furthermore, 67% patients had answered that they could not have started the biologic therapy without curtailment of medication costs. For the patients refusing biologics due to the cost, this protocol (reduce the frequency of ETN injection and medical fees) will enable the them to start the better treatment.

P2-064

Risk factors for serious infection in elderly patients with RA treated with biologics

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Conflict of interest: None

[Objective] To evaluate risk factors for serious infections in elderly patients with RA treated with biologics. **[Method]** We analyzed some clinical factors between 10 elderly RA patients (≧65 yo) admitted by infection within 1 year after biologics treatment and 25 elderly RA patients who didn't admit by infection for 1 year. **[Results]** DAS28-ESR tended to be higher in admitted group (4.91±1.07, 3.96±1.54 $p=0.099$). Estimated GFR at beginning of biologics tended to be lower in admitted group (60.7±15.2 ml/min./1.73m^2, 78.8±26.2 ml/min./1.73m^2, $p=0.071$). There was no difference between two groups about glucocorticoid dose or coexisting pulmonary disease. **[Conclusion]** Our study suggested that sustention of high disease activity and decline of renal function at the beginning of biologics treatment may be the risk factors for serious infection in elderly RA patients.

P2-065

The serum levels of anti-CCP antibody from Japanese patients with tuberculosis were not higher than the that of the normal healthy persons.

Tomoshige Matsumoto
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Conflict of interest: None

[Objectives] Anti-citrullinated peptide (anti-CCP) antibodies have high specificity (90%) and sensitivity (96%) for rheumatoid arithritis (RA). Therefore anti-CCP antibodies are useful in the diagnosis of early polyarthritis. There was a report in which 15/47 (32%) patients with tuberculosis (TB) have positive levels of anti-CCP. Although the presence of anti-CCP correlated with fever, it was not associated with symptoms and signs of arthritis. [Methods] In this study, we aimed to evaluate the prevalence and association of anti-CCP in 17 patients with TB. [Results] The mean level of anti-CCP antibody from patients with tuberculosis was 0.39, that from normal healthy persons was 1.47. Welch's t test showed no difference between them ($p = 0.206$). The levels of antiCCP were not higher than the that of the normal healthy persons.

P2-066

Efficacy and Safety of Anti-TNF Therapy for Rheumatoid Arthritis in Twelve Patients with Tuberculosis

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Conflict of interest: None

[Objectives] Keane et al. reviewed the clinical and laboratory findings in 70 cases of tuberculosis that developed after the initiation of treatment with infliximab. How should we treat RA after we successfully treated tuberculosis? Decisions regarding the treatment of patients with refractory RA in the setting of active tuberculosis remain difficult (1). [Methods] We successfully treated RA in twelve patients with tuberculosis, including seven reactivated by infliximab therapy. [Results] These demonstrate that infliximab therapy can be considered for patients with refractory RA who have recovered from active tuberculosis and in whom antituberculosis therapy can be maintained.

(1) Matsumoto T, Tanaka T, and Kawase I. ***N Engl J Med.*** 2006, 355(7):740-741.

P2-067

A case of disseminated tuberculosis during treatment with adalimumab (ADA) for rheumatoid arthritis (RA)

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Conflict of interest: None

[Objectives] To evaluate the problems of disseminated tuberculosis during treatment with ADA for RA. [Case] 67-year-old man, who had been treated with methotrexate and ADA for 3 months, consulted a nearby doctor because of fever and feeling of abdominal distension. Abdominal CT examination revealed left pleural effusion, ascitis and diverticulitis of the descending colon. He was introduced to the internist in our hospital and was diagnosed as the peritonitis related to diverticulitis and cholecystitis and pleurisy due to and the pneumonia. After the failure of the treatment with antibiotics for a month, he was consulted us. The physicians searched possibility of his tuberculosis by our advice. His sputum and pleural effusion examination was positive for Mycobacterium tuberculosis and QuantiFERON-TB-G was positive, and his pulmonary CT examination revealed miliary nodules in both lung. He was diagnosed as disseminated tuberculosis and moved to a tuberculosis special hospital to be treated for tuberculosis. [Conclusion] Not only rheumatologists but all physicians have to recognize that it is important to take possibility of tuberculosis particularly extrapulmonary tuberculosis into consideration when we examine a patient during treatment with antiTNF α antibody such as ADA.

P2-068

Organizing pneumonia (OP) in 2 RA patients who had been treated with golimumab

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Conflict of interest: None

[Case 1] A 67 year-old female was diagnosed as RA in May 1996. Though bucillamine was discontinued because of remission in 2006, MTX (6 mg/week) was started in September 2008 for the relapse of RA. Then she joined the golimumab clinical trial(combination with MTX) in December 2008 to get the remission state. In November 2009, she developed dyspnea accompanied by infiltrative shadow in the left lower lung. Because antibiotics were not effective and no bacteria was detected in sputa cultures, we considered she had OP and treated her with 30mg/day of PSL successfully. [Case 2] A 71 year-old female was diagnosed as RA in August 2008 and treated with 1,000mg/day of SASP without significant improvement. She joined the golimumab clinical trial(monotherapy) in December 2008. She developed wet cough in April 2009. As a chest X-ray revealed a infiltrative shadow in the right upper lung, antibiotics were prescribed without any improvement. We treated her with 30mg/day of PSL with immediate improvement. There are some case reports about OP during the treatment with other biological agents. Though the mechanism of developing OP during such therapy is unknown, OP should be kept in mind during the treatment with golimumab.

P2-069

Resumption of etanercept after recovery from organizing pneumonia in a patient with RA

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Conflict of interest: None

[A case report] A 66-years-old man with 14-year history of rheumatoid arthritis (RA) had been treated with methotrexate (MTX), tacrolimus (TAC) and etanercept (ETN) for recent three years. He was a non-smoker. He presented with dyspnea, non-productive cough and moderate-grade fever. A chest radiograph and a CT scan revealed consolidation in the right lower lung field. Despite of the treatment with antibiotics for two weeks, his symptoms and radiological abnormalities had not improved. Transbronchial biopsies revealed intra-alveolar exudate and alveolar thickening. No organisms were cultured from the bronchoalveolar lavage. Drug lymphocyte stimulation test (DLST) showed negative both for MTX and TAC. Because very early organizing pneumonia (OP) was suspected, we started oral prednisolone 30 mg a day, with dra-

matic improvement allowing the dose to be tapered off. After 3 months arthralgia recurred at the time the prednisolone dose was tapered down 5mg a day. Despite of re-introduction of MTX and TAC, the articular symptoms were not improved. We confirmed that provocation test of ETN was negative. The arthritis was improved by treatment with ETN 25mg twice a day. Because DLST might be false negative, carefully performed provocation test is the safe and useful.

P2-070

The 2cases report that was RA with lung serious harmful phenomenon during the TNF inhibitor treatment

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Conflict of interest: None

[Objectives] There are many reports about harmful phenomenon during the biologics treatment. Especialy, the lung infection reports are well known. We experienced 2 case, and report that was RA with lung serious harmful phenomenon during the TNF inhibitor treatment. [Results] case1) 60-years old woman, got RA at 2001, in 2010 Etanercept treatment started. After started ETN, improved RA activity and decreace CRP valew. In august 2011, suddenly CRP valew elevated. We checked chest X-ray, there was consolidation at right upper lung. We suspected opportunistic pneumonia and started antibiotic treatment, but treatment was ineffectived. So, we did bronchoscopy, the diagnosis was COP, after PSL 30mg treatment started, chest X-ray image improved. case2) 57-years old man, got RA at 2007, 2008 started adarimumab treatment. After started, he got redmisson for over 2 years. In august 2011, he got right shoulder pain, but blood test was no changed. In september, CRP valew elevated. We checked chest X-ray, there was effusion in the right thoracic cavity. So, we tested effusion, the quality was bloody. After, we checked chest CT, there was mass at right lower lung. After find out mass, we diagnosised small cell cartinoma, and consulted tumor supesialist. Now the patient treatments speciality hospital.

P2-071

Case Report of a Rheumatoid Arthritis Patient with Concomitant Synovial Listeriosis Treated with MTX and Tocilizumab (TCZ)

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Conflict of interest: None

Patient: 57-year-old female Primary symptoms: Pyrexia, malaise Past history: Nothing noteworthy Present history: Onset of rheumatoid arthritis occurred in 1994. MTX treatment was initiated in 2002. Etanercept treatment was initiated in September 2007, but the patient was switched to TCZ in January 2010 due to lack of efficacy. On September 12, the patient developed malaise and a fever of 39°C. The patient was admitted to our department on September 22. Course: After admission, the patient's impairment of consciousness progressed rapidly. A cerebrospinal fluid test found elevated cerebrospinal index, cell count, and LDH, and hypoglycemia. Listeria monocytogenes was isolated from blood and cerebrospinal fluid cultures, and the patient was given a diagnosis of synovial listeriosis and treated with ABPC + TOB. Conclusions: Synovial listeriosis is an opportunistic infection that occurs when there is decreased cellular immunity. Scattered cases have been reported in patients receiving anti-TNF-alpha inhibitors, but to date there have not been any reports of such infections in patients receiving TCZ. Caution should be exercised regarding the possibility of opportunistic infections, including listeria infections, when using biologicals.

P2-072

Peripheral nerve palsy during the treatment of rheumatoid arthritis using anti-TNF agents

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Conflict of interest: Yes

[Objectives] Peripheral nerve palsy during the treatment of rheumatoid arthritis using anti-TNF agents was assessed in our hospital. [Results] Among 237 patients treated with biologic agents, 2 cases with rheumatoid arthritis (RA) developed peripheral nerve palsy. One case was a 45-year-old man with RA developed left peroneal nerve palsy after 10th infusion of infliximab (IFX). The nerve palsy resolved 7 months later after stopping IFX. The second case was a 33-year old woman with RA who developed bilateral median and ulnar nerve palsy after two months' therapy with etanercept (ETN). After stopping ETN, these palsies partially resolved. [Discussion] These cases indicated that peripheral nerve palsy should be recognized as the adverse effect of biologic agents, specially anti-TNF agents.

P2-073

The efficacy of golimumab on psoriasiform skin eruption induced by etanercept and adalimumab

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Conflict of interest: None

[Objectives] Recently, attention has focused on a wide spectrum of skin lesions arising in patients treated with TNF antagonists. Shealy et al reported that keratinocyte chemoattractant and interferon-inducible protein-10 showed significant reductions in the combined golimumab-treated mice versus untreated controls. We expected the regulative effect of replacement of golimumab on psoriasiform skin eruption induced by other TNF antagonists. [Methods] The four patients with skin lesions induced by adalimumab or etanercept were replaced to treat with golimumab. The psoriasis area and severity index (PASI) at the 8 week assessment was compared with that at baseline. [Results] The PASI at the 8 week assessment (0.35±0.31) was significantly lower than PASI in the baseline assessment (1.1±0.68), (P=0.043). [Conclusion] A replacement of golimumab will improve skin lesions arising in patients treated with other TNF antagonists.

P2-074

A case of bullous pemphigoid developed after administration of etanercept in patients with RA

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Conflict of interest: None

Development of various autoimmune diseases such as SLE, and vasculitis and others has been reported after administration of biologics (BIO) to patients with RA. We report a case of bullous pemphigoid (BP), a rare complication, developed after administration of etanercept (ETN). The patient is a 74 year-old woman with RA who had been treated with SASP and BUC because of ILD, but because the activity of RA was so high that ETN was introduced in March 2008. The activity of RA decreased, then SASP and BUC were stopped. In July 2011, bullous lesions with itching developed on lower and upper extremities and she was referred to a dermatologist. After skin biopsy, 14mg/day of PSL and 100mg/day of MINO were started but the effect was not good. Skin biopsy findings were compatible with BP, but because leukocytocrastic vsculitis was also present, the dose of PSL increased to 30mg and skin lesions improved. This case has an atypical feature as BP because of the combination with leukocytocrastic vasculitis. We speculate that ETN induced 2 types of autoimmune phenomenon, i.e., BP and leukocytocrastic vasculitis.

P2-075

A case of rheumatoid arthritis which developed erythema nodosum-like lesion during treatment with infliximab.

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Conflict of interest: None

A 66-year-old Japanese woman was diagnosed with sero-negative RA 23 years previously. She began treatment with infliximab 200 mg every 2 months along with methotrexate 4 mg weekly 14 months previously. She had been under good control up until 6 weeks previously on those medications when joint pain and swelling began to exacerbate. At the same time, palpable purpura developed on her right flank. Skin lesion resembling erythema nodosum developed on the anterior halves of both lower legs. Hospital admission was needed to examine the cause of the skin lesion, increased CRP, and exacerbation of arthritis. Skin biopsy showed necrotizing vasculitis in the dermis with some inflammation in adipose tissue surrounding the arteries. Prednisolone was introduced at 30 mg daily and was very effective in both skin lesion and arthritis. Although there were reports of vasculitis during the treatment with TNF inhibitors, in some the latter might be causative, we understood that the inflammation of her RA became so high, in such a short period of time after the secondary failure of infliximab, to a level where it also induced rheumatoid vasculitis.

P2-076

Henocho-Scholein purpura after etanercept therapy for rheumatoid purpura.

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Conflict of interest: None

We report the case of a 37-year-old man with ten-year history of sever rheumatoid arthritis, who developed Henoch-shonlein purpura(HSP) while receiving etanercept. He started etanercept at 25mg in 2009. Two years later, he noticed purpuric papules and ulcers on both legs. Histopathology showed cutaneous vasculitis of small vessels in the upper dermis with IgA deposition by immunoflurescence. He discontinued etanercept, and started prednisolone at 40mg/day. Laboratory examinations showed; Antinuclear Antibody(ANA) was positive(1:160), anti-dsDNA antibodies, anticardiolipin antibodies were detected. Both C3 and C4 levels were depressed. Laboratory data before receiving etanercept revealed ANA titre 1:40. We suspect that the above case suggest a relationship between the introduction of therapy with etanercept and HPS occurring.

P2-077

TNF-α antagonists -induced to systemic lupus erythematosus (SLE) in two patients with rheumatoid arthritis (RA)

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Conflict of interest: None

【case】①63-years-old female. H10/8, she was diagnosed as RA, and had been treated with methotrexate and salazosulfapyridine. Since she had continued active joint inflammation, H16/11 adalimumab(ADA) (40mg s.c./2w) was added. H19/6, fever and enteritis were presented. We could find no evidence of infection, and later serositis, proteinurea, pancytopenia, positive ANA and positive dsDNA antibodies were presened. Since ADA-induced SLE was considered, ADA was stopped and prednisolone(1mg/kg/day) was begun. Her symptoms resolved gradually. ②64-years-old female. H20/12, she was diagnosed as RA, and had been treated bucillamine and ADA, which were discontinued because of side effects. H21/10, etanercept(ETN)(50 mg s.c./w) was started. H23/6, malar rash, proteinuria, positive ANA and positive dsDNA antibodies were presented. Renal biopsy confirmed lupus nephritis type V(ISN/RPS). Her symptoms resolved after discontinuing ETN and starting prednisolone(1mg/kg/day) and tacrolimus hydrate.【conclusion】TNF-α antagonist therapy has been associated with the development of ANA and ds DNA antibodies, and the infrequent development of SLE. We present the two rare case of enteritis and serositis, and of biopsy-confirmed lupus nephritis and review the literature of SLE induced to TNF-α antagonists.

P2-078

Development of sarcoidosis during Etanercept therapy.

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Conflict of interest: None

We report a 63-year-old woman with 17-year history of rheumatoid arthritis patient developing sarcoidosis possibly induced by etanercept. She had an incomplete clinical response and intolerance to several disease-modifyng drugs including methotrexate. The treatment with infliximab in combination with methotrexate from July 2005 until March 2006 showed a good response but was stopped because of second ineffectiveness. Alternatively, the treatment of etanercept was started, with good response, but the nodular lesion and the tumor was noticed in right upper eyelid in 2009, and in left leg in December 2010, respectively. The skin and muscle biopsy was performed and histology showed noncaseating granulomas. The patient also gradually developed uveitis, so etanercept was stopped and the treatment of oral predonisolone at an initial dose of 30mg/day led to complete remission.

P2-079

A case of hepatitis B virus reactivation in an RA patient treated with adalimumab

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Conflict of interest: None

A 52-year-old female had been suffering from RA for 24 years. Since July 2009, she had been treated with adalimumab (ADA) at 40 mg/2 wk combined with MTX. HBsAg was negative before receiving ADA. In August 2010, HBsAg was identified incidentally. Serum Positivity for HBV-DNA (6.7 LC/ml) and HbeAg was recognized. She was treated immediately with entecavir. ADA and MTX were discontinued at the same time. In December, the serum HBV-DNA level was 3.3 LC/ml and HbeAg was negative. In April 2011, serum HBV-DNA could no longer be found. The serum transaminase level was not elevated throughout the progression. Before starting biologics therapy, the risk of HBV reactivation must be considered. Not only screening for HbsAg, but also screening for HbcAb and HBsAb is required. Due to the fact that HBV reactivation cannot be identified early on only monitoring the transaminase level, HBV-DNA monitoring is required.

P2-080

Solid cancer risks in patients with rheumatoid arthritis treated with anti-tumor necrosis factor therapy

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Conflict of interest: None

[Objective] To determine the risks of solid cancer in RA patients receiving anti-TNF therapy. [Method] Using medical records, 295 patients receiving anti-TNF therapy and 284 patients who have never received biologics were investigated in the view point of occurrence, origins, time of onset and stage of cancer. [Results] Ten patients (3.4%) receiving anti-TNF therapy developed cancer; 3 colon cancer, 2 lung cancer, 1 esophageal cancer, 1 oral cancer, 1 breast cancer, 1 cervical cancer, and 1 malignant melanoma. On the other hand, 14 patients (4.9%) not receiving anti-TNF therapy developed cancer. The frequency, time of onset, stages were not significantly different between two groups. [Discussion and Conclusion] There are reports both that anti-TNF therapy raised the cancer risks and that it did not. However, as cancer is life-threatening, patients should be watched carefully.

P2-081

Study of QOL using AIMS-2 in patients with rheumatoid arthritis(1)- By treatment regimen of biologicals -

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Conflict of interest: None

Objective: At now 6 types of biologicals are available; its selection is sometimes based on treatment regimens. We studied whether or not the QOL of rheumatoid arthritis (RA) patients differs by treatment regimens of biologicals using AIMS-2 (Arthritis Impact Measurement Scales version 2), a scale for assessing QOL. **Methods**: We conducted an AIMS-2 survey in RA patients receiving biologicals at our clinic. **Results**: A total of 147 RA pts agreed to cooperate with the survey; 91 treated by I.V. infusion (47 infliximab, 29 tocilizumab, 15 abatacept) and 56 treated by self-injection (54 etanercept, 2 adalimumab). Mean age was 60.3 yo in I.V. infusion group and 53.5 yo in self-injection group; the former group being significantly higher ($P<0.001$). None of other parameters differed markedly. AIMS-2 appeared to be better in self-injection group for all scales, with significant difference for mobility, walking, dexterity, arm function, household activity, pain, work anxiety, and depression. Satisfaction with health and attribution of problems to arthritis was also significantly better. While selecting regimens based on patients' request or lifestyle is important, proactive recommendation of self-injection at home considering QOL may also be important.

P2-082

A Study of the Efficacy of Tocilizumab (TCZ) in RA by Disease Duration

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Conflict of interest: None

[Objectives] To investigate the efficacy of TCZ by disease duration based on experience with the use of TCZ at Itabashi Chuo Medical Center. [Methods] We studied patients on TCZ therapy by time since onset (< 2 years; ≥ 2 years). The patients' MMP-3, mHAQ, DAS28, SDAI, and Boolean remission scores prior to treatment initiation were compared to those after 6 months of treatment. [Results] There were 21 patients with time since onset < 2 years and 23 patients with time since onset ≥ 2 years. No statistically significant differences were found between the groups in the male:female ratio, anti-CCP antibody level, RF quantitative results, MMP-3, DAS28, SDAI, or mHAQ scores, in the cumulative doses of PSL or MTX received, or in the proportion of patients receiving MTX. The patients with time since onset ≥ 2 years were older, more likely to have advanced RA, and had higher mHAQ scores. In both groups, statistically significant improvement was found after 6 months in all of the measures studied. Particularly statistically significant improvement was found in the DAS, SDAI, and Boolean remission measures in patients with time since onset < 2 years. [Conclusions] Early initiation of TCZ therapy in RA can be expected to significantly increase the SDAI and Boolean remission rates.

P2-083

The evaluation of serum oxidative stress and serum pentosidine in patients with rheumatoid arthritis under tocilizumab treatment

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Conflict of interest: None

【Objective】 To examine the correlations between disease activity and serum oxidative stress or pentosidine (PGE) in patients with rheumatoid arthritis (RA) treated with tocilizumab (TCZ). 【Patients and Methods】 Group A: 4 cases (59.4 year old in average and 9.4 years in average disease duration) followed before TCZ and 3, 6, and 12 months after TCZ treatment. Group B; 15 cases (55.8 year old and 11.5 years in duration) followed 1, 2, and 3 years after TCZ treatment. DAS28, serum d-reactive oxygen metabolites (d-ROM), and serum PGE were measured and time

course of each parameter in each group were statistically analyzed. 【Results】 Group A; DAS28 was 4.59 just before TCZ, and 3.55, 3.29, 3.86 on 3, 6, and 12 months after TCZ. d-ROM was 258 before TCZ, and 195, 177, and 236 U.CARR. PGE was 0.0476 before TCZ, and 0.048, 0.070, and 0.039 μg/ml. Group B; DAS28 was 2.52, 2.56, and 3.22 on 1, 2, and 3 years after TCZ. d-ROM was 290, 292, and 306 U.CARR, and PGE was 0.046, 0.047, and 0.035μg/ml. There was no significant difference between each parameter time course in both groups. 【Conclusion】 These data suggest that TCZ can decrease oxidative stress in the short term after induction and can preserve it in the long term and that TCZ can decrease serum PGE in both terms after TCZ.

P2-084

Efficacy of tocilizumab (TCZ) in RA patients with and without prior biologicals

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Itabashi Chuo Medical Center

Conflict of interest: None

[Objectives] The efficacy of tocilizumab (TCZ) was examined in RA patients with and without prior biologicals (Bios). [Methods] We examined patients in TCZ therapy, 15 with prior Bios and 25 naive to Bios. The observation was 6 months, and MMP-3, mHAQ, DAS28, SDAI and Boolean remission were compared before therapy and after 6 months. Statistical analysis was by Fisher's exact test and Wilcoxon rank test. [Results] At the start there were no statistically significant differences between groups in sex ratio, age, RA duration, anti-CCP antibody, quantitative RF, MMP-3, DAS28, mHAQ, PSL use, and MTX use and dose. After 6 months both groups showed statistically significant improvement in MMP-3, mHAQ, DAS28, SDAI and Boolean remission, with no significant difference between groups. However, SDAI and Boolean remission was 33.3% each in the prior treatment (+) group and 62.1% and 48.3% in the prior treatment (-) group, and efficacy in the naive group. [Conclusions] Therapeutic effect can be expected with TCZ regardless of prior Bios. However, by SDAI and Boolean remission criteria, efficacy tended to be higher in the naive group: thus TCZ could be the first option for patients with high active RA.

P2-085

Switching of tocilizumab to other biologics in patients with rheumatoid arthritis

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Conflict of interest: None

[Objectives] In patients with RA, there are few reports that assessed the effect of switching of tocilizumab to other biologics, and its effect still remains unknown. The present study was undertaken to assess the effect by monitoring CDAI. [Methods] Thirteen RA patients treated with tocilizumab (mean age 65, 9 women and 3 men, mean treated period 25 months, 9 treated with methotrexate, and 7 for first biologics) were enrolled. Before switching, 7 showed moderate and 6 showed high disease activity. The reason of switching was 5 for primary inefficacy, 4 for secondary inefficacy, 3 for severe infection, and 1 for liver dysfunction. Switching drugs were 3 for Infliximab, 3 for Etanercept, 4 for Adalimumab, and 3 for Abatacept. [Results] After switching, 5 patients achieved low disease activity (1 for Etanercept, 2 for Adalimumab, and 2 for Abatacept; except one case for Abatacept, 4 were treated with methotrexate), while 6 patients showed moderate and 2 patients showed high disease activity. Although number of enrolled patients is small, effective rate of switching tocilizumab to other biologics were relatively low.

P2-086

Safety and Efficacy of Tocilizumab (TCZ) monotherapy inpatients with rheumatoid arthritis

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Conflict of interest: None

[Objectives] To assess the safety and efficacy of TCZ monotherapy in patients with rheumatoid arthritis. [Methods] At the 24 weeks, evaluation of 21 RA patients (6 males,15 females) treated with TCZ monotherapy was performed retrospectively. [Results] The mean age of these 21 patients was 62.5±12.3 years old and disease duration was 11.4±8.8 years. They were treated with mean dosage of predonisolone 5.5±3.8mg/day. Eight patients were biologics naive and 13 were previously treated with anti TNF inhibitors. Of the 21 patients, 5 patients discontinued TCZ therapy because of adverse events (4 cases : abdominal pain, sepsis, worsened ASO, death for other disease) and unsatisfactory response (1case). EULAR response showed good response :8 cases(38.1%), moderate response: 5 cases (23.9%), no response :3 cases (14.3%). These 3 no response cases showed clinical impairment and they continued TCZ therapy at 24weeks. DAS 28 remission (≦2.6) was obtained in 3 cases(14.3%) and CDAI/SDAI remission was achieved in 1 case(4.8%). [Conclusions] TCZ monotherapy is considered to be effective therapy although attention for adverse events are needed.

P2-087

Analysis of Retrospective Data on Tocilizumab Therapy for Rheumatoid Arthritis (3rd Report)

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Conflict of interest: None

[Objective] Evaluating the efficacy and safety of tocilizumab (TCZ) for the treatment of rheumatoid arthritis in medical institutions in Yamaguchi Prefecture. [Subjects and Methods] This analysis included 75 subjects who could be followed up for at least 48 weeks. Patient demographic data were as follows: mean age, 58.6 years; mean disease duration, 9.9 years; DAS28-ESR, 5.0; and prior use of TNF inhibitors, 62.7%. Efficacy was evaluated based on DAS28-ESR scores using the LOCF technique. [Results] At 48 weeks, DAS28-ESR was significantly improved to 2.2, with a clinical remission rate of 68.0%. The percentage of subjects continuing with treatment was 88.0% at 48 weeks. Of 33 subjects who continued with treatment and achieved clinical remission at 12 weeks, 75.8% remained in clinical remission at 96 weeks. Factors that contribute to sustained remission identified by a univariate analysis included shorter disease duration and a lower DAS28-ESR at baseline, as well as a lower DAS28-ESR and achievement of TJC, SJC and CRP of ≤1 at 12 weeks. [Conclusion] Based on high remission induction rates and long-term sustained remission provided by TCZ, it was suggested that early therapeutic intervention and favorable treatment response at 12 weeks may contribute to mainte-

nance of remission.

P2-088

Clinical results and comparison of tocilizumab and etanercept in bio-naïve patients not using MTX

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Conflict of interest: None

[Objectives] Usefulness of tocilizumab (TCZ) and etanercept (ETN) was compared in rheumatoid arthritis (RA) patients in whom methotrexate (MTX) could not be used because of side effects or complications. [Methods] Bio- naïve RA patients who cannot take MTX observed for at least 12months divided into 20 in the TCZ group and 30 in the ENT group. [Results] The mean disease activity score 28 (DAS28) with c-reactive protein (CRP) and MMP-3 was 3.92 and 281.2ng/ml in the TCZ group, 3.93 and 345.2ng/ml in the ENT group; no significant difference was seen between the two groups. After 12 months, DAS28 CRP and MMP-3 was significantly reduced to 2.21 and 146.3ng/ml in the TCZ group, 2.29 and 171.7ng/ml in the ENT group, and no significant difference was seen between the two groups. TCZ and ENT show about the same excellent effects in patients who cannot use MTX.

P2-089

Comparative Study of the Clinical Remission Maintenance Rates of Biologicals in Rheumatoid Arthritis Patients

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Conflict of interest: None

Objective: The therapeutic objective in rheumatoid arthritis is the achievement and maintenance of clinical remission, based on the "treat-to-target" (T2T) concept. We verified, based on the data, which biologicals are consistent with the T2T concept. Subjects and Method: The subjects were 123 patients whom we were able to observe for at least 52 weeks following treatment initiation. The following three groups were compared, primarily in the clinical remission maintenance rate: group 1, which received TNF antibody drugs (IFX:17and ADA:12 patients), group 2, which received a TNF receptor drug (ETN:65 patients), and group 3, which received an anti-IL-6 drug (TCZ:29 patients). Results: The remission rate at 52 weeks was 41.4% in group 1, 58.5% in group 2, and 72.4% in group 3. The treatment continuation rate at 52 weeks was 69% in group 1, 86.2% in group 2, and 89.7% in group 3. The treatment continuation rate was therefore lower in group 1. The remission continuation rate at 52 weeks in patients who had been able to achieve clinical remission at 12 weeks was 54.6% in group 1, 73% in group 2, and 82.4% in group 3. Conclusions: Group 3 exhibited high clinical remission maintenance and treatment continuation rates, suggesting that this treatment might best match the T2T concept.

P2-090

Study on switching of biologics from TNF inhibitors to tocilizumab in rheumatoid arthritis

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Conflict of interest: None

[Objectives] To evaluate the efficacy of biologics switching from TNF inhibitors to tocilizumab(TCZ) in rheumatoid arthritis. **[Methods]** Nineteen patients(female 14, male 5) who resulted in no effect or inadequate response to the treatment by infliximab, etanercept or adalimumab and started TCZ were assessed. Das28-4ESR, SDAI and Boolean-based definition were used to evaluate disease activity. **[Results]** The mean age of patients was 58.2±19.8 years. The mean disease duration was 11.5±9.5 years. Steinbroker stage was I in 2, II in 1, III in 12, IV in 4 patients. Reasons for switching were no effect in 11, inadequate response in 8 patients. DMARDs administrated during TCZ treatment were MTX in 8, tacrolimus in 3, leflunomide in 2, SASP in 1, actarit in 1 and none in 4 patients. TCZ was continued in 15 out of 19 patients after a year (one year survival rate;78.9%) and discontinued in 4 patients because of no efficacy. The average DAS28-4ESR decreased from 5.22±1.20 to 2.46±1.29 and the average SDAI decreased from 23.0±12.4 to 8.19±8.29. The proportion of patients achieved clinical remission were 47.4% in DAS28-4ESR, 36.8% in SDAI and 36.8% in Boolean -based definition. **[Conclusion]** Switching to TCZ is beneficial in RA patients failed to TNF inhibitors.

P2-091

Tocilizumab is effective rheumatoid arthritis who had an inadequate to etanercept

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Conflict of interest: None

【objective】To clarify the effectiveness of switch to TCZ for RA patients who indicated secondary failure with ETN.【methods】The targets are 19 cases on 23 joints in which the patients switched to TCZ due to secondary failure with ETN and received operations. The pathological findings on the synovial tissue were examined with use of the Rooney score. The influences of the TCZ treatment periods and CDAI over the Rooney scores were examined. The presence of synovitis and bone marrow edema were examined by MRI.【results】The average period after the switch to TCZ before operations was 374 days. The average CDAI upon the start of TCZ was 32.3 and this improved to 15.9 at time of operations. The pathological findings on the synovial tissue were that a less number of synovial lining cells became single-layered and neoangiogenesis as well as cellular infiltration decreased. Correlation was recognized between TCZ treatment periods and fibrosis scores, showing the tendency that conditions improved 6months after switch. In MRI, synovitis was found with 33%, bone marrow edema was frond with 53.3%.【conclusion】It was suggested that the switch to TCZ is effective for cases of secondary failure with ETN and that the effect of TCZ was mild and appears after approximately a half year.

P2-092

Comparison of the effectiveness of tocilizumab as the second biologics between a group who received antibody preparations and another who received receptor preparations as first biologics

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Conflict of interest: None

[Objectives] Tocilizumab (TCZ) is often used as second bio-

logics for cases where anti-tumor necrosis factor therapy (TNF) has been suspended. We have examined the clinical effect of TCZ on cases where antibody preparations had been used as the first biologics and where receptor preparations had been used as the first biologics. [Methods] The database used was Tsurumai Biologics Communication, TBC. The subjects were 69 cases that had received anti-TNF therapy as the first biologics and were observed for 52 weeks after receiving TCZ as the second biologics. We examined DAS28-ESR, and DAS component, MMP-3 at 52 weeks after taking TCZ. [Results] The group who received antibody preparations as the first biologics (Group mab) consisted of 29 cases, whereas the other who received receptor preparations (Group cept) consisted of 40 cases. The percentage of subjects additionally using MTX was significantly higher in Group mab. The ESR was significantly high level in group Cept at a start. Among the DAS components, the VAS significantly improved in Group mab as compared to Group cept. Though no significant differences were recognized between the groups in DAS28(ESR), TJ, SJ, and MMP-3, there were tendencies that Group mab fared better than Group cept.

P2-093

Primary lack of efficacy of infliximab therapy for rheumatoid arthritis: pharmacokinetic characterization and assessment of switching to tocilizumab

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Conflict of interest: None

[Objective] To characterize primary failure to infliximab and determine the efficacy of switching to tocilizumab in patients with RA [Methods] we examined 24 patients who had started infliximab therapy as their first biological agent. [Results] Nine of the 24 cases were found to be primary nonresponders, defined as patients who had never achieved an ACR20 during induction therapy. A higher HAQ score was markedly associated with primary unresponsiveness to infliximab. Six of the 9 primary nonresponders showed rapid clearance of infliximab: their trough concentrations of infliximab were under 1 mg/ml. The other 3 were classified as exhibiting the residual type of unresponsiveness: they maintained serum infliximab levels above 1 mg/ml. Primary nonresponders to infliximab were started on tocilizumab therapy. All the nonresponders, excepting a single rapid-clearance patient, had achieved an ACR20 clinical improvement after 24 weeks. [Conclusion] Primary nonresponders to infliximab can be classified into rapid-clearance and residual types, but both types of nonrsponders seems to benefit fom an early dicision to discontinue infliximab and switch to tocilizumab

P2-094

Study for Clinical Benefit of Tocilizumab for Treat to Target from Multi Center Study, Tsurumai Biologic Communication Registry

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Conflict of interest: None

[Objectives] "Treat to Target: T2T" was released in 2010. In this recommendation, the primary target for treatment of rheumatoid arthritis should be a state of clinical remission, and the desired treatment target should be maintained throughout the remaining course of the disease, were strongly recommended. We consider the T2T practice can do in Tocilizumab (TCZ) administration. [Methods] 122 RA patients treated with TCZ at member institutions of Tsurumai Biologics Communication Registry (TBCR) which was a collaborative biologics treatment group supported by department of orthopedics, Nagoya University, with 12 months of observation, were available on. The efficacy of TCZ was measured at 6 months after administration, also at 12 months after. Clinical remission was evaluated by with less than 2.6 disease activity measured by DAS28-ESR. We evaluated remission rate and remission continuation at 6months and 12mounths after. [Results] DAS28-ESR was 0M:5.8 ±1.3, 6M:3.2 ±1.5, 12M:3.0±1.6, improved up to six months, was maintained until after 12 months. Percentage of clinical remission was 38.5% after 6 months, 43.4% after 12 months. 83.0% of clinical remission at 6months maintained until 12 months. TCZ for RA was good enough for introduction and maintenance of clinical remission.

P2-095

Clinical consideration of tocilizumab therapy in combination with MTX for RA patients

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Conflict of interest: None

[Objectives] We investigated the clinical efficacy of tocilizumab(TCZ) treatment with MTX combination for RA patients. [Methods] 19 patients, who were administered TCZ in our institution, were followed for more than 12 months. The mean age was 60.7 years old, and the average duration of disease was 9.7 years. 6 of the 19 patients had continued at least 6mg per week MTX administration for more than 12 months(Groop C). Another 6 of them had dicontinued(Group D). The others had not recieved MTX combined therapy(Groop N). The clinical response was measured by changes in ESR, PtGA, Hemoglobin(Hb), MMP-3, CARF, DAS28-ESR, CDAI, Boolean definition. [Results] The reasons the patients in Groop D and N could not continue or receive MTX administration were side effects of MTX and previous complications. The average clinical data of all 19 patients had improved in DAS28-ESR, CDAI, ESR, Hb, PtGA. 16 of them had achieved clinical remission in DAS28-ESR. All 6 patients of Groop C achieved clinical remission in DAS28-ESR, and five of them in Boolean definition. The average clinical data of Groop D had got worse. [Conclusion] We recomend that the patients receive combined therapy with TCZ and MTX. and that once they receive MTX administration, they continue it as long as possible.

P2-096

Efficacy of tocilizumab (TCZ) therapy in rheumatoid arthritis patients with and without MTX

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Conflict of interest: None

[Objectives] We examined differences in efficacy with and without MTX in our experience with TCZ. [Methods] Subjects were patients in TCZ therapy, 26 with MTX and 18 without MTX.

The observation period was 6 months, and MMP-3, mHAQ, DAS28, SDAI and Boolean remission were compared before treatment and after 6 months. Statistical analysis was by Fisher's exact test and Wilcoxon rank test. [Results] The dosage of MTX was 6.79 mg. At the start there were no statistically significant differences between the 2 groups in sex ratio, age, disease duration, anti-CCP antibody, quantitative RF, MMP-3, DAS28, mHAQ, PSL usage or prior history of biologicals. After 6 months both groups showed significant improvement in MMP-3, mHAQ, DAS28, SDAI and Boolean remission, with no statistically significant difference between groups. DAS28, MMP-3 and mHAQ tended to be numerically lower in the MTX group before and after treatment, but SDAI remission and Boolean remission at 53.9% and 42.3% in the MTX group and 50% and 44.4% in the non-MTX group showed equivalent efficacy. [Conclusion] The efficacy of TCZ therapy is high even without MTX administration, and it could be a useful option for patients who can't take MTX.

P2-097

Does Tocilizumab treatment have influence on a clinical remission in the use situation of MTX? -Examination in four kinds of clinical remission evaluations-

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Conflict of interest: None

[Objectives] In four kinds of clinical remission evaluations, it is investigated whether influence is seen in the use situation of MTX to a Tocilizumab (TCZ) treatment. [Methods] The TCZ treatment was enforced and 77 without the deficit of first time data were divided into 3 of a combined use (C) group, a past use (P) group, and an intact (I) group groups from the use situation of MTX. And in those groups, the remission rate for one year estimated DAS28, SDAI, CDAI, and Boolean definition (BD). [Results] The average disease duration was comparatively short, and a significant difference were not by C group, P group, and I group. BIO history and CRP were the significant difference between three groups, and were both high by the C group. The quantity of MTX in C group was decreased from the TCZ medication early stage with many cases. Moreover, the case which has stopped MTX was about 70%. AS the remission rates for one year, it was that the significant difference was not seen between three groups in every clinical remission evaluations. TCZ treatment is prescribing a medicine for the patient from a disease early stage, and is the biological agent which can demonstrate high clinical effectiveness regardless of the use situation of MTX.

P2-098

Efficacy of tocilizumab for rheumatoid arthritis in view of serum MMP-3 levels.

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Conflict of interest: None

[Objectives] To investigate the effect of IL-6 receptor inhibition with tocilizumab(TCZ) in RA patients. Evaluation of correlation between DAS28ESR and MMP-3 especially. [Methods] 22 patients were treated by TCZ from July 2007. 16patients had been treated with TNF inhibitor.6patients had never been treated with a biologic DMARD. [Results] During initial 12months serum MMP-3 levels was significant decrease in all patient and patients who had been treated by biologic DMARD. DAS28ESR was significant response in same group. Serum MMP-3 had correlation with DAS-28ESR at one and twelve months after. TCZ was effective for TNF agent fails to work in improvement of the serum MMP-3.

P2-099

Examination of usefulness of tocilizumab treatment for patients with rheumatoid arthritis in our department

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Conflict of interest: None

[Objectives] To investigate the efficacy and safety of tocilizumab (TCZ) in patients with rheumatoid arthritis (RA) in our department. [Methods] We examined 23 patients with RA who were treated with TCZ in our department during from July, 2008 to October, 2011. 18 patients were examined for continuation ratio and reason of discontinuation. And 14 patients who were continuously treated for 52 weeks and able to analyze the data were examined for efficacy. [Results] 18 patients; the average age was 56.6±18.1, the male:female ratio was 1:17, the average disease duration was 5.8±9.4 years. 9 (50%) were treated with biologic agent before introduction of TCZ. Methotrexate and glucocorticoids were given in 12 (67%) and 16 (83%) of 18 with TCZ, respectively. DAS28-ESR was 5.4±1.1. In 4 of 18 TCZ was discontinued and adherence to treatment was 77.8%. 14 were examined for Boolean Component. The achievement of TJC, SJC and CRP were significantly increased at 24 and 52 weeks compared to before TCZ treatment and the efficacy was considered. The safety was also suggested because only one patient discontinued for adverse event. [Conclusions] TCZ treatment was considered to be useful because adherence to treatment was comparatively high, the efficacy and safety of TCZ treatment were suggested.

P2-100

Clinical course of tolcilzumab administration to 84 patients at a rheumatology clinic

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Conflict of interest: None

[Objective] The efficacy and safety of tolcilizumab (TCZ) were examined in patients with rheumatoid arthritis (RA). [Methods] We started 107 RA patients on TCZ from April 2008 to July 2011. Retrospective analysis was performed on 84 of them who started TCZ by July 2010 to examine the remission and retention rates for TCZ. DAS28-CRP was used for clinical remission. Remission rate was subjected to stratified analysis by history and type of prior treatment with biologicals. [Results] Before treatment patients were an average age of 60.2 years, stages 2/3/4 (24/30/30 patients) with mean DAS28-CRP of 3.64 and mean MMP-3 of 249.1. Remission rates after 6 months and 1 year were 59% and 61% and retention rates were 98.8% and 92.8%, respectively. There were no differences in comparison of prior or type of BIO treatment, and the remission rate was 55% or higher and the retention rate 88% or higher in each group. [Conclusions] It is possible to maintain high long-term remission and retention rates with TCZ by fully grasping the precautions for starting biologicals and establishing a system for safe treatment.

P2-101

A Clinical Study of Patients Receiving Tocilizumab at Our Hospital

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Conflict of interest: None

[Objectives] To investigate the efficacy and safety of tocilizumab (TCZ) in RA [Methods] We retrospectively analyzed the proportions of patients achieving remission and continuing TCZ therapy in 40 patients started on TCZ therapy at our hospital. The DAS28 ESR was used as a measure of clinical remission, and a stratified analysis was performed by disease duration and history of treatment with biologics. [Results] After 24 weeks the remission rate was 62.5% and after 48 weeks it was 76.9%. After 24 weeks, 85.7% of the patients were still receiving TCZ, as were 85.7% of the patients after 48 weeks. Long-term use was not found to result in any attenuation of efficacy (secondary failure). After 24 weeks, improvement in the DAS28 ESR was significantly greater in the biologic-naive patients. There was no difference in improvement in the DAS28 ESR at 24 weeks by disease duration. More patients continued using TCZ than is seen with other drugs, and no differences were found in the proportion of patients continuing TCZ therapy between patients who had received biologics in the past and those who had not. The adverse drug reaction incidence was 30%, which was virtually identical to the rate reported postmarketing.

P2-102

Study of tocilizmab treatment for patients with rheumatoid arthritis.

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Conflict of interest: None

[Objective] To evaluate the effect of tocilizmab (TCZ) on patients with rheumatoid arthritis (RA) by using disease activity score based on 28 joints and ESR(DAS28-ESR), clinical disease activity index (CDAI) and the new ACR/EULAR criteria (Boolean approach), and analyze disease-associated factors contributing to achieve complete remission (CR). [Methods] A total of 50 patients with active RA were enrolled at Kobe University Hospital. Patients' profiles were age 55.9 ± 11.4 (female 43, male 7), class 2.0 ± 0.6 and X-ray stage 2.0 ± 0.7. 26 weeks after TCZ-introduced, results were evaluated by disease-associated factors including patients' age, disease-duration, tender-joint numbers, swollen-joint numbers, patients' global assessment, CRP, ESR, MTX-doze, and past histories of biologics agents. [Results] Treatment with TCZ reduced disease activity: DAS5.2±1.0→2.6±1.0(CR rate 42.0%), CDAI22.3±10.9→6.4±6.4(CR rate 22.0%) and BooleanCR36.0%, respectively. CRP and MTX-dose in DAS, MTX-dose in CDAI and MTX-dose in Boolean appeared to contribute in achieving CR. Good responders in DAS were significantly increased in patients who were introduced TCZ as a first biologic agent.

P2-103

Short-term efficacy of toclilizumab (TCZ)

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Azuma Rheumatology Clinic

Conflict of interest: None

[Background] Toclilizumab (TCZ) rapidly improves parameters, such as CRP, but improvement of joint symptoms is considered slow. [Objectives] The short-term efficacy of TCZ was evaluated with regard to joint symptoms, clinical test results, and evaluation by patients to investigate its efficacy. [Methods] The efficacy after a single administration was evaluated with regard to DAS28ESR, the numbers of painful (TJC) and swollen (SJC) joints, ESR, and overall VAS of patients in 11 RA patients newly treated with TCZ. [Results] The DAS28-ESR had improved from 5.07 to 3.86, TJC: from 8.3 to 4.1, and ESR: from 50.7 to 25.7, showing significant improvement. No significant improvement was noted in the overall VAS of patients (from 43.6 to 40.3). [Conclusion] A single TCZ administration significantly improved DAS28-ESR and joint symptoms (TJC and SJC), suggesting that the efficacy of TCZ is ultrashort-acting. DAS28-ESR was 3.86, showing moderate activity, which may have been influenced by the absence of improvement of the overall VAS of patients.

P2-104

Contribute factor (CF) on functional remission (FR) and clinical remission (CR) by Tocilizumab (TCZ) therapy in patients with Rheumatoid Arthritis (RA)

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Conflict of interest: None

[Objectives] To evaluate efficacy and safety of TCZ therapy with 45 RA patients. [Methods] The evaluation was performed at 24- week of TCZ therapy. We use mHAQ score as FR and use Boolean definition as CR. Meta-analysis was performed to extract CF on FR and CR. [Results] Overall FR rate was 68.4% at 24-week TCZ therapy. CF of FR were SJC, mHAQ, DAS-28ESR. Especially lower mHAQ before therapy reached FR frequently. Overall CR was 12.8%. The most important component on CR was PtGA. CF on CR was the status of Stage. Early Stage before TCZ therapy reached CR frequently. There were no serious side effects throughout the study. Therefore TCZ therapy can induce high rate of CR and FR before irreversible joint destruction of RA, even restrict CR definition of Boolean.

P2-105

Assessment of the disease activity using tender joint counts and swollen joint counts in rheumatoid arthritis patients treated with tocilizumab

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Conflict of interest: None

(Introducton/Objectives) Tocilizumab(TCZ), an IL-6 receptor inhibitor, has been shown its effectiveness in the treatment of RA patients. However the disease activity assessment including inflammatory markers such as ESR and CRP was of apprehension because TCZ significantly reduced them. Then we assessed the validity of relevant and easy disease activity evaluation using tender joint counts(TJC) and swollen joint counts(SJC) without inflammatory markers. (Methods) The eighteen RA patients who have been treated by TCZ for >24 weeks from April 2008 was included. (Results) TJC+SJC<1 was cleared by five patients and DAS28-CRP<2.3 was also satisfied. Furthermore TJC<1 was achieved in 85.7% and SJC<1 was 42.9%. Five patients among 7 RA patients who acquired the normalized MMP-3 value has achieved DAS28-

CRP<2.3, remission. (Conclusion) In assessing the disease activity of RA patients treated with TCZ, not only DAS28 but also TJC/SJC parameters was very useful and convenient at daily medical practice. Furthermore RA patients who acquired the normalized MMP-3 value were expected a good prognosis.

P2-106

Differential regulation of serum cytokine profiles in patients with rheumatoid arthritis treated with tocilizumab: Possible involvement of macrophage migration inhibitory factor

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Conflict of interest: None

[Objectives] To examine the effect of tocilizumab (TCZ) on serum cytokine levels in patients with rheumatoid arthritis (RA). [Methods] Serum levels of cytokines, TNF-α, IL-6, macrophage migration inhibitory factor (MIF), CCL2, CCL3, CXCL8, CXCL10 and CX3CL1 were quantified using ELISA. Measurements were made prior to and after 12 weeks of TCZ treatment in 21 RA patients. The disease activity was assessed using the clinical disease activity index (CDAI). The moderate and major responses to TCZ were defined as an improvement of greater than 6 and 14 points, respectively, from the baseline CDAI, in consistent with the improvement criteria proposed by Smolen et al. [Results] After 12 weeks of TCZ administration, 15 patients achieved a major/moderate response. Basal levels of MIF, CCL2 and CXCL10 were significantly higher, and a significant reduction in MIF was seen in responder group. When compared with lower (<1347 pg/ml; median of MIF levels) and higher basal MIF levels, MIF levels were diminished in patients with higher basal MIF levels in response to TCZ. [Conclusion] Our results suggest that in patients with active RA, serum MIF may be sensitive to tocilizumab therapy and that regulation of MIF via the IL-6/IL-6 receptor plays a crucial role in the pathogenesis of RA.

P2-107

Decrease of tocilizumab by monitoring serum IL-6 with sustained triple remission in rheumatoid arthritis: 6-STAR

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Conflict of interest: None

Objectives: To investigate the effectiveness of tocilizumab (TCZ) decrease strategy by monitoring serum IL-6 with sustained triple remission for rheumatoid arthritis (RA). **Methods:** 6STAR treatment strategy was adapted based on the criteria, which was satisfied with Disease activity Score in 28 joints (DAS28≤2.6), Health Assessment Questionnaire Disability Index (HAQDI)≤0.5, MMP-3 normalization and serum IL-6 level<35pg/mL. If the criteria were meted, the dose TCZ was decreased by 80mg. After the month later, if the criteria were not meted, TCZ was increased of 80mg. A total of 37 RA patients with DAS28>3.2 were enrolled, 7 patients were met criteria. Radiographic damage was assessment by total Sharp Score (TTS). Comprehensive remission is consisted of the proportions of patients showing clinical remission, radiographic nonprogression and normal physical function. **Results:** After 1 year, simplified Disease Activity Index (SDAI) remission, DAS28 index, radiographic nonprogression (ΔTSS≤0.5), normal physical function (HAQDI≤0.5), and comprehensive remission rate were 33%, 100%, 67%, 100%, 33%. **Conclusions:** Results of the 6-STAR is recommended for one additional benefit in terms of long-terms cost effectiveness of TCZ treatment.

P2-108

Evaluation of interleukin-6 and tumor necrosis factor-alpha in peripheral blood of patients with rheumatoid arthritis treated with tocilizumab

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Conflict of interest: Yes

[Objectives] To evaluate the change in levels of IL-6 and TNF-α in the peripheral blood of RA patients treated with tocilizumab (TCZ) alone or in combination with MTX. [Methods] The 11 RA patients comprising the study had not been administered any biological DMARD during the previous 5 years, and had not been administered MTX within the month before registration. The patients will receive TCZ (8 mg/kg) alone every 4 weeks, and will be evaluated by SDAI at Week 24. Patients who do not achieve remission at that point will then be started on MTX combination therapy. IL-6 and TNF-α levels and DAS28 will be evaluated at the baseline, Week 24, and Week 36. [Results] The mean age was 52.5 years and mean disease duration was 1.3 years. The mean DAS28, IL-6, and TNF-α levels at baseline were 4.2±1.5, 8.3±10.8 pg/mL, and 1.7±0.8 pg/mL, respectively. At present, only 6 patients have been able to be evaluated at Week 24 (LOCF), and the mean DAS28 was 2.0±1.0. Because this study is currently under-way, only a few cytokine levels have been revealed for Week 24. [Conclusion] We will investigate and report the relationship between these cytokine levels and the efficacy of TCZ or MTX combination therapy.

P2-109

Serum interleukin-6 (IL-6) before and after therapy with tocilizumab is a principal biomarker in patients with rheumatoid arthritis

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Conflict of interest: None

[Objectives] To analyze the *in vivo* active mechanism of tocilizumab (TCZ) treatment in cytokine-network, of RA. we measured serum proinflammatory cytokine concentrations. [Methods] Serum samples were collected from 57 patients with RA who met the criteria of the American College of Rheumatology (28 patients to be treated with TCZ and 29 patients to be treated with infliximab (IFX)) and 13 healthy donors. [Results] Although IL-1b, IL-2, IL-6, IL-17A, IL-17F, IFNa, and TNFa were all increased in sera from patients with RA before treatment compared with healthy donors, only IL-6 level was significantly correlated with DAS28. The serum IL-6 concentration was significantly decreased by IFX but increased by TCZ treatment. The increased serum IL-6 after TCZ treatment correlates with DAS28 at baseline. Our analyses also showed that serum IL-6 level at baseline was positively correlated with DAS28 after TCZ treatment, which may reflect residual disease activity. Although both TNFa and IL-6 are the major targets of therapeutic intervention in RA, the serum IL-6 but not the TNFa level before treatment could be a clinical biomarker reflecting dis-

ease activity. Furthermore, measurement of serum IL-6 in RA before treatment might be useful to estimate residual disease activity after TCZ treatment.

P2-110

Effect of tocilizumab on bone destruction in rheumatoid arthritis -Regulation of Dickkopf-1 and receptor activator of nuclear factor-kappaB ligand (RANKL)-

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Conflict of interest: None

[Objectives] Dickkopf-1 (DKK-1), an inhibitor of Wnt signaling pathway, plays an important role in osteoclastic bone destruction via regulation of RANKL-osteoprotegerin (OPG) balance in rheumatoid arthritis (RA). Recently, it was reported that circulating DKK-1 was correlated with bone erosion and inflammation in RA. In this study, we investigate the effects of Tocilizumab (TCZ) on biochemical markers of bone, serum RANKL, OPG, and DKK-1 in patients with active RA. **[Methods]** 28 patients with active RA were started on treatment with TCZ 8mg/kg intravenously every 4 weeks. Circulating levels of osteocalcin, NTx, sRANKL, OPG, and DKK-1 were examined by ELISA at baseline and after12 weeks. **[Results]** Average of NTx, sRANKL, and DKK-1 levels at 12 weeks after the treatment of TCZ decreased significantly from the baseline (19.20 nmol BCE/l vs 16.43 nmol BCE/l; $p<0.01$, 0.819 pmol/l vs 0.689 pmol/l; $p<0.05$, and 2536 pg/ml vs 2065 pg/ml; $p<0.01$, respectively). Average of osteocalcin levels at 12 weeks increased significantly from the baseline (5.31 ng/ml vs 5.67 ng/ml; $p<0.05$). Average of OPG levels did not change significantly. **[Conclusions]** These results suggest that TCZ may improve osteoclastic bone destruction in RA through the regulation of DKK-1 and RANKL expression.

P2-111

The Effect of Cytokine Profile in Patients with Rheumatoid Arthritis Treated by Tocilizumab and TNF-Inhibitors

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Conflict of interest: None

[Objectives] We measured serum concentrations of cytokines in rheumatoid arthritis (RA) patients received biological agents to identify the mechanisms and predictors of tocilizumab (TCZ) efficacy. [Methods] In 42 RA patients (TCZ group 27, TNF-inhibitor [TNFi] group 15), serum concentrations of IL-1β, IL-2, IL-4, IL-5, IL-6, IL-7, IL-8, IL-10, IL-12, IL-13, IL-17, G-CSF, GM-CSF, INFγ, MCP-1, MIP-1β, TNFα, CCL-20, IL-23 and TWEAK before/after treatment (0M/6M) were measured by the multiplex method and ELISA. Clinical response was evaluated with DAS28-CRP and EULAR response criteria. [Results] DAS28-CRP was 4.7 ± 0.9 in the TCZ group and 5.1 ± 1.3 in the TNFi group (p=0.16) at M0. The ratio of good/moderate/no responders at 6M was 16/9/2 in the TCZ group and 4/7/4 in the TNFi group, respectively. Analysis of the cytokine profiles at 0M and 6M in good responders or moderate responders revealed that various cytokines were inhibited mainly in the TCZ group (IL-1, IL-2, IL-7, IL-8, IL-10, IL-12, GM-CSF, IFN-γ, MCP-1, TNFα, TWEAK), while chemokines were inhibited mainly in the TNFi group (IL-6, MIP-1β, CCL-20). Interestingly, cytokines at 0M tended to be higher in good responders than in moderate responders (IL-1, IL-2, IL-6, IL-7, IL-10, IL-12, GM-CSF, IFN-γ).

P2-112

Adiponectin and biomarkers of fat metabolism analysis in the biologics tratment of rheumatoid arthritis

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Conflict of interest: None

【Objectives】 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. 【Methods】 Thirty three cases treated by biologics were investigated. We comparatively studied Responders [DAS28<2.6; n=8] and Non-responders [DAS28>=2.6; n=25]. 【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 level of β-Lipoprotein was significantly higher in the Responders. 【Conclusion】 The results show that lipid metabolism is involved in pathology of RA and indicate that β-Lipoprotein can be a predictor for the effects of biologics in RA.

P2-113

Development of an Air-removal Device for the Self-injection of Biologics

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Conflict of interest: None

[Objectives] Air is usually contained in syringes where self-injection is admitted in biologics. Despite there being no problems when air enters the body upon injection, some patients feel unease. Before injection, the patients themselves remove the air. However, some patients with rheumatoid arthritis cannot remove the air entirely or push too hard and cause leakage of the liquid due to deformation or limited finger motion range. We invented a device which would allow easy air removal even for those with a handicapped hand. [Methods&Results] When removing the air, position the syringe tip up to collect the air at the tip-end, push the plunger to push some liquid out, and stop the plunger. We calculated the length of the air remover by measuring both the length between the end fitting and the flange, and the length of the air bubble in the syringe. Before removing the air, place the air remover to the plunger and push the plunger until it stops. Essentially, the air remover acts as a support. No air remains within the syringe when the support is removed. [Considerations] Some patients with rheumatoid arthritis and with hand deformations are unable to smoothly remove air. We developed this air remover to alleviate the unease coming from air entering the body.

P2-114

Remission rates of rheumatoid arthritis defined by various criteria 1 year after initiation of biologic therapy

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Conflict of interest: None

Objective: To compare the 2011 ACR/EULAR remission criteria with the conventional DAS28 remission criteria in patients with rheumatoid arthritis (RA) during tumor necrosis factor (TNF) inhibitor therapy. Methods: RA patients were assessed 1 year after initiation of TNF inhibitors, and categorized into remission according to the DAS28, the Simplified Disease Activity Index (SDAI), the Clinical Disease Activity Index (CDAI), and ACR/EULAR Boolean-based definition. Results: A total of 268 patients were enrolled in this study: 204 patients were treated with etanercept (ETN group), 45 with infliximab (IFX group) and 19 with adalimumab (ADA group). Remission rates with DAS28 criteria, SDAI criteria, CDAI criteria, and ACR/EULAR Boolean-based criteria were 40.7%, 27.5%, 27.5% and 28.4% in the ETN group, 22.2%, 17.8%, 15.6% and 20.0% in the IFX group, and 47.4%, 36.8%, 36.8% and 42.1% in the ADA group, respectively. Conclusion: Remission rates varied among criteria, and those defined by DAS28 were higher than those by SDAI, CDAI and Boolean criteria. The SDAI, CDAI and Boolean criteria were found to be more stringent in defining remission.

P2-115

Comparison disease activities among clinical assessment criterias (DAS28-ESR, SDAI, CDAI, Boolean) under the biologics treatment for rheumatoid arthritis. –DAS28 cut-off point for Boolean criteria–

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Conflict of interest: None

[Objectives] The aim of this study was to compare disease activities evaluation methods (DAS28-ESR, SDAI, Boolean) and examine the cut-off point of DAS28-ESR against Boolean remission. [Methods] The analysis included 74 patients (9male, 65female, mean age: 57y.o, mean duration: 14years) diagnosed RA using biologics in our department. These consist of 15 patients using Infliximab, 36 using Etanercept, 8 using Adalimumab, 10 using Tocilizumab and 5 using Abatacept. The DAS28-ESR cut-off point required to achieve remission under the new Boolean remission criteria was analyzed by ROC analysis. [Results] In DAS28-ESR, Remission; 47%, low disease activity (LDA); 18%, moderate disease activity (MDA); 29%, high disease activity (HDA); 6%. In SDAI, Remission; 21%, LDA; 52%, MDA; 24%, HDA; 3%. In Boolean, Remission rate was 17%. ROC analysis showed that the DAS28-ESR cut-off point for Boolean remission was DAS28-ESR<2.47 (sensitivity;100%, specificity;75%). It was lower than DAS28 remission criteria <2.6. Meanwhile, Six of 19 patients with MDA in DAS28 corresponded LDA in SDAI. Two of 4 patients with HAD in DAS28 corresponded MDA in SDAI. Boolean was most stringent criteria for remission. SDAI and DAS28 was important indicators of LDA to HDA.

P2-116

Comparison of remission induction rates by four remission criteria in RA patients treated with each of four biological agents

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Conflict of interest: None

【Objectives】We compared remission induction rates defined by four clinical remission criteria in our RA patients treated with each of four biological agents.【Patients and Methods】All the patients were treated with any biological agent and were followed in our department for more than 52 weeks. Infliximab(IFX);120, Eternercept(ETN);223, Tocilizmab(TCZ);110, Adalimumab (ADA);89. We used DAS28-ESR≦2.6, SDAI≦3.3, CDAI≦2.8, Boolean criteria as remission criteria and compared them at the 52 week after starting biologics.【Results】Remission induction rates by each remission criteria (DAS28-ESR, SDAI, CDAI, Boolean) in each biological agent (IFX, ETN, TCZ, ADA) user group was as follows; IFX(30.1%, 24.1%, 21.6%, 15.6%), ETN (43.8%, 26.2%, 23.1%, 17.7%), TCZ (60.9%, 36.3%, 33.6%, 19.1%), ADA (29.0%, 22.4%, 22.4%, 14.1%).【Conclusion】The remission rate defined by DAS28-ESR was the highest and the Boolean criteria gave the lowest remission rate in each biological agent group. In TCZ users, all four remission induction rates seemed to be higher than those seen in the other groups.

P2-117

The correlation among the time of beginning of biological DMRDs, functional status and X-ray findings

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Conflict of interest: None

[Objectives] [Methods] Recently, it was reported that the bone destruction progresses between 2 or 3 years from RA onset. Early diagnosis, early treatment and absolute management especially first several years are important. They say that the biologics should be introduced on early stage for uncontrollable patients. We investigated the correlation among functional status by using a modified health assessment questionnaire (mHAQ) score, X-ray findings by using a modified total Sharp (mTSS) score and the time of beginning of biologics. [Results] All of 5 patients who had received biologics within 2 years from onset have achieved mHAQ remission. On the other hand, the only one of 6 patients who had received biologics more than 2 years after onset has achieved mHAQ remission. There is not clear correlation between mHAQ and mTSS in patients who have achieved mHAQ remission. The all patients who had achieved mHAQ 0 had received biologics between 6 months from onset and mTSS were low. It should be considered the RA patients who cannot achieve remission with conventional DMARDs will receive biological DMAARDs before bone destruction starts and this decision makes functional status since then.

P2-118

Analysis of the Patients' Background which Affects the Appropriateness of Patient Global Visual Analogue Scale in Japanese Patients with Rheumatoid Arthritis

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Conflict of interest: None

[Objectives] Although patient global visual analogue scale (PtGV) is important for evaluation of disease activity of rheuma-

toid arthritis (RA), it is the report based on subjectivity and physician may doubt its appropriateness. We studied about inappropriate PtGV for physician in order to know the effect to the ACR/EULAR remission criteria, and to find the causative factors in it. [Methods] In 250 Japanese RA patients, PtGV, physician GVAS (PhGV), and clinical indicators were measured, multiple regression analysis for the difference of PtGV and PhGV was conducted with age, disease duration and CRP, JHAQ, and EQ5D score as independent variables. [Results] 103 patients (41.2%) satisfied the remission criteria except PtGV in Boolean method and 48 patients (19.2%) satisfied the complete criteria. The number of patients with remission increase to 75 (30.0%), using PhGV in place of PtGV. According to multiple regression analysis, the variables which contribute to the difference are CRP (β=-0.365, $p< 0.0001$) and EQ5D score (β=-0.280, $p= 0.003$), and no other variables showed statistical significance. It is presumed that inappropriate PtGV for physician is seen not in patients with long disease duration and severe functional disability, but in patients with mild inflammation and lower QOL.

P2-119

Study on evaluation of disease activity in RA patients evaluated by the same doctor

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Conflict of interest: None

Early diagnosis of RA was possible by the new classification criteria in 2010. Then, in The 10 recommendations of the T2T committee, mentioned as a distinct therapeutic target for clinical remission or low disease activity, in determining the therapeutic strategy in routine clinical practice, composite measure of disease activity including the articular findings was stated to be used. Composite measure of disease activity as DAS (disease activity score) in addition to, SDAI (simplified disease activity index) CDAI (clinical disease activity index) and the like. Now, 106 patients attending the same physician outpatient, were evaluated by DAS, SDAI and CDAI, the results were compared for each composite measure of disease activity. Physician VAS was evaluated by the same physician. Between disease activity indices are well correlated, overall remission of SDAI / CDAI was 22, DAS remission was 45, approximately twice. When DAS (CRP) remission criteria was tightened to >1.7, the number of the patients with DAS remission was 24, including all SDAI/ CDAI remission patients in it. Remission/non-remission SDAI / CDAI was greater the effect of VAS. There were some patients with physician VAS and patient VAS divergence.

P2-120

To Introduce the Concept of Minimal Disease Activity in daily practice

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Conflict of interest: None

[Objectives] Minimal disease activity (MDA) was proposed by OMERACT as a useful target of treatment by both the patient and the physician, given current treatment possibilities and limitations. Two definitions of MDA are proposed, a core data set definition and a DAS-based definition (DAS28 ≤ 2.85). However, the definitions were not intended to guide decisions in individual patient care [Methods] We analyzed the Japanese National Database (NinJa 2009) using the core set definition of MDA. We performed the ROC analysis procedures to propose new MDA criteria of SDAI, CDAI and RAPID3. Two modifications were applied for the analysis. First, "mHAQ=0" was used in place of "HAQ≤0.5". Second, RAPID3 was estimated by the following method: RAPID3=0.265+1.034×(mHAQ×10/3 + Pain VAS + Patient global VAS) [Results] By the core set definition of MDA, 30% of patients (1348/ 4478) were categorized as MDA. Based on the ROC analysis, we proposed SDAI≤6, CDAI≤5, and RAPID3≤5 as new MDA criteria. These new criteria showed better agreement for the core set definition of MDA than the DAS-based definition of MDA, DAS28≤2.85. (Kappa: SDAI 0.729, CDAI 0.718, RAPID3 0,717, DAS28 0.654) In conclusion, the concept of MDA may be applicable in daily practice.

P2-121

Investigation of the 2011ACR/EULAR Definitions of remission using for the clinical assessment.

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Conflict of interest: None

[Objectives] To investigate whether ACR/EULAR rdefinitions of remission is suitable for clinical assessment. [Methods] Patients arrived at our clinic were scored using ACR/EULAR remission definitons, SDAI and Boolean-based definition. [Results] 96 cases(18 males, 82 females, average age 53.3 years old) were enrolled to this study. ACR/EULAR remission for all 4 measures was obserbed in 25% of the observations. All of the patients who scores ≤1 on tender joint count, swollen joint count(SJ), CRP and patient global assessment (PGA) showed DAS28<2.6. 19 out of 56 (33.9%) patients with DAS28<2.6 showed remission in ACR/EULAR definiton (Boolean-based definition). 22 of 96 cases showed no remission because of lacking 1 parameter. The reason of no remission were due to PGA (86.3%) and SJ (13.6%). PGA is 2.2-4 times higher than MD global assessment in the patients achived remission in SDAI but not in Boolean-based definition. Conclusion: There is a possibility that PGA is one of the factor affect to the result of definitons of remission.

P2-122

Silicon implant arthroplasty for the rheumatoid thumb

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Conflict of interest: None

[Objectives] We evaluated the clinical results of Silicon implant arthroplasty for the rheumatoid thumb. [Methods] Five thumbs in 5 patients were treated between 2009 and 2011. There were 5 females with an average age of 69.7 years. The mean duration of the disease before surgery was 31.7 years. The average follow-up period was 15.2 months. [Results] Pain was completely resolved in all thumbs. The average active extension angle of the metacarpophalangeal (MP) joint before the surgery was -41 degrees and became -8.8 degrees after the surgery. The average active flexion angle of the MP joint before the surgery was 58 degrees and became 37.5 degrees after the surgery. DASH score improved from 54.9 to 36.1 points. All patients were satisfied with their surgical outcomes.

P2-123

Analysis of three-dimensional computed tomogram of the rheumatoid hand with Swanson implant arthroplasty of the metacarpophalangeal joint

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Conflict of interest: None

[Objectives] Using a X-ray, precise imaging of palmoulnar flexion deformity at the MP joint affected by RA is difficult. The objective of this study is to show analysis of the deformity using a 3D-CT. [Methods] Between April 2006 and April 2011, Swanson implant arthroplasty at the 2nd through the 5th MP joints was performed at 179 joints in 46 hands of 40 patients with RA. Using a posteroanterior view of the hand X-ray, Larsen grade and ulnar flexion angle were assessed. Using a 3D-CT, ulnar flexion angle, palmar flexion angle, grade of MP joint dislocation and resected bone length were assessed by Aquarius iN tuition (Tera Recon). [Results] Preoperative ulnar flexion angle in a X-ray was approximately 9 degrees less than that in a 3D-CT. With progression of Larsen grade, palmar flexion angle of the MP joint increased, and with progression of MP joint dislocation, ulnar flexion angle increased. Average length of bone resection at the metacarpal neck was 9.6mm and that at the proximal phalangeal base was 4.5mm. With progression of MP joint dislocation, resected bone length increased. [Conculusions] A 3D-CT is useful to assess alignment at the severely deformed MP joint. It gives information about an appropriate length of bone resection in the preoperative planning.

P2-124

Clinical results of surgical treatment for spontaneous extensor tendon rupture in the rheumatoid hands

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Conflict of interest: None

[Objectives] We evaluated the surgical outcomes of tendon reconstruction of the spontaneous extensor tendon rupture due to rheumatoid arthritis hands and early mobilization after surgery. [Methods] We carried out the tendon reconstruction of the spontaneous extensor tendon rupture due to rheumatoid arthritis on 21 hands in 19 patients. There were all females with an average age of 60.5 years.. The average period from the onset of the tendon rupture to surgery was 2.2 months. One patient had the rupture in EPL, seven patients had in little finger, ten patients had in ring and little fingers, one patient had in middle, ring and little fingers, two patients had in middle and ring fingers. Surgical procedures included end to side suture in 7 hands, tendon transfer in 13 hands, bridge graft in one hand. The Sauvé-Kapandji procedure for the reconstruction of the distal radioulnar joint and synovectomy were performed for all patients. The average follow-up period was 4 years. [Results] The average active extension angle of the MP joint after surgery became – 19.8 degrees at the time of investigation. All cases had no limited flexion in the MP joint and no re-rupture after surgery. [Methods] Early mobilization is very useful to prevent the limited flexion in the MP joint.

P2-125

The Darrach procedure for the rheumatoid wrist. Guidelines to prevent occurrence of complications.

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Conflict of interest: None

[Objectives] To investigate clinical results of the Darrach procedure for the rheumatoid wrist and obtain guidelines to prevent complications. [Methods] Forty-seven wrists which underwent a surgical treatment were followed for more than one year. Six patients were male and 34 were female. Their average age at surgery was 63 years. Preoperative Larsen grade was, Grade I: 5; II: 10; III: 20; IV: 11; V: 1. [Results] Preoperative wrist pain was decreased postoperatively in all patients. None of the patients complained of a phenomenon that ulnar stump impinged on the radius. An extensor tendon rupture occurred in two patients two or three months after surgery, but no complication in terms of extensor tendons has been observed since a current procedure was adopted. Radiological findings showed ulnar displacement of carpal bones in 12 wrists. In seven of the wrists, dislocation of carpal bones did not occurred because a shelf at the radius was formed. In the other five wrists, the shelf formation was not recognized and the carpal bones were dislocated. Biological drugs were used in six of the seven patients whose wrists were saved from ulnar dislocation of carpal bones. By contrast, none of the patients whose carpal bones were dislocated has been treated before by any biological agents.

P2-126

Total Wrist Arthrodesis Using Intramedullary Rods for Rheumatiod Wrists

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Conflict of interest: None

【Objective】We reviewed outcomes of wrist arthrodesis for the mutilating rheumatoid wrists using the intramedullary rods.【Methods】We retrospectively reviewed 5 wrists of 3 patients performed the total wrist arthrodesis using the intramedullary rods, Wrist Fusion Rod (WFR), at our hospitals from 2005 to 2009. Mean age of the patients at operation was 55 years (51 to 62). Operations were performed for 2 right and 3 left wrists. All wrists were classified as Larsen grade V. Mean duration of follow-up was 44 months (27 to 72). Three wrists of 2 patients were complicated with rupture of extensor tendons. Bone fusion after surgeries was assessed by radiography. Radiographic assessment was also performed by carpal height ratio (CHR), carpal ulnar distance ratio (CUDR) and volar carpal subluxation ratio (VCSR).【Results】All wrists achieved radiographic fusion. Mean CHR at the time of pre-operation, post-operation and final follow-up was 0.34, 0.30 and 0.29, respectively. Mean CUDR at those of each time points was 0.14, 0.20 and 0.20 respectively. Mean VCSR at those of each time points was 0.31, 0.15 and 0.16 respectively. Total wrist arthrodesis by this procedure resulted in successful fusion without time-dependent change after wrist arthrodesis.

P2-127

Modified limitted arthrodesis for Reumatoid wrist

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Conflict of interest: None

[Objectives] Since 1996, Limitted arthrodesis using Herbert screw were operated for rheumatoid wrist with destruction of radiocarpal joint spared midcarpal joint. [Methods] Operative technique is combined limitted arthrodesis and Kapandii method in all

cases. We used dorsal approach. Curettage were performed on radiocarpal joint. Bone graft from ulna which was resected by Kapandii method inseted between lunate and radius. Next, two canulated Herbert screw were inserted from dorsal radius to lunate. 20 cases were operated, include 4 male, and 16 female, and mean age was 52 years old. Postoperative observation periods was 3.2 years. Pain score and R.O.M. were examined clinicaly. Movement of ulnar carpal bone and volar subluxiation were examined on X-P. [Results] Bone union was obtined in 18 cases, but fibrous union remained in 2 cases. Pain was daiappeared in all cases. Range of motion was improved in supination and pronation, but dorsiflexion, palmar flexion was worse than before surgery. X-P showed movement the ulnar carpal bone improved from 0.132 ± 0.037 to 0.129 ± 0.064 significantly.

P2-128

Short-term clinical outcomes of FINE Total Knee System in patients with RA and OA

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Conflict of interest: Yes

FINE Total Knee System is a unique implant with different geometry between medial and lateral compartment, designating physiological movement. It has two types, CR, cruciate retaining; and PS, posterior stabilized, of which we studied short-term clinical outcomes in patients with RA and OA with minimal follow up 6 months. 20 knees of 16 patients were studied; 6 of 5 RA and 14 of 11 OA. All patients were female and mean age was 70.1. We studied preoperative as well as postoperative range of motion (ROM), Japanese Orthopaedic Association Knee OA Score (JOA Score), and femorotibial angle (FTA) on AP radiographs. We also measured α, β, γ and Δ angle on postoperative radiographs, based on Knee Society Radiographic Evaluation Form. Mean ROM was -7.4 degree extension and 114.2 degree flexion preoperatively, while they were -3.5 and 119.3, respectively at the final follow up. Mean JOA Score improved from 52.1 preoperatively to 79.7 at the final follow up. Mean FTA was 184.8 degree preoperatively and 174.2 at the final follow up. Mean α, β, γ and Δ angle were 96.7, 89.1, 1.5 and 88.5 degree, respectively. Promising short-term clinical outcomes were confirmed in this study. Further kinematical studies will be necessary for determination whether designated motion is realized in this implant.

P2-129

Gender-specific total knee arthroplasties for the patients with rheumatoid arthritis

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Conflict of interest: None

[Objectives] A new gender-specific system of the femoral components for total knee arthroplasty (TKA) was designed, because recent anatomic and radiographic studies have been reported that there are anatomic differences of the femur in between female and male. We retrospectively reviewed the patients with rheumatoid arthritis (RA), who had undergone primary TKA utilizing either a NexGen Legacy Posterior Stabilized prosthesis or a Gender Solutions NexGen Legacy Posterior Stabilized prosthesis. [Methods] The average age at the time of TKA was 73.1 years. The average follow up duration was 12.2 months. These patients were classified into two groups, Traditional group with the former prosthesis and Gender group with the Gender Solutions prosthesis. Range of motion (ROM) of the knee was measured and clinical evaluation was made using a Japan Orthopedic Association (JOA) RA knee score system. [Results] Seven knees (37%) out of 19 were found in Traditional group, and 12 knees (63%) in Gender group. The postoperative improvement rate of ROM compared to the preoperative ROM was as much in Traditional group as the one in Gender group. The postoperative improvement rate of JOA score compared to the preoperative JOA score in Traditional group was 212%, and the one in GS group was 198%.

P2-130

Clinical short-term results of IBIS Total Knee System against RA patients

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Conflict of interest: None

Objective: IBIS Total Knee System has a simple design with stable mobility. It was developed in Niigata Rheumatic Center in 2006. The design and the size of the femoral and tibial components fit Japanese build, and it is easy to install. The objective of this study is to clarify the short-term results of this system to the RA patients. ***Patients and methods:*** Between 2006 and 2011, this system was used 128 knees in 105 patients (male: 24, female: 81). The mean age at the operation was 65 (39-86) yrs., and the mean follow-up period 25.6 (6 -61) mos. We checked the Japan Orthopedics Association Score (JOA score) in knee and the X-ray with the knee Society Roentgenographic Evaluation system. ***Results:*** JOA score is removed from 46 to 75($P<0.05$). Range of motion (ROM) was changed from -12/119 to -3/112. ROM was almost same, but there was insufficient knee flexion ($P>0.05$). In X-ray, there was no radiolucent line in all operated knees. There was no infection and revision. ***Conclusion:*** Short-term results of IBIS Total Knee System against RA patients were almost favorable.

P2-131

Surgical treatment and rehabilitation for severe valgus knee of rheumatoid arthritis

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Conflict of interest: None

[Objectives] Deteriorated knee joint destruction of rheumatoid arthritis can advance valgus deformity which suffers daily living. In such case, we perform total knee arthroplasty that demands technical skills in correcting valgus deformity. Hereby, we report our operative techniques and postoperative rehabilitation of severe valgus knee underwent total knee arthroplasty. [Operative technique] After cutting of femur and tibia in accordance with suitable component using medial approach, we cut iliotibial tract at Gerdy tubercle to adjust balance. We select surface replacement or constrained prosthesis depending on balance. [Postoperative rehabilitation] Because almost all patients can't walk alone without self-help device before operation, they showed giving way for the time being after operation. For that reason, extension brace application was effective for gait exercise. [Complication] One delayed wound healing and one skin necrosis of anterior leg owning to subcutaneous hematoma were occurred but cured by appropriate wound ther-

apy. [Conclusion] Selection of implants and proficiency of surgical technique were necessary for successful result.

P2-132

The Experiences of MIS-TKA for Patients with Severely Deformity

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Conflict of interest: None

[Objectives] We showed the new medial para-patellar approach with added release of posterolateral corner for MIS TKA of patients with severely deformity. [Methods] 23Knees of 7RA and 12OA patients were evaluated. 1 Knee of Severe flexed deformity, 2 of ankylossis, 15 of severe valgus deformity were contained. [Results] The mean skin incision was about 11.9 cm. The post-operative JOA was 91 points at the latest follow-up. We consider this approach is beneficial and supplys the wide view during MIS-TKA operation.

P2-133

Size of the femoral and tibial components during PS-TKA in OA and RA knees

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Conflict of interest: Yes

[Objectives] Size of the femoral and tibial components was assessed during PS-TKA in OA and RA knees. [Methods] Size of the femoral and tibial components based on the preoperative planning and actual size during PS-TKA by means of the modified gap control technique were assessed in 472 OA knees and in 28 RA knees. Actual size of the femoral component was decided according to the gap distance, and actual size of the tibial component was decided based on the distance between the lateral edge of the tibial condyle and the central line of the tibial shaft duringPS-TKA [Results] The size was the same between the femur and the tibia in 76.5% in OA and in 82.1% in RA on the preoperative planning. The actual size of the femur was larger than the actual tibia in 65.9% in OA and in 60.7% in RA. The actual size of the femur was larger than the planning in 43.6% in OA and in 42.9% in RA. The actual size of the tibia was smaller than the planning in 42.2% in OA and in 14.3% in RA. The size of the femur was larger in PS-TKA by means of modified gap control technique because of PCL resection. The actual size of the tibia was smaller in OA than in RA. Size of the components was different between modified gap control technique and the measured bone resection technique, and between OA and RA.

P2-134

Radiographic change of total knee arthroplasty with Deltafit prosthesis in rheumatoid arthritis patients after over fifiteen years

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Conflict of interest: None

[Objectives] To estimate loosening of Detafit prosthesis in RA knee after over fifteen years. [Methods] We estimated five RA patients (eight knees) who underwent cementless total knee arthroplasty with Deltafit prosthesis (Stryker) between 1994 and 1996 and still visit out institute. Patella was also replaced in four knees. No patients have pain in rest and on motion. They were sixty-two years old in average at the surgery and sixteen years in average have passed since the surgery. We estimated the apparent radiolucent line around the proshtesis in the X-ray at the last visit. [Results] The survival rate of Deltafit prosthesis was a hundred percent as far as these patients were concerned. We found the radiolucent line at the anterior part of the femoral and tibial component relatively frequent. One tibial component was apparently loosed. Overall, cementless Deltafit prosthesis in RA knee was well fixed after over fifteen years in this study.

P2-135

Clinical Results of Primary Total Knee Arthroplasty with Use of Stem Extension, Augmentation Metal, and/or Constrained Condylar Knee Prosthesis in Patients with Rheumatoid Arthritis

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Conflict of interest: None

[Purpose] Between 1999 and 2010, 20 rheumatoid arthritis (RA) patients (27 knees) with severely deformed knees were treated with total knee arthroplasty (TKA) using stem extension, augmentation metal, and/or constrained condylar knee (CCK) prosthesis in our hospital. [Patients] The preoperative diagnosis was RA in all 19 female and 1 male patients. Twenty seven knees were implanted in patients with a mean age of 63 years. Two knees received posterior-stabilized (PS) TKA (NexGen LPS, Zimmer) with tibial extension stem, 19 knees received PS TKA with tibial augmentation metal and extension stem, and 6 knees received CCK (NexGen LCCK, Zimmer). [Results] The complication rate was 7.4%. Of the 27 knees with a mean follow-up of 4.4 years, there was one early failure: fragile interprosthetic femoral fracture which was revised with femoral extension stem. One infected joint received itraarticular antibiotic infusion after debridement, while retaining the implant. There was a high rate of success with survivorship of 96% and a low rate of loosening (0%). [Conclusion] Primary TKA with use of stem extension, augmentation metal, and/or CCK prosthesis in RA had reproducible clinical success, but a complication rate of up to about 8% can be expected at short-, and intermediate-term follow–up.

P2-136

Clinical results, the patella were not resurfaced in total knee arthroplasty (TKA) for rheumatoid arthritis (RA)

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Conflict of interest: None

[Objectives] We have performed TKA, patella should be not resurfaced from 2006. We report that clinical results. [Methods] In primary TKA, patella was not resurfaced in 18 knees from 2006. 10 knees were observed more 3 years. Clinical evaluations were pain, swelling, weak of muscular power. Radiographic studies were patella tilt angle, lateral shift ratio and thickness of patella in the skyline view, at post operation, 2years after, the recently. [Results] No patient complained pain, but 1 knee swelled. Radiographic studies, patella tilt angle, lateral shift ratio and thickness of patella were no significant at post operation, at 2years after, at the recently. [Discussion] The merit of resurfacing patella in TKA,

pain around patella is improved in long time. But there are some problems, for example, patella fracture, patella necrosis, friction wear patella component, and so on. The other side, the merits of non resurfacing patella in TKA there are not risk of patella fracture or patella necrosis. But there are risks of anterior knee pain, patella getting thinner. The third period TKA, patella groove are designed anatomical, so complications in patella-femoral joint are decrease. Non resurfacing patella in TKA may produce good results for RA.

P2-137

Mid-term results of minimally invasive total knee arthroplasty in patients with rheumatoid arthritis

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Conflict of interest: None

【Background】 The purpose of this study was to evaluate clinical and radiographic results of minimally invasive total knee arthroplasty (MIS-TKA) in patients with rheumatoid arthritis (RA) after mid-term follow-up.【Methods】 We investigated 38 MIS-TKA cases in 30 patients who aged on average 60.1 years old (range 34-75 years) with rheumatoid arthritis at our institution between April 2004 and August 2008. We evaluated the outcomes of using Japanese Orthopaedic Association (JOA) knee scores, as well as range of motion and radiographic findings. The average follow-up period after the TKA was 4.8 years (range, 3-7 years). 【Results】 JOA score significantly improved. Flexion contracture decreased from an average of 14 degrees preoperatively to 2 degrees at the final follow-up examination. There were no cases of deep infection and re-operation. There were no cases of aseptic loosening of any component and progressive radiolucent lines. 【Conclusions】 We found good results of MIS-TKA for rheumatoid arthritis after mid-term follow-up.

P2-138

Arthroplasty for Rheumatoid Arthritis with Giant Born Cyst (Geodes) of Knee Joint

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Conflict of interest: None

(Objectives) We report a case of total knee arthroplasty (TKA) for rheumatoid arthritis with giant born cyst (geodes) in tibial plateau. (Patients and Methods) The patient was 64 years old man who diagnosed with rheumatoid arthritis for 15years (Steinbrocker stage IV class III DAS28-CRP3.63). After removed the geodes, bone defect was filled up autologous bone resected in operation. TKA with a modular stem for tibia was performed and fixed using bone cement. (Results) JOA score improved 60 points preoperatively to 85 points at the final examination while the range of motion was never noted any change (0-135 degrees). (Discussion) TKA was performed before tibial plateau fracture, and favorable outcome was obtained.

P2-139

Autologous bone grafting for tibial defects for primary total knee arthroplasty in rheumatoid arthritis

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Conflict of interest: None

[Objectives] It is unclear whether large bone stock deficiencies treated with autologous bone grafts show good bone union in primary total knee arthroplasty (TKA), in especially, rheumatoid arthritis (RA) patients who do not have good bone quality. The aim of this study is to evaluate the autologous bone grafting for tibial defects in RA. [Methods] We performed an autogeneous bone graft to tibia in TKA for 16 knees of 14 patients in RA. After cut at the height of 8 to 10 mm from tibial surfaces, the resected tibial structural bone was implanted at defected part with cancellous screw. An average follow up period was 5.1 years. We investigated about radiographic finding, clinical outcome (JOA score, knee score, and function score), and complication. [Results] Fourteen knees (88%) were seen a bone union. There was observed a bone absorption in 1 knee (6.3%). An atrophy of graft bone was seen in 1 knee (6.3%). JOA score in RA changed 44.0 points preoperatively to 89.9 points postoperatively. Knee and function score were significantly recovered from 38.0 and 36.3 preoperatively to 93.8 and 68.0 postoperatively, respectively. There was admitted no complication. [Conclusion] The good results were showed for the autologous structural bone grafting with screw for tibial defects in RA.

P2-140

Target blood MMP-3 level for remission of rheumatoid arthritis

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Conflict of interest: Yes

[Background] With the advent of biologicals, remission has become an attainable goal in the treatment of rheumatoid arthritis. However, consensus has not yet been reached as to the definition of clinical remission. A simple, objective goal based on blood values is needed in the treatment of RA. **[Subjects and Methods]** In 1928 patients with rheumatoid arthritis of at least 1-year duration, the correlations between the serum levels of MMP-3 and each of DAS28, CDAI and SDAI were studied, and the influence of kidney dysfunction as well as prednisolone on the MMP-3 levels were also evaluated. **[Results]** Serum MMP-3 was weakly correlated with each of DAS28ESR, SDA and CDAI, with the correlation becoming stronger in patients with GFR>60 and receiving PSL≤5mg. The serum MMP-3 values corresponding to DAS28ESR=2.6, SDAI=3.3 and CDAI=2.8, which have been obtained from correlation regression analysis for each, were 118.5 ng/mL, 94.1 ng/mL and 95.1 ng/mL, respectively, in the entire patient population (N=1928). In the 233 patients with Class 1 and Stage 1 disease, GFR>60 and receiving PSL≤5mg, the values were 83.3 ng/mL, 80.7 ng/mL and 80.3 ng/mL, respectively **[Conclusion]** MMP-3 concentrations corresponding to DAS28ESR, SDEI and CDAI were determined.

P2-141

The clinical significance of normal CRP and elevated ESR in arthritis patients

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Conflict of interest: None

[Objectives] We often encounter the situations that the two markers of inflammation do not match such as elevated ESR and normal CRP in routine clinical practice of rheumatoid arthritis (RA) patients. We examined the factors that affect their interpretations and the clinical significance of ESR and CRP in RA. [Methods] We conducted the prospective cohort study (TOMORROW study) from 2010 that comprised 208 RA patients and 205 age- and sex-matched healthy volunteers (N=413). We analyzed the date from this cohort. [Results] Although nobody had an elevated CRP in volunteers, 43.9% showed a higher ESR. ESR was significantly higher in anemia group. In RA patients 41.3% showed a disagreement in ESR and CRP (elevated ESR/normal CRP in 96.5%). The elevated ESR/normal CRP group showed significantly lower hemoglobin (Hb) (12.5mg/dl) than the normal ESR/normal CRP group (13.6mg/dl). Next, RA patients were divided into Hb normal group and anemia group with Hb level. There was no difference in the disease duration, CRP, RF, MMP-3, DAS28-ESR and mHAQ between two groups, but ESR and DAS28-ESR were significantly higher in the anemia group. In the anemic condition, to use CRP seems to be more appropriate for the evaluation of inflammation.

P2-142

Clinical evaluation of anti-CCP Ab with immunochromatographic method: MEBChrom CCP test

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Conflict of interest: None

[Objectives] To evaluate the anti-CCP antibody with immunochromatographic (IC) method(MEBChrom CCP test). [Methods] We examined 168 samples from RA patients and 41 samples from other rheumatic disease patients. The patients with RA comprised 30 men and 138 women with a mean age of 62.4 years and a mean duration of disease of 12.9 years. Assay results of 2 types anti-CCP Ab with ELISA and those with IC method were compared. [Results] The sensivity and specifecity of MEBChrom CCP test (83.9%, 92.7%) were equivalent to MESACUP CCP test(85.1%, 87.8%) and MESACUP-2 CCP test (85.1%, 90.2%). There was a high concordance rate of judgement between 2 kinds of anti-CCP Ab value and MEBChrom test value. Respectively, MESACUP CCP test was 94.7% and MESACUP-2 CCP test was 95.2%. [Conclusion] This study showed that the immunochromtographic method has a similar perormance with conventional ELISA method to measure anti-CCP Ab. IC method enables easy and rapid anti-CCP Ab measurement and may help a diagnosis of RA in daily practice.

P2-143

Comparative study of Multi-Biomarker Disease Activity (MBDA) score to clinical composite measures (DAS28, SDAI, CDAI, and Boolean criteria) in the BeSt study

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Conflict of interest: None

[Objectives] A simple, objective blood-based disease activity index is expected to be useful for management of rheumatoid arthritis (RA). Herein we compared the multi-biomarker disease activity (MBDA) score to clinical composite measures (DAS28, SDAI, CDAI, and Boolean criteria) in the BeSt study. [Methods] A total of 125 patients, 179 visits, in the BeSt study were analyzed. 12 biomarkers (VCAM-1, EGF, VEGF-A, IL-6, TNF-RI, YKL-40, MMP-1, MMP-3, leptin, resistin, SAA, CRP) were measured by Meso Scale Discovery (MSD) at 0 and 52 weeks after starting treatment and input into the Vectra DA algorithm to calculate a single MBDA score between 1-100. Spearman correlation and AUROC were performed. [Results] Baseline characteristics were: age 54 [45-63], DAS28 5.9 [5.2-6.5], and disease duration 25 [13-57] mo (Median [IQR]). The MBDA score correlated to DAS28, SDAI, and CDAI (rho = 0.66, 0.67, 0.56, 95%CI = 0.57-0.74, 0.58-0.75, 0.44-0.65, $p < 0.001$, < 0.001, <0.001), respectively, and distinguished remission +/- in DAS28, SDAI, CDAI, and Boolean criteria (AUROC = 0.84, 0.80, 0.78, 0.83), respectively. [Conclusion] The MBDA score is validated as a useful blood test index to identify the clinical remission in RA patients in the BeSt study.

P2-144

Association of clinical diagnosis for acute interstitial lung damage and neutrophil CD64 molecule expression in patients with rheumatoid arthritis

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Conflict of interest: None

[Objective] To assess the relationship between clinical causes developing acute interstitial lung damage (AILD) in patients with rheumatoid arthritis (RA) and the number of neutrophil CD64 molecule expression **[Methods]** 38 patients with RA who had admitted to our hospital due to AILD since 2005 were used. Clinical diagnoses for AILD were retrospectively reviewed based on the medical records. The positive rate and the number of neutrophill CD64 molecule expression before treatments of AILD were statistically compared among the groups classified according to the primary disease developing AILD. **[Results]** Of 38 cases, 12 cases were *Pneumocystis jiroveci* pneumonia (PCP), 15 cases were methotrexate-induced pneumonia (MTX-IP) and 11 cases were originated from extra-articular pulmonary involvement of RA (RA-IP). The positive rate of neutrophil CD64 expression (cut off: <2000 molecules/cell) was 83.3% in PCP, 73.3% in MTX-IP and 81.8% in RA-IP, respectively. The value was significantly higher in PCP compared with MTX-IP or RA-IP, but there was no difference between MTX-IP and RA-IP in neutrophil CD64 expression. **[Conclusion]** Neutrophil CD64 molecule expression in RA patients with AILD could up-regulate in case of drug-induced lung damage or rheumatoid lung other than infectious disease.

P2-145

A comparative study of QuantiFERON TB-2G and 3G as screening examination for latent Mycobacterium Tuberculosis infection in patients with rheumatoid arthritis

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Conflict of interest: None

[Objectives] To compare QuantiFERON(QFT) TB-2G and 3G as screening for latent Mycobacterium Tuberculosis infection in patients with rheumatoid arthritis(RA) [Methods] RA patients in whom QFT-2G or 3G was performed in our department were included in this study. Patient characteristics and results of QFT were compared between 2G group and 3G group. Chest CT findings and clinical course were investigated in patients with positive QFT. [Results] 178 cases and 57 cases were included in 2G group and 3G group, respectively. Mean age in 2G group and 3G group were 59.3 yo and 60.4 yo, respectively. 5 cases in 2G group have past history of TB infection and none in 3G group. 5 cases in 2G group (2.8%) and 6 cases in 3G group (10.5%) have positive results and there was a significant difference (p=0.027). 157cases in 2G group (88.2%) and 42cases in 3G group(73.7%) have negative results and there was a significant difference (p=0.011). In 10 cases who had positive results of QFT 2G or 3G, none had past history of TB, chest CT was normal in 4 cases and chemoprophylaxis of isoniazid was performed in 5cases. Althogh biologics was used in 7 cases among 10 QFT-positive cases, no active TB was occured until now. Higher positive rate and lower negative rate were seen in QFT-3G compared with in QFT-2G.

P2-146

Usefulness of a computer program that was made by means of the file maker pro for the treatment of RA

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Conflict of interest: None

[Objectives] Usefulness of a computer program for the treatment of RA was assessed. [Methods] We have created this program by ourselves. This program has been made using the file maker pro that is commercially available and is very popular in Japan. This program has some characteristics. Those are; painful joints and swollen joints are input in analogue using a schema of human body, those data were converted to digital data, visual analogue scale and modified health assessment questionnaire are also input in analogue and are converted to digital data, values of DAS28-CRP, DAS28-ESR, SDAI, CDAI are automatically calculated and are shown on the display, RA disease activity such as remission, low disease activity, moderate disease activity, high disease activity is shown automatically, histories of medicines that have been used are also shown, all analogue and digital data will be recorded permanently. This program has been used since September 1st 2009 until August 31st 2011, the usefulness of this program was assessed. [Results] Clinically, this program is useful because painful/swollen joints can be shown in analogue, and all parameters for RA activity are also shown. This program is also useful in clinical researchs because all data can be transferred to Microsoft office Excel.

P2-147

A comparison between physical examination and ultrasonography of joint swellings in rheumatoid arthritis

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Conflict of interest: None

【Objectives】To assess the validity of physical examination (PE) in diagnosing joint swelling compared to ultrasonography (US) in patients with rheumatoid arthritis (RA). 【Methods】Twenty-six RA patients underwent independent physical and US examinations of 40 joints involving both IPs/PIPs, MCPs, wrists, elbows, shoulders, knees, ankles, and MTPs. In the US assessment, we defined grade 1 or higher synovial proliferation in gray scale as "joint swelling". In the PE, joints were classified depending on the existence of "swelling" or "swelling or tenderness". 【Results】The agreement between US and PE "swelling" was moderate (kappa=0.46). The concordance rate of the wrist joint was high (kappa=0.87), whereas the MTPs and knees were low (kappa=0.25, 0.31, respectively). The agreement between US and PE "swelling or tenderness" improved slightly compared to PE "swelling" alone (kappa=0.54). Defining US as the gold standard, PE "swelling or tenderness" was specific but not sensitive in the detection of joints swelling in RA (sensitivity=52.2%, specificity=95.6%).

P2-148

Auto-feedback from ultrasound images provides rapid improvement in palpation skills for identifying joint swelling in rheumatoid arthritis

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Conflict of interest: None

[Objectives] To assesse the utility of ultrasound assessments in enhancing physical joint examination skills. [Methods] We examined 1944 joints (bilateral shoulder, elbow, wrist, 1–5 MCP, and knee joints) in 108 RA patients during April–July 2011. We first physically examined and confirmed joint swelling; subsequently, the same rheumatologist graded the joint swelling by ultrasound. When the two results differed, auto-feedback from the ultrasound results was provided. The sensitivities and specificities of physical examination for joint swelling, the correlation coefficient (CC) of the swelling joint counts, and the concordance rate for joint swelling position with the κ-coefficients for the physical and ultrasound examinations were compared over time. [Results] The sensitivity of physical examination of joint swelling increased by 42 percentage points (pp), while the specificity decreased by 18 pp. The average CC in June–July was greater than that in April–May. Moreover, the percentage of physical examinations showing a κ-coefficient > 0.8 increased from 8.8% to 17%. Our results thus suggest that auto-feedback from the ultrasound assessment provides quick improvement in palpation skills for identifying joint swelling in the patients with RA.

P2-149

Relation between an evaluation of disease activity index using joint echo and clinical index at the patients who were administered abatacept

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Conflict of interest: None

[Objectives] Consider the relation between the blood-flow evaluation in the joint synovial membrane by the joint echo to the abatacept administration patients, and disease activity indexes including DAS28, and then the usefulness of investigation and a joint echo. [Methods] It was aimed at eight examples which could evaluate the synovial membrane blood flow by joint echo by the department of this the inside of 11 examples which introduced adalimmab, and administration before after after administration 12

week in November, 2010 and afterwards. The evaluation by a joint echo evaluated the sum total of the blood flow of finger and a wrist joints by 0 to 66point using power Doppler method. The value of the point, DAS28 and CDAI, and SDAI and correlation with each of that component were considered. [Results] The rate of an improvement of the number of enlargement joints (r= 0.961) accepted the rate of an improvement of the synovial membrane blood-flow evaluation by power Doppler, and strong correlation. In addition, the rate of an improvement of CDAI (r= 0.763), the rate of an improvement of SDAI (r= 0.734), and the rate of an improvement of MMP-3 value (r= 0.552) accepted moderate correlation.

P2-150

Usefulness of joint evaluation with ultrasonography in rheumatoid patients

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Conflict of interest: None

[Objectives] Usefulness of ultrasonographic joint evaluation was checked. [Methods] Some cases would be presented. [Results] Case 1. 83-year-old seronegative RA female. She had left wrist swelling for three months, and treatment with salazosulphapyridine started. At one month, her wrist swelling was decreased, but progressive joint destruction and Grade 3 doppler signal was observed, then MTX was added. Case2. 30-year-old RA female with high disease activity. After 6 months with MTX treatment, CRP was 0.4mg/dl, but her daily life was limited due to right shoulder pain. Ultrasonography showed swelling of long head of biceps and Grade 3 doppler signal. After two months of etanercept treatment, pain, swelling and doppler signal was disappeard. Case 3. 60-year-old RA female who fulfilled remission treated with tocilizumab. But her right wrist pain remaining for one year, progressive joint destruction and Grade 2 doppler signal was observed, synovectomy was informed. Case 4. 55-year-old RA female with non-tuberculous mycobacteria, whose swelling right wrist was operated under MTX treatment due to progressive joint destruction and Grade 3 doppler signal. Grade of doppler signal in radial side was more than in ulna side, but histological finding did not show significant difference.

P2-151

Tenosynovitis is more commonly detected by ultrasound in symptomatic ankles with early RA than in those with established RA.

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Conflict of interest: None

[Objectives] To study the association between US findings in RA ankles and disease duration (DD). [Methods] US records of symptomatic RA ankles were analyzed. Pts were classified into early RA (ERA, DD<6 months), and long-standing RA (LRA). [Results] Among 100 ankles of consecutive 74 pts (62 ankles in 47 ERA pts, and 38 ankles in 27 LRA pts), synovitis of talocrural, subtalar, and talonavicular joint were detected in 35, 33, and 27 ankles. Overall joint synovitis was observed in 56 ankles. Tenosynovitis was detected in 46 ankles at medial recess, in 29 ankles at lateral recess, and in 10 ankles at anterior aspect. Overall tenosynovitis was observed in 61 ankles. AT involvement was observed in 39 ankles. DD was significantly shorter in the ankles with tenosynovitis (11.4 Ms) than in the ankles without it (32.0 Ms). Joint synovitis, tenosynovitis, and AT involvement were observed in 48%, 69%, and 39% of ankles with ERA, and in 68%, 47%, and 39% of ankles with LRA. Tenosynovitis was significantly more common in ankles with ERA than with LRA. Tenosynovitis not associating with joint synovitis was significantly more common in ankles with ERA (39%) than with LRA (16%). US examination of symptomatic ankles with early RA should include medial and lateral scan for ankle tenosynovitis.

P2-152

Ultrasonography of inflamed joints in rheumatoid arthritis; comparison with histological analysis.

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Conflict of interest: None

[Objectives] To investigate differences between the findings of ultrasonography in inflamed joints and histopathological investigation in patients with rheumatoid arthritis. [Materials and Methods] 9 RA patients (7 female, 2 men) were enrolled in the study. The patients had a mean age of 62±10 years at the operation. Ultrasound examinations were performed before joint surgery and Power Doppler (PD) signals were graded from 0 to 3. Synovial tissues were extracted from these patients at the time of operation and histopathological examination was performed using hematoxylin and eosin to evaluate differences. [Results] The US preoperatively showed synovial proliferation in all patients. The PD Grade0 was 3, Grade1 was 3, and Grade2 was 3 patients. The results of histopathological examination showed inflammatory cell infiltration and vascularization in all cases of Grade1 and Grade2. However, inflammatory cell infiltration and vascularization was revealed even in two cases of Grade0. [Conclusion] This study suggested the possibility that active inflammation was occurred even if PD shows Grade0.

P2-153

Subclinical arthritis in primary Sjogren syndrome. An ultrasonographic evaluation

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Conflict of interest: None

[Objectives] Musculoskeletal ultrasound (MSUS) provides a sensitive assessment of synovial hypertrophy and articular tissue hyperemia in rheumatoid arthritis. We performed MSUS of primary Sjogren syndrome (pSS) and correlate them with laboratory tests and clinical evaluation. [Methods] Forty patients with pSS without clinical apparent arthritis were enrolled. Bilateral MSUS was performed in MCP, PIP, IP joints. Synovial hypertrophy and pulse Doppler (PD) signal were recorded in each site using semiquantitative score (0 to 3). Serum levels of anti-SS-A antibody, anti-SS-B antibody, anti-centromere antibody (ACA), rheumatoid factor, and matrix metalloproteinase-3 were measured. The presence of Raynaud's phenomenon and renal tubular disease were also evaluated. [Results] In 5 patients (13%), moderate or severe synovial hypertrophy was found in one joint or more. In 11 patients (28%), mild PD signal was present in one joint or more. No

PD signal was detected in any joint in the patients with a positive ACA. The subclinical arthritis did not correlate with the laboratory tests except ACA and clinical evaluation. In pSS patients, MSUS may be considered a useful tool for detecting subclinical arthritis.

P2-154

Ultrasound examination for rheumaoid arthritis patients with swelling in lower leg.

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Conflict of interest: None

[Objectives] We investigate the usefullness of ultrasound examination for rheumaoid arthritis patients with swelling in lower leg. [Methods] Ultrasound examination of the lower leg was performed in 10patients. There were one male and nine females. [Results] D-dimer in seven cases were high and CRP showed a positive in 8cases, however venous thrombosis were observed only in three patients. On the other hand synovial cyst extending from knee joint to the lower leg were observed in all patients. Active synovitis around tendons and enthesis were observed in six patients. In one patient who underwent steroid injections into the knee joint based on the ultrasonofic results, significant improvements can be observed at one week after the examination. In conclusion, ultrasound examination for the patients with swelling of the lower legs were very usefull in not only differential diagnosis for the cause of the swelling but also the evaluation of treatment outcome.

P2-155

The association between clinical remission and power Doppler ultrasonography (PDUS) in rheumatoid arthritis (RA) patients receiving biologic therapy

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Conflict of interest: None

Objective: To assess the association between clinical remission and PDUS in RA patients receiving biologics. **Methods:** 56 RA patients receiving biologics (IFX n=17, ETN n=6, ADA n=3, TCZ n=27, ABT n=3) were assessed using Disease Activity Score (DAS28-ESR<2.6, DAS28-CRP<2.3, Clinical Disease Activity Index (CDAI)≦2.8, Simplified Disease Activity Index (SDAI)≦3.3, and Boolean index as definitions of clinical remission, which was observed in 16, 21, 6, 6 and 6 patients, respectively. PD signals were scored from 0 to 3 in 22 joints (bilateral wrist, metacarpophalangeal and proximal interphalangeal joints). For each joint assessed, association between PD score of 0 or less than 1 and clinical remission were evaluated. The association between PD score 0 and clinical remission were Q=1(DAS28-ESR), 0.813(DAS28-CRP), 0.6(CDAI), 0.6(SDAI), 08022(Boolean index). Associations between PD score of less than 1 and clinical remission were Q=0.9494(DAS28-ESR), 0.8551(DAS28-CRP), 0.5309(CDAI), 0.5390(SDAI), 07977(Boolean index). Our study confirmed an association of PD scores of 0 and less than 1 and clinical remission in all cases. DAS28-ESR, DAS28-CRP and Boolean index were strongly associated with PD score of 0, and DA28-ESR and DAS28-CRP were strongly associated to PD score of less than 1.

P2-156

Ultrasound assessment and differences in seronegative rheumatoid arthritis, polymyalgia rheumatica and RS3PE.

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Conflict of interest: None

[Objectives] High contribution of power Doppler signal (PD) with ultrasound (US) to early RA diagnosis is reported, however, we have experienced that other RA-related diseases also have PD and become difficult to make a differential diagnosis. Here we assess US images and those differences in seronegative RA, PMR and RS3PE. [Methods] We evaluated bilateral shoulder, elbow, wrist, metacarpophalangeal joints (MCP), proximal interphalangeal joints (PIP), knee joints, subdeltoid bursa, long head of biceps brachii muscle and wrist extensor tendon in RA (n=9), PMR (n=8) and RS3PE (n=5) by US with grayscale and PD. [Results] %PD (≥ moderate) in seronegative RA, PMR and RS3PE patients' joints was 67%, 38%, 70% at wrist, 11-22%, 0%, 30-50% at MCP and 5-11%, 0%, 0-10% at PIP. % Severe PD was 22%, 0%, 20% at wrist and 6-22%, 0%, 0-10% at MCP. PMR showed lower at wrist and no %PD (≥ moderate) at MCP and PIP. RS3PE showed same or higher %PD (≥ moderate) at wrist and MCP compared with seronegative RA. %Severe PD at MCP was higher in seronegative RA than RS3PE. We should know the differences of distribution, extent of US findings and those sensitivity and specificity to make it be helpful in the differential diagnosis of RA-related diseases.

P2-157

Ultrasound is useful for the differential diagnosis of crystal arthritis and psoriatic arthritis

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Conflict of interest: None

A 67 year-old man. He had a history of acute alcoholic pancreatitis, diabetes, and hyperuricemia. At the age of 40, he developed gouty attack in his right leg and the attack occurred many times thereafter. He was diagnosed as having psoriasis at age of 45 and was treated with topical medication alone by a dermatologist. From around March 2011, he noticed pain and swelling in his many joints and visited our hospital. On examination, knee, ankle, DIP, PIP, and wrist joint swelling and tenderness were found. Anti-CCP antibodies and rheumatoid factor were negative. Calcifications were not observed on his joint X-ray. Based on the history of psoriasis and the duration and distribution of arthritis, psoriatic arthritis was initially suspected. We considered the administration of adalimumab treatment for psoriasis and psoriatic arthritis. On joint ultrasounds, high-echo images were observed in wrist and finger joints. Because uric acid crystals were found in joint puncture, it was considered that a main cause of arthritis was gouty arthritis. Treated with colchicine and prednisone 10 mg/day, arthritis improved rapidly. It was suggested that joint ultrasound is useful for the differential diagnosis of crystal arthritis and psoriatic arthritis.

P2-158

Comparison between phase contrast radiography (PCR) and conventional x-ray in the early diagnosis of rheumatoid arthritis using the 2010 ACR/EULAR classification criteria for RA.

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Conflict of interest: None

[Objective] To examine the utility of phase contrast radiography (PCR) images compared with conventional x-ray in the early diagnosis of rheumatoid arthritis (RA) using the 2010 ACR/EULAR classification criteria for RA. [Patients] Thirty patients (7males), average age of 57.93 years old, registered from October 2006 to October 2011 at our Hospital, were analyzed. [Methods] We examined whether PCR detected bone erosions in hands that could not be detected by conventional x-ray. We also analyzed of 2010 ACR/EULAR RA criteria classified early RA with help of PCR. [Results] Only PCR could confirm bone erosions in thirteen patients. Of these, three patients were not diagnosed as RA because of less than 6 counts by 2010 ACR/EULAR classification criteria for RA. Erosions detected only by PCR could suggest the possibility of RA in these patients and lead to find the previous symptoms met the new criteria. [Conclusion] It is suggested that using PCR may add more specificity to 2010 ACR/EULAR classification criteria in early diagnosis of RA.

P2-159

Progress of bone lesion in spite of negative inflammatory reaction in Rheumatoid Arthritis

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Conflict of interest: None

[Purpose and Method] We have treated of rheumatoid arthritis (RA) aiming at clinical, serological and radiological remissions, and classified the combination of those remission achievements into eight patterns. This time, the ratio and the examination value were evaluated about cases of progression of bone lesion in spite of negative inflammatory reaction in RA. [Results] In 65 cases of continuous negative inflammatory reaction, 14 cases (21.5%, all females) of bone lesion had progressed. MMP-3 value of this group was not high, and titer of anti CCP antibody or rheumatoid factor was not recognized significant difference. [Discussion] The inflammatory reaction or MMP-3 value doesn't necessarily reflect the progress of the bone lesion. We consider that it is necessary of regulatory image evaluation because the activity index of RA is lower by negative inflammatory reaction. It reports on the cytokine value and the joint echo of these cases.

P2-160

Development of early diagnostic techniques for rheumatoid arthritis using [^{11}C]PK11195 and [^{11}C]Ketoprofen

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Conflict of interest: Yes

[Objectives]*In vivo* detection of pathological insults during early stages of rheumatoid synovitis is essential to allow early anti-inflammatory treatment and prevention of joint destruction. However, there are not many useful tools for early diagnosis of arthritis before joint destruction. In this study, we undertook this study to investigate whether rheumatoid synovitis pathology and the efficacy of therapies can be visualized by PET tracers specific for the inflammatory process. [Methods] During early stages of a collagen-induced experimental rat model of rheumatoid arthritis, we performed *in vivo* imaging using PET tracer ^{11}C-PK11195 (PK), which binds to the translocator protein, and the newly developed PET tracer ^{11}C-Ketoprofen (KTP), used for cyclooxygenase imaging. [Results] We observed that ^{11}C-PK and ^{11}C-KTP uptake on inflamed paw PET scans was significantly higher than control. The resulting data showed a correlation analysis between uptake values and paw swelling. After treatment of Etanercept, ^{11}C-PK uptake in inflamed regions did not change compared with the untreated group. Consequently, by using ^{11}C-PK and ^{11}C-KTP, PET imaging for rheumatoid synovitis can provide diagnostic evidence of early synovitis and allow monitoring of inflammatory cell activity during treatment.

P2-161

Inflammatory synovial vascularization visualized and quantitatively assessed by near-infrared camera in finger joint of rheumatoid arthritis

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Conflict of interest: None

Pathological and imaging approach revealed that abnormal vascularization occurred in joint synovial tissue in the process of inflammation. Simple and easy method to detect the vascularization should be connected to accurate and detailed joint inflammatory assessment. Near-infrared camera could visualize vascular flow by fluorescent image with indocyanine green venous injection. We had reported using near-infrared camera to detect finger joint synovial vascularization. Werner et al. reported semi-quantitative assessment of the method. Quantitative assessment had not yet been reported. We devised a novel quantitative assessment for the method.

P2-162

The role of S1P3 receptor signaling in the bleomycin-induced pulmonary fibrosis 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, we in-

jected bleomycin intratracheally into S1P3-deficient (KO) and wild type (WT) mice. [Methods] Mice were anesthetized with ether and received bleomycin intratracheally. Both lungs were excised on the 14th or 42nd day after bleomycin administration. A paraffin section of lung, stained either with H&E or Masson's trichrome, was systematically scanned in a microscope. We observed the body weight of these mice in the acute phase. Bronchoalveolar lavage fluid (BALF) was collected and analyzed for total and differential leukocyte counts on 7th day. Activated TGF-b1, CTGF, and MCP-1 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 MCP-1 and TGF-β1 levels between WT and KO mice.

P2-163

An animal model of overt lupus nephritis by repetitive immunization of BALB/c mice with human Herp protein

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Conflict of interest: Yes

[Objectives] The O-81 human anti-DNA mAb crossreacts with a human endoplasmic reticulum stress-inducible protein, Herp. Immunization of Herp to BALB/c mice elicited anti-dsDNA Abs and caused glomerular IgG deposition, but proliferative glomerulonephritis has not been observed. There is a report that immunization with apoptotic cells and LPS to BALB/c mice elicited anti-dsDNA Abs and caused proliferative glomerulonephritis. As Herp can be expressed on apoptotic blebs, the following experiments were performed. The aim of this study is to generate a mouse model of overt lupus nephritis not depending on genetic abnormality. [Methods] Groups of seven 6-wk-old female BALB/c mice were immunized intraperitoneally with Herp and LPS (group A), Herp (group B), LPS (group C), or PBS (group D) on days 0, 14, 28, and 42, followed by immunization every four weeks for one year [Results] In all mice in group A and B, anti-dsDNA Abs were elicited and glomerular IgG and C3 deposition were observed. In three of seven mice in group A, significant proteinuria and overt glomerulonephritis closely resembling human lupus nephritis was observed. No significant abnormality was observed in group C and D. This model may be helpful for investigating how lupus nephritis develops.

P2-164

Fli-1 transcription factor is involved in inflammatory chemokine production and inflammatory cell infiltration in the kidneys in animal models of autoimmune disease

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Conflict of interest: None

Fli-1 expression is associated with nephritis in lupus model mice. Monocyte chemotactic protein-1 (MCP-1) and Chemokine (C-C motif) ligand 5 (CCL5) have an important role in inflammatory cell infiltration and nephritis development. To examine the role of Fli-1 on chemokine production and inflammatory cell infiltration, we generated Fli-1 heterozygous knockout (Fli-$1^{+/-}$) NZM2410 mice. The expression levels of MCP-1 and CCL5 in the kidneys were analyzed by real-time PCR. Pathological scores and inflammatory cells of the kidneys were assessed. Production of MCP-1 in endothelial cells was measured after expression of Fli-1 was inhibited with small interfering RNA (siRNA). We found that expression of MCP-1 and CCL5 in the kidneys from Fli-$1^{+/-}$ NZM2410 mice was significantly decreased. Fli-$1^{+/-}$ NZM2410 mice had significantly reduced inflammatory cells in kidneys with decreased renal pathology scores. The production of MCP-1 in endothelial cells transfected with Fli-1 siRNA was significantly reduced. We also demonstrated that Fli-1 directly binds to the promoter region of the MCP-1 gene by Chromatine Immunoprecipitation assay. Our data indicate that Fli-1 plays an important role in production of inflammatory chemokine MCP-1 and CCL5, and inflammatory cell infiltration in the kidneys.

P2-165

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 (RORγt Tg) mice. 2) Cytokine production from collagen type II (CII) reactive T cells was analyzed by ELISA. 3) Transcription factors expression on CII reactive $CD4^+$ T cells was detected by intracellular staining method, and analyzed by FACS. 4) Correlation of the expression between CCR6 and transcription factors on $CD4^+$ T cells was analyzed by FACS. [Results] 1) CIA was significantly suppressed in RORγt Tg mice compared with B6 mice. 2) IL-17 production from CII reactive T cells was significantly increased in RORγt Tg mice. 3) Higher expression of RORγt was observed in RORγt Tg mice. There was no significant difference of Foxp3 expression on $CD4^+$ T cells between B6 and RORγt Tg mice. 4) Higher expression of CCR6 was observed on $CD4^+$ T cells, especially in $Foxp3^+$ $CD4^+$ regulatory T cells in RORγt Tg mice. [Conclusion] CIA was significantly suppressed in RORγt Tg mice, although IL-17 production from CII reactive T cells was increased. The inhibition of arthritis was might be related with the increase in $CCR6^+$ regulatory T cells in RORγt Tg mice.

P2-166

Invariant natural killer T cell ligand alpha-galactosylceramide and its analogue alpha-carba-galactosylceramide ameliorate murine autoimmune arthritis.

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Conflict of interest: None

Objective : Alpha-galactosylceramide(α-GC) is an exogenous glycolipid ligand of invariant natural killer T (iNKT) cells. Alpha-carba-galactosylceramide (α-car-GC) is an analogue ofα-GC which is able to induce higher interferon-gamma (IFNγ) production via

activation of iNKT cells. We investigated the effects of these glycolipids on collagen-induced arthritis (CIA) and glucose-6-phosphate isomerase (GPI) peptide-induced arthritis. Methods : 1) DBA/1 mice were administered withα-GC orα-car-GC at the same time as induction of CIA. 2) In vitro CII specific cytokines responses were evaluated using draining lymph node cells from mice immunized with CII and each glycolipids. 3) DBA/1 mice were administered withα-GC at the same time as immunization of GPI peptide. Results : 1) α-car-GC significantly reduced the severity of CIA compared toα-GC. 2) CII reactive IL-17 production was reduced inα-car-GC treated mice but not inα-GC treated mice. 3) α-GC significantly suppressed the severity of GPI peptide-induced arthritis. Conclusion : The different effects on CIA ofα-GC andα-car-GC might be due to the distinct cytokine production in the generation of arthritis. The difference in the effects ofα-GC on these two arthritis models might be due to the role of IFNγ in these models.

P2-167

Overexpression of HC gp-39 in the generation of GPI-induced arthritis.

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Conflict of interest: None

【Backgrounds and objective】Human cartilage glycoprotein-39 (HC gp-39) is believed to be involved in tissue remodeling events occurring in rheumatic joints and bone, however its function in arthritis is still obscure. In this study, we examined a role of HC gp-39 on GPI-induced arthritis (GIA).【Methods】1) Expression of HC gp-39 mRNA on splenocytes and splenic $CD4^+$, $CD19^+$, $CD11b^+$ cells were analyzed in GIA. 2) The concentration of HC gp-39 protein in the serum from arthritic mice was measured by ELISA. 3) Fluctuated expression of HC gp-39 mRNA on joints was analyzed in GIA. 4) Localization of the expression of HC gp-39 was detected by immunohistochemical staining in joints.【Results】1) The expression of HC gp-39 mRNA in splenocytes and splenic $CD4^+$ and $CD11b^+$ cells were significantly upregulated at the early phase of arthritis (day7). 2) The concentration of HC gp-39 protein in serum was highly elevated on day7. 3) The expression of HC gp-39 mRNA in joints was significantly increased at the swelling peak of GIA (day14). 4) HC gp-39 protein was detected in infiltrated cells in arthritic joints.【Conclusion】These results suggest that HC gp-39 might be involved in the generation of arthritis.

P2-168

Anti-Arthritic Effect of the Vascular Endotherial Growth Factor Receptor Tyrosine Kinase Inhibitor Sunitinib in Murine Arthritis Model.

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Conflict of interest: None

[Objectives] To investigate the anti-arthritic effect of sunitinib, a angiogenesis inhibitor that mainly targets vascular endothelial growth factor receptor (VEGFR), on type II collagen-induced arthritis (CIA) in mice. [Methods] Sunitinib was administrated intraperitoneally once daily at 0, 30, 60mg/kg/day for 14 days from the day of the booster immunization (day 21) in CIA induced mice. Anti-arthritic effects were evaluated by visual arthritis scores, incidence rates, histological scores, and bone deformity on a computed tomography scan. Synovial microvascular density (MVD) was measured by immunostain with CD31. The results were compared with no treated CIA group. [Results] The treatment of 30, 60mg/kg/day sunitinib from day 21 to 34 significantly and pronouncedly diminished visual arthritis scores in a dose dependent manner. Histological scores, bone deformity and synovial MVD were also similar tendency. Novel angiogenic inhibitor, sunitnib, had an arthritic inhibiting effect in a murine autoimmune arthritis model. This compound could have therapeutic potential for rheumatoid arthritis in human.

P2-169

Investigation of bone marrow-derived cells in mice with collagen-induced arthritis.

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Conflict of interest: None

[Objectives] To investigate bone marrow-derived cells in mice with collagen-induced arthritis(CIA). [Methods] Bone marrow chimera DBA/1J mice created by bone marrow transplantation between different sexes were devided into two groups, and CIA was prepared in one group. The other group were regarded as control. Tissue sections from ankle joints were stained for CD68 (macrophage), CD31(endothelial cell), α-SMA(pericyte), NG2 (pericyte), TRAP(osteoclast), and fluorescence in situ hybridization (FISH) were subsequently performed to identify Y chromosome+ bone marrow-derived cells. [Results] Part of CD68+ macrophages, CD31+ endothelial cells, NG2+ immature pericytes and TRAP+ osteoclasts were Y chromosome+ bone marrow-derived cells.

P2-170

Interleukine-6 blockade augmented anti-arthritic effect of methotrexate in glucose-6-phosphate isomerase-induced arthritis model

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Conflict of interest: None

Background; Methotrexate (MTX) enters cells via the reduced folate carrier SLC19A1. It was reported that the efficacy of MTX varies among patients. We examined the relationship between the efficacy of MTX and the expression of SLC19A1. **Methods;** Glucose 6-phosphate isomerase (GPI)-induced arthritis was induced by immunization with GPI. MTX was given from the first day of immunization. Mice were injected MR16-1 10 days after immunization. The levels of SLC19A1 mRNA in the hind limbs were measured. Synovial cells were cultured with MTX and IL-6, and were measured cell proliferation and gene expressions. **Results;** MTX inhibited the development of arthritis; however, its efficacy gradually diminished. SLC19A1 expression in arthritic mice was lower than normal mice. Although MR16-1 did not improve arthritis at all, concomitant use of MTX and MR16-1 more potently reduced the development of arthritis compared with MTX alone. When used in combination with MTX, MR16-1 apparently reversed the decrease in SLC19A1 induced by MTX alone. In an in

vitro study, IL-6 weakened the anti-proliferative effect of MTX and reduced SLC19A1 expression in synovial cells. **Conclusions;** We demonstrated that anti-IL-6R antibody augmented the efficacy of MTX by up-regulating expression of the reduced SLC19A1.

P2-171

Sec61 is required for the development of lupus tissue injuries

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Conflict of interest: None

[Objectives] We found the 'self-organized criticality theory' explaining the cause of systemic lupus erythematosus (SLE). We repeatedly immunized mice normally not prone to autoimmune diseases with the same antigen to show that repeated immunization reproducibly led to the development of SLE. Over-stimulation of $CD8^+$ T cell *via* antigen cross-presentation generated cytotoxic T lymphocyte (CTL) to produce lupus tissue injuries. Here we examine the contribution of Sec61, which is known as a translocon, for antigen cross-presentation in relation to lupus tissue injuries. [Methods] BALB/c mice were repeatedly immunized with ovalbumin (OVA) to induce tissue injuries. Exotoxin A was co-immunized with OVA to inhibit Sec61. IFNγ-producing $CD8^+$ T cell in spleen was detected to examine the generation of CTL under flow cytometry. To examine the development of nephritis, proteinuria were detected. [Results] 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 maturation of IFNγ-producing effector CTL and the development of lupus nephritis. [Conclusion] Sec61 is required for the pathogenesis of lupus tissue injuries.

P2-172

Yaa-Mutation Induces Phenotype Shift in FcgRIIB-Deficient B6 Mice

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Conflict of interest: None

Objectives: We previously obtained a FcγRIIB-deficient C57BL/6 (B6) congenic strain of mice, which developed severe rheumatoid arthritis (RA). The development of systemic lupus is accelerated by the *Yaa* (*Y-linked autoimmune acceleration*) mutation. To examine the effect of the *Yaa* mutation on the autoimmune disease, we established B6. FcγRIIB$^{-/-}$.*Yaa* mice by introducing *Yaa* mutation into the RA-prone FcγRIIB-deficient B6 mice. **Methods:** Serum levels of RF, IgG antibodies against double-stranded DNA and chromatin were measured using ELISA. The severity of renal disease was monitored by testing for proteinuria. Histopathological examination was also performed. **Results:** The disease phenotype shifted from RA to SLE in B6.FcγRIIB$^{-/-}$.*Yaa* mice. They did not develop RA, instead they showed the marked increase in serum levels of rheumatoid factor and SLE-related autoantibodies such as anti-chromatin and anti-ds DNA antibodies. These developed glomerulonephritis with the high incidence of positive proteinuria even at 6 months of age. **Conclusions:** The present studies suggest that the common genetic pathways play a role in the disease process shared by RA and SLE, and the environmental factors such as the stimulation of innate immune system may control separate autoimmune diseases RA and SLE.

P2-173

Successful treatment of massive ascites with intraperitoneal administration of triamcinolone in a case of systemic lupus erythematosus complicated wth thrombotic thrombocytopenic purpura.

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Conflict of interest: None

Massive ascites is a rare manifestation of systemic lupus erythematosus (SLE) and has a poor response to systemic glucocorticoid therapy and immuosuppresive agents. We describe a woman presenting with lupus peritonitis complicated with thrombotic thrombocytopenic purpura (TTP) in the course of rheumatoid arthiritis and SLE. Peritoneal effusion was resistant to the corticosteroid pulse therapy, cyclospine A, intravenous immunoglobulin, plasmapheresis and the conventional therapies for ascites such as intravenous administration of diuretic and albumin. Intraperitoneal injection of triamcinolone, an insoluble glucocorticoid, induced dramatic remission of massive ascites, with no adverse event or recurrence. Chronic lupus peritonitis has been reported as the cause of massive ascites. The peritoneal histological examination in reported cases showed edematous change, inflammation and small vessel vasculitis. Because of impairment in peritoneal circulation, the poor response to systemic corticosteroid therapy might be present. Intraperitoneal administration of glucocorticoid might be an effective therapy about drug delivery system.

P2-174

Two cases of panniculitis in the sacrum during the progress of SLE

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Conflict of interest: None

【case1】A 32 year-old female, who developed SLE when she was 17 years old, was hospitalized due to lower abdominal pain. She was diagnosed as ischemic colitis of the sigmoid colon. Once she was recovered from enteritis, panniculitis in front of the sacrum emerged. Therapeutic colostomy and drainage were performed, and then her fever and buttock pain disappeared.【case2】A 29 year-old female who developed SLE when she was 16 years old, was referred to our hospital due to fever and lower abdominal pain. We diagnosed her with panniculitis in front of the sacrum by the findings of CT and MRI. We thought the inflammation was one of the symptoms of SLE, methylprednisone pulse therapy was performed twice and her symptoms were improved.【conclusion】These two cases have very similar clinical profiles, panniculitis in front of the sacrum. In this case, it was quite difficult to distinguish from infectious disease to SLE, although there were no positive findings suggesting infection. However panniculitis of the skin and peritoneum are well-known symptoms of SLE, localized panniculitis in the pelvis is rare.

P2-175

A patient with periorbital edema as the intitial symptoms of systemic lupus erythematosus complicated with protein-losing enteropathy

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Conflict of interest: None

28-year old Japanese woman was admitted to our hospital for periorbital edema that had started 5 months before. She was diagnosed systemic lupus erythematosus(SLE), because of arthritis, leucopenia, thrombocythemia and antiphospholipid antibody and antinuclear antibody. Periorbital edema was evident and pleural effusion and ascites were also recognized by X-ray computed tomography. We diagnosed protein-losing enteropathy by protein-losing scintigraphy. Pleural effusion was exudative and 40mg/day of prednisolone was administered but her symptoms persisted. So we administered steroid pulse therapy (intravenous methylprednisolone 1g/day for 3 days), and symptoms were ameliorated. Follow up protein-losing scintigraphy showed no abnormality. Then azathioprine was added and her symptoms resolved and her serum complement levels recovered. Prednisolone was tapered and she discharged. We report a case with periorbital edema as the intitial symptoms of systemic lupus erythematosus complicated with protein-losing enteropathy. There was 6 cased of protein-losing enteropathy complicated with connective tissue diseases in our department in 15 years. (Four cases were SLE, 1 was MCTD and 1 was Sjogren's syndrome.)

P2-176

Examination of 3 Patients with Systemic Lupus Erythematosus (SLE) Complicated by Protein-Losing Enteropathy (PLE)

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Conflict of interest: None

We report 3 cases of SLE complicated by PLE. Case 1: A 47-year-old woman with Graves' disease experienced febricula and malaise. She had photosensitivity, hypoalbuminemia, positive antinuclear antibody, and anti-dsDNA antibody (17 U/mL) with Sjogren's syndrome. Scintigraphy confirmed the diagnosis of PLE. Methylprednisolone (mPSL) pulse and Oral prednisolone (PSL) (40 mg) therapy relieved her symptoms. Case 2: A 40-year-old man developed edema and malaise. He had a butterfly rash, antinuclear antibody level 160 times the normal, anti-dsDNA antibody (14.7 U/mL), and hypocomplementemia. Duodenal biopsy revealed C3 deposition on the vessel walls around the ducts. Oral PSL (40 mg) and mPSL and cyclophosphamide pulse therapy relieved his symptoms. Case 3: A 62-year-old man had Sjogren's syndrome and prior autoimmune hepatitis. Diarrhea and edema persisted. He had hypoalbuminemia, thrombocytopenia and positive antinuclear antibody. Anti-dsDNA antibody and LE cell tests were transiently positive. He was diagnosed with PLE and autoimmune thrombocytopenic purpura (AITP). Pulse mPSL and high-dose PSL and gamma-globulin were ineffective; only AITP was improved by rituximab. PLE improved after subcutaneous octreotide and low-fat diet therapy using medium-chain triglyceride.

P2-177

systemic lupus erythematosus complicated with nodular cutaneous mucinosis

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Conflict of interest: None

We describe an 18-year-old female with systemic lupus erythematosus (SLE) and nodular mucinosis. About 2 years ago, she developed photosensitivity and hair loss. About 1 year ago, she presented with butterfly rash and multiple subcutaneous nodules without tenderness at extremities and upper part of her back. Although anti-nuclear antibody was positive, her conditions did not meet diagnostic criteria for SLE (systemic lupus erythematosus), and her symptoms had not been improved by low-dose prednisolone. In February 2011, she was admitted for low-grade fever and subcutaneous nodules worsened at the 18th weeks of pregnancy. Laboratory data showed leukopenia, Coombs test-positive anemia, hypocomplementemia, positive of anti-nuclear antibody and anti-double strand DNA antibody, fulfill the diagnostic criteria for SLE. The biopsy specimens of a subcutaneous nodule showed that linear IgM deposit was seen at basement membrane, and remarkable mucinous deposit was seen in dermis, compatible with nodular mucinosis. After abortion, she was treated with high-dose prednisolone, then her symptoms including butterfly rash, low-grade fever, hair loss and multiple subcutaneous nodules were disappeared. As cases of SLE with nodular mucinosis are relatively rare, we reported this case with review of literature.

P2-178

A case of SLE with inflammation of the large vessels and hypertrophic pachymeningitis

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Conflict of interest: None

A 27 year-old woman was diagnosed as having SLE with CNS lupus and hemophagocytic syndrome in May 2010. She was improved with steroid pulse therapy and intravenous cyclophosphamide. In early January 2011, during the tapering of oral PSL, fever, cough, headache and joint pain appeared. She was treated with antibiotics on suspicion of bronchitis, but the symptoms did not improve. On February 3, she was admitted for the evaluation and treatment. No abnormalities were found in the lung by chest CT, but FDG-PET showed slight accumulation around the pulmonary artery and aorta. Although CSF examination showed a mild increase in cell number and IL-6 level, various viral antibody and culture were negative. Brain MRI showed no abnormalities. Considered the possibility of aseptic meningitis due to SLE, PSL 25 mg and tacrolimus 3 mg were administered and the symptoms were improved. In September 2011, the same symptoms relapsed. Brain MRI revealed thickening of the dura mater, indicative of hypertrophic pachymeningitis. FDG-PET showed the same findings as previous admission. Treated with PSL 40 mg and intravenous cyclophosphamide, clinical symptoms and abnormal findings of MRI and FDG-PET improved. We report a case of SLE showing inflammation of the large vessels and pachymeningitis.

P2-179

a case of lupus cystitis compicated by bilateral hydronephrosis and nephrotic syndrome

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Conflict of interest: None

64-year-old woman presented with vomiting, diarrhea and fever. Laboratory studies revealed a hypoalbuminemia and urinalysis

showed 3+ proteinuria. Computed tomograghy of the abdomen showed bilateral hydronephrosis. Few weeks later, anasarca developed and she was transferred to our hospital for probable nephrotic syndrome. Laboratory studies showed lymphopenia and serological analysis revealed positive antinuclaer antibody and anti-double stranded DNA antibody. Bladder biopsy revealed interstitial cystitis. Diagnosis of systemic lupus erythematosus with lupus cystitis was made. She was treated with intravenous pulse methylprednisolone followed by oral prednisolone. Vomiting and diarrhea disappeared and edema was ameliorated. Urinalysis showed markedly reduced proteinuria, but bilateral hydronephrosis persisted. Bilateral hydronephrosis finally improved with the addition of tacrolimus. Lupus cystitis is usually complicated by gastrointestinal symptoms. Early steroid therapy is effective for the improvement of vesicourinary disturbance and hydronephrosis. Because diagnostic delay might lead to vesicourinary fistula formation, diagnostic procedure for SLE needs to be started as early as possible when bilateral hydronephrosis and gastrointestinal symptoms are observed.

P2-180

Subcutaneous extensor tendon rupture of the middle finger complicated with SLE

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Conflict of interest: None

Subcutaneous tendon rupture complicated with systemic lupus erythematosus (SLE) is a very rare occurrence. This report presents one case of a subcutaneous extensor tendon rupture of the middle finger complicated with SLE. A 72-year–old woman was diagnosed SLE in 1980 and was treated with steroids. She noticed an MP joint extension lag of the left middle finger in December, 2009, and saw a doctor in January, 2010. The extensor tendon was not palpable at the MP joint. No bone erosion and joint destruction was seen on x-ray films. The MR image showed the left middle finger extensor tendon was ruptured at the MP joint. Surgery confirmed that the middle finger extensor tendon had ruptured at the MP joint. The articular capsule and the extensor tendon had degenerated. No active arthritis was seen at the MP joint. She received a tendon transfer using the palmaris longus tendon. Active extension of the left middle finger at the MP joint was possible, and the patient has made good progress approximately 18 months after the surgery. The long-term steroid administration, Jaccoud arthritis and mechanical irritation by the head of metacarpal bone probably led to the subcutaneous rupture of the extensor tendon in this case.

P2-181

[Case Report] A case of systemic lupus erythematosus with hemophagocytic syndrome as an initial manifestation

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Conflict of interest: None

Hemophagocytic syndrome (HPS) is a systemic clinical condition that presents fever and severe pancytopenia. It may also be lethal. This clinical condition occurs by various etiologies such as infections, autoimmune diseases and malignant disorders. Autoimmune diseases-associated HPS is comparatively milder than due to other etiologies, but we experienced a case of severe HPS due to systemic lupus erythematosus (SLE). Twenty-years old female complained of fever, purpura and arthralgia, and a diagnosis of SLE was made. She received 0.5mg/kg of prednisolone, but the symptoms were not improved and referred to our hospital because of elevations of transaminases. Significant pancytopenia, a hyperferritinemia suspected HPS. Steroid pulse therapy followed of 1mg/kg of prednisolone resulted in a good outcome. We reported a case of SLE presenting HPS as an initial manifestation. Because HPS is sometimes life-threatening, physicians should take into consideration upon a diagnosis of HPS at an early stage in a patient with SLE.

P2-182

A case of refractory thrombocytopenia in SLE successfully treated with a thrombopoietin receptor (TPO) agonist

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Conflict of interest: None

[Introduction] A refractory type of secondary immune thrombocytopenia (ITP) is not a rare symptom in SLE. We report a case of refractory ITP in SLE successfully treated with a TPO receptor agonist. [A case report] The patient was a 33-year old female. SLE was diagnosed at 26 years old. Her ITP had been resistant to steroid and immunosuppressant drugs (CyA etc). Rituximab had shown efficacy to prolong nonhospital care periods. At Feb. 2011, she was admitted to our hospital due to ITP deteriorated by odontitis. Increased doses of steroids and IVIg showed only temporary improvement. Taking careful consideration to therapeutic options, we decided to use a TPO receptor agonist, eltrombopag. After the informed consent, 12.5-mg daily doses of eltrombopag were started. 25-mg daily doses proved to stabilize platelet counts around 100,000/μL without side effects, and enabled her to switch to outpatient care. [Discussion] Eltrombopag ameliorated refractory ITP in SLE treated with steroid and immunosuppressant drugs. We should keep it in mind that a TPO receptor agonist therapy is supportive one and has no effect on SLE activity. Long-term tolerance of eltrombopag is unknown. We are considering that splenectomy is a future therapeutic option because her ITP showed response to IVIg.

P2-183

A case of systemic lupus erythematodes (SLE) on maintenance hemodialysis (HD) complicated with acute interstitial pneumonitis (NSIP-like)

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Conflict of interest: None

[Objectives] We experienced a case of overlapping syndrome of SLE and Sjögren's syndrome(SjS) on maintenance HD, complicated with pneumonitis. [Case] 46 y.o. female. CC: high fever, chill and dyspnea. PH: 20 and 23 y.o. sialolithotomy. PI: At 26 y.o., she had a butterfly rash, polyarthralgia, renal dysfunction, positive ANA and leucocytopenia, then was suspected SLE and took steroid therapy. At 31 y.o., she experienced Raynaud's phenomenon and diagnosed as SjS in the following year. Moreover, she was elucidated to have renal tubular acidosis(RTA) type1 and chronic interstitial nephritis. Renal dysfunction and anemia progressed to end stage, therefore HD has started Feb.10 this year. She had chief complaints at Sept. 20. Chest X-rays suggested abnormal shadow

and she admitted to a certain medical center. Cyanosis was not observed, but oxygen saturation decreased to 84%. Laboratory data showed CRP 8.99 mg/dl and KL-6 1,270 U/ml. Clinical course was followed by steroid half pulse therapy and good response was done. [Conclusion] We think that this case followed a rare clinical course. It may be contributing factor to pulmonary lesion that she has overlapping syndrome with SjS and positive anti-RNP antibody. We should pay careful attention on follow-up observation like that case.

P2-184

A case of CNS lupus rapidly progressive and fatal during treatment for SLE

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Conflict of interest: None

A 33-year-old woman had been depressive for one year, and developed Raynaud phenomenon, photosensitivity, and stomatitis for half year. A month before admission, laboratory tests showed antinuclear antibody, anti-dsDNA antibody, anti-Sm antibody, and urinary protein. Therefore, she was diagnosed with SLE, and had been treated with prednisolone of 25mg/day. Two days before admission, she developed fever, and painful cyanosis of her extremities. She was admitted, and developed decrease in blood pressure, convulsion, and consciousness disturbance. We thought she had septic shock, CAPS, or CNS lupus. She was treated with antibiotics, anticoagulation therapy, steroid pulse therapy, and supportive care. Three days after admission, she had anisocoria with sudden onset. A CT scan showed slight cerebral edema in her brain. Soon after that, she developed cardiopulmonary arrest for 7 minutes, and was successfully resuscitated. But, she had mydriasis without spontaneous respiration. A MRI revealed occlusion of both internal carotid arteries and severe cerebral edema. Also, electroencephalography showed a flat wave. Seven days after admission, she was dead. Pathological autopsy finding revealed infiltration of inflammatory cells around the vessels, which were consistent with CNS lupus.

P2-185

A case of systemic lupus erythematosus (SLE) with cerebral venous sinus thrombosis (CVST)

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Conflict of interest: None

A 54-year-old woman was diagnosed with SLE in 1993. She was admitted to our hospital and treated with PSL30 mg/day. Her symptoms completely resolved. PSL was tapered and azathioprine 25 mg/day was added to the regimen. In 2001, she was re-admitted because of hemophagocytic syndrome. She was administered PSL 50 mg and CYA150 mg/day. After discharge, PSL was tapered to 5 mg/day and CYA to 25 mg/day. In 2007, She exhibited SLE relapse and was recived PSL60mg/day. After discharge, PSL was tapered to 6mg/day. In July 2010, She was diagnosed with idiopathic thrombocytopenic purpura-induced SLE and thereafter underwent oral administration of PSL 20 mg/day. In September 2010, she complained of a headache and was admitted because of right palsy. MRI did not show cerebral infarct. Based on neurological findings, she was diagnosed with CVST. Heparinization was immediately started. The following day, she had a hemorrhagic infarction. According to stroke guidelines, we continued intravenous heparin combined with aspirin. She was discharged without sequelae. CVST is rare when compared to other thrombotic events in SLE. Early suspicion and diagnosis are essential as delayed treatment may lead to clinical outcomes. We report this case of SLE accompanied with CVST, with a review of the literature.

P2-186

A case of systemic lupus erythematosus with Podcytic infolding glomerulopathy

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Conflict of interest: None

[Case] A 57 yo woman was admitted to our hospital because of abdominal pain. She was diagnosed at age 54 as systemic lupus erythematosus due to lymphocytopenia, anti-nuclear Ab+, anti-Sm Ab+/-, arthritis, proteinuria. The histology of the kidney, however, was podcytic infolding glomerulopathy (PIG). She had several episodes of abdominal pain, but was followed without corticosteroids. At admission, anti-Sm Ab showed high titers and anti-dsDNA Ab was positive. Reexamination of the kidney hisotology revealed no lupus nephritis but PIG. Prednisolone (30mg/day) was started because of lupus colitis. [Disuccion/Conclusion] PIG has been known as a novel nephropathy and associated connective tissue diseases. In our case, despite the increased lupus activities, renal histology was not changed. This suggested a possible pathophysiology of PIG independent from the lupus nephritis.

P2-187

Cervical Cancer in Japanese SLE Women

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Conflict of interest: None

[Objectives] To determine the incidence of cervical cancer among Japanese SLE women and risk factors of cervical cancer in SLE women. **[Methods]**We performed a retrospective study of SLE women who were treated at our hospital from October 2008 to September 2011. Women who were diagnosed with cervical cancer before the diagnosis of SLE and women with endometrial cancer were excluded. **[Results]** There were five cases of cervical cancer among 129 women, and the incidence of cervical cancer was significantly higher compared to Japanese women in general (77.2 vs. 37.6 per 100000 women per year, p=0.01). Women with cervical cancer were diagnosed with SLE at a younger age than women without cervical cancer (24.8 years old vs. 36.7 years old, p=0.03). They were more likely to have been treated with immunosuppressants (100% vs. 40%, p=0.00). The incidence of lupus nephritis was higher among women with cervical cancer, but the difference was not significant (80% vs. 45%, p=0.16). **[Conclusion]** Japanese SLE women are at a higher risk for cervical cancer than Japanese women in general, and they should be encouraged to have Pap smears performed regularly.

P2-188

A case of childhood limited Wegener's granulomatosis with a cervical mass and neurological involvement

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Conflict of interest: None

Wegener's granulomatosis (WG) is a necrotizing granulomatous small vessel vasculitis that often involves the upper and lower respiratory tracts and kidneys. Although any organ systems can be affected, WG rarely presents with tumor masses. We report a case of childhood limited WG with a cervical mass and neurological involvement, which was distinguished from a nasopharyngeal tumor. A 10-year-old girl who had suffered from left intractable otitis media and hearing impairment visited our hospital because of left facial paralysis. Then, although this symptom resolved with steroid treatment, she was admitted complaining of a left cervical mass. We detected left recurrent and hypoglossal nerve paralysis. She had low grade fever and her serum CRP was slightly elevated. Urinary findings and renal function were normal. Chest X-rays showed no lesion. CT scans revealed a left epipharynx tumor. A biopsy specimen of the tumor identified granulomatous inflammation and necrotizing vasculitis. Her serum PR3-ANCA titer was high. She was finally diagnosed as limited WG. Her condition, except for left hearing loss, improved with the administration of steroids, immunosuppressants and TMP/SMX. Variable clinical pictures of vasculitic diseases like WG should always be kept in mind even in children.

P2-189

A boy with multiple fasciitis

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Conflict of interest: None

[case] 12-year-old boy [CC] swelling of shoulder, knee and abdomen with rash in legs [PI] He complained swelling of left shoulder, left abdomen and right knee. [physical findings and exams] He had joint limitation, but didn't have arthritis or skin sclerosis. WBC 8800/μl(neut76%, lym 13.8%, eos3.1%), CRP 1.3mg/dl, ASO 790U/ml, RF 0IU/ml, CK 66IU/l, aldolase 3.9U/l, ESR 78mm/h. CT and MRI showed that he had multiple fasciitis. [course] We gave him antibiotics assuming necrotizing fasciitis, but it didn't go well. Inflammation worsened (WBC 12400/μl, CRP 9.1mg/dl) and swelling areas moved to left elbow, right hand and right jaw. All infection tests are negative and he didn't meet any criteria of collagen disease. Biopsy of skin lesion showed lobular panniculitis with suspicious vasculitis, then we diagnosed that he had non-infectious fasciitis and gave oral corticosteroid (PSL2mg/kg). Every complaint and abnormality of exams disappeared, and we withdrew PSL gradually. We suspect that his symptom came as poststreptococcal reactive fasciitis, because he had increased rate of ASO/ASK and didn't have typical findings of eosinophilic fasciitis. Though there still are possibility of other disease like PN, PM/DM and fasciitis –panniculitis syndrome and we need to observe him carefully.

P2-190

Aortitis syndrome developed in a girl patient who had Crohn's disease during treatment with infliximab.

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Conflict of interest: None

The patient was 13-year-old girl. She was diagnosed as Crohn's disease in 2008(11-year-old). She was received nutrition therapy and treated with mesalazine, prednisolone and azathioprine. However the disease activity was not controlled, then she was treated with infliximab in October 2009. Infliximab was administered three times with favorable response and prednisolone was tapered. However inflammatory response was elevated after a few weeks, and she complained malaise of her left arm. We examined the enhanced CT and detected the stenosis of left subclavian artery and abnormal wall thickening of aortic arch. We stopped infliximab and started prednisolone and MTX.

P2-191

Two cases of Bicipital Synovial Cyst in Systemic-Onset Juvenile Idiopathic Arthritis

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Conflict of interest: None

Bicipital synovial cyst is a rare manifestation of systemic-onset juvenile idiopathic arthritis (s-JIA). Here we report two cases of bicipital synovial cyst in s-JIA. Case 1. Eight-year-old boy was diagnosed as s-JIA at age of 4. He was treated with tocilizumab (TCZ) at age of 5. The disease relapsed at age of 7 with fever and swelling of upper left arm. Ultrasonography (US) revealed a cyst of hyperechogenic along the margin of the biceps muscle. A cyst biopsy revealed infiltration of macrophages, and there were no tumor cells and abscess. A diagnosis of synovial cyst was made. The cyst disappeared as disease activity improved. Case 2. Twelve-year-old boy was diagnosed as s-JIA at age of 8. He was treated with prednisolone. He was admitted to our hospital at age of 12. He presented with swelling of upper right arm. US revealed a cyst of hyperechogenic in the biceps muscle fascia. A cyst biopsy revealed infiltration of macrophages. The cyst disappeared with TCZ treatment. Pathophysiology of bicipital synovial cysts remains unclear. The findings in these patients suggest that the fluid arises within the shoulder joint and then the tendon eventually ruptures, leading to collection of fluid in the bicipital area and synovial cysts arise from the biceps muscle fasciitis.

P2-192

Radiological Analysis on Hands and Large joints in Systemic Juvenile Idiopathic Arthritis Treated with Tocilizumab

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Conflict of interest: None

[Objectives] We radiologically evaluate the effects of tocilizumab(TCZ) on the joints with carpal ratio (Poznaski score) and Larsen score of sJIA patients. [Methods] Forty sJIA patients treated with 8mg/kg of TCZ every 2 weeks were included in this study. We examined radiographs of bilateral hands for the Poznanski score, and those of large joints, such as sholders, elbows, hips, knees and ankles, for the Larsen score before and during treatment. Their clinical response was assessed by active joint counts, joints with limited motion, and laboratory data. [Results] Their mean age at the start of TCZ was 9.2 years, and mean followup period was 3.8 years. With TCZ, mean active joint counts, WBC, CRP, ESR and MMP-3 were significantly improved from 4.6 to 0.8 joints, from 15400 to 7200/μl, from 5.7 to 0mg/dl, 40 to 2mm/h, and from 338 to 169ng/ml respectively. The Posnaski score improved from -0.9 beforeTCZ to -0.7 after TCZ; however, the Larsen score increased from 10.3 to 10.8. Poznaski score improved in 19 cases

(48%), however, the Larsen score improved in only 13 cases (33%, improved group), and worsened in 19 cases (48%, worsened group). There is significant difference between 2 groups in MMP-3 (53 in improved group and 226 in worsened group) at the final follow-up ($P<0.05$).

P2-193

Arthroscopic synovectomy in the treatment of the articular juvenile idiopathic arthritis

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Conflict of interest: None

[Objectives] In the articular juvenile idiopathic arthritis (JIA), affected joints often show flexion contracture. We reported usefulness of the arthroscopic synovectomy for improving the range of motion (ROM) in the affected joints in the treatment of JIA. [Methods and Results] We treated five cases, which were one to three years old girls, and four cases had a solitary arthritis in the knee joint and they were underwent the arthroscopic synovectomies. In two cases with the arthroscopic surgery, rice bodies in the knee joint were demonstrated and remission of arthritis was obtained without any drug therapy. In these cases, ROM of the knee joints returned to the normal range in a few months after surgery. Other two cases with the arthroscopic synovectomy, the knee joints were shown 30 degrees flexion contracture. These cases were treated with ibuprofen, and ROM of the knee joints returned to the normal range in almost one year after surgery. One case had arthritis in the right elbow and in the bilateral knee joints, and was treated with ibuprofen only. In this case, 40 degrees of flexion contracture in the elbow and 20 degrees of flexion contracture in the knee joints were shown, and it took almost three years to improve the ROM into normal range.

P2-194

Psychological health status in JIA patients treated with biological agents.

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Conflict of interest: None

[Objectives] To evaluate whether biologic agents improve their psychological health condition in accordance with the improvement of physical function in JIA patients who were refractory to conventional therapy. [Methods] JIA patients aged 8 to 18 years referring to our pediatric rheumatology outpatient clinic were surveyed by using Pediatric Quality of Life Inventory version 4.0 (PedsQL) Generic Core Scales for measuring core health of physical and psychological (emotional, social, and school functional) dimensions. [Results] Total PedsQL® score of 47 JIA patients reflected the Steinblocker.'s Class classification. Therefore, the correlation between the physical and psychological health score of PedsQL® were analyzed in 27 JIA patients treated with biologic agents. A significant positive correlation was observed between the physical and psychological scores ($R2=0.528$, $P<0.0001$). There was a significant negative correlation ($R2=0.345$, $P=0.0167$) between the disease duration at initiating biologic agents and the psychological score. [Conclusion] Psychological support is still necessary for JIA patients even if his/her physical conditions improved by newly developed biologic agents, especially in polyarticular JIA patients who had long disease duration before initiating the biologics.

P2-195

The clinical feature of pediatric onset systemic lupus erythematosus mimicking idiopathic thrombocytopenic purpura.

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Conflict of interest: None

[Objectives] The aim of study is to detect the clinical feature of pediatric onset systemic lupus erythematosus mimicking idiopathic thrombocytopenic purpura(ITP). [patients] Pediatric onset SLE who were mimicking ITP. [Results] Four patients (M/F 1/3) were eligible, and age at ITP diagnosis was 11 -13 years old. Symptoms which observed at the time of diagnosis as ITP were bleeding tendency in 3 patients. Durations from the ITP diagnosis to final diagnosis were within one month in two patients, within one year in two patients. In one patient symptom which observed at the time of diagnosis as rheumatic disease was bleeding tendency only, but in others various symptoms like arthritis, erythema, urine abnormalities and subacute necrotizing lymphadenitis were appeared. At the time when patients were diagnosed as SLE, all patients fulfilled SLE classification criteria (ACR 1997). But the titers of anti-ds DNA antibody were low. [Conclusion] SLE mimicking ITP may be another cluster in pediatric onset systemic lupus erythematosus.

P2-196

A case of systemic lupus erythematosus complicated by group B streptococcus meningitis and subarachnoid hemorrhage

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Conflict of interest: None

We report a 16-year-old boy with systemic lupus erythematosus (SLE) who developed *Streptococcus agalactiae* meningitis and subarachnoid hemorrhage. He was diagnosed as having SLE at 13 years old, and had been treated with predonisolone and mycophenolate mofetil (1g/day). He suffered from headache at 14 years of age, and MRI scan showed multiple microinfarction. After one month, he admitted to our emergency room because of convulsion and unconsciousness. The CT scan showed subarachnoid hemorrhage. Cerebrospinal fuid (CSF) analysis revealed pleocytosis, elevated protein level and depressed glucose level. In bood and CSF culture, *Streptococcus agalactiae* was identified. He was diagnosed as having bacterial meningitis and treated by antibiotics and methylprednisolone pulse therapy. He recovered completely without neurological sequelae despite complication of another lesion of cerebral infarction. In case of SLE patient with central nerves symptoms, central nerves infection as well as cerebrovascular accident should be ruled out.

P2-197

Clinical analysis of anti-NR2 glutamate receptor antibodies and interleukin-6 with neuropsychiatric systemic lupus erythematosus

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Conflict of interest: None

Abstract. Neuropsychiatric (NP) involvement is a serious man-

ifestation of Systemic Lupus Erythematosus (SLE). The American College of Rheumatology (ACR) has established the standardized 19 symptoms to diagnose of NPSLE. We herein report two cases of Japanese girls with NPSLE. They had a fever and severe headache. T2-weighted brain MRI showed high intensity lesions around of basal ganglia. Marked elevation of the cerebrospinal fluid (CSF) interleukin (IL)-6 was noted, and her serum and CSF IgG anti-NR2 glutamate receptor antibody titers were elevated. We diagnosed them with headaches and cerebrovascular disease resulting from NPSLE. They were treated with immunomodulatory and anticoagulation medications. Their clinical symptoms improved, and her CSF IL-6 and anti-NR2 levels were decreased. The etiology of NPSLE remains unclear. There have been few reported pediatric cases of NP-SLE. Our cases indicate that brain MRI and the CSF IL-6 and anti-NR2 level might be useful in not only in the diagnosis of NPSLE, but also in assessing the activity and response of NPSLE

P2-198

A case of overlapsyndrome complicated by pulmonary hypertension.

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Conflict of interest: None

[Back ground] Patients with pediatric rheumatic disease rarely develop pulmonary hypertension (PH), and the expected prognosis had been very poor. With advances in medical therapy for PH in recent years, we can expect better prognosis. [Case report] We have observed a 13 years old female patient. At age seven, she developed autoimmune hepatitis. At the age of ten she was diagnosed with lupus nephritis from pathological finding, and treated with immunosuppressive therapy (methylprednisolone pulse therapy, cyclophosphamide pulse therapy and Mycophenolate Mofetil). Comprehensive examination about PH was carried out at age 12. DLco was within normal range in lung function tests. In 6 minute walk test, she could walk 490m but SpO2 was decreased to 83%. In ultrasound, increased pressure gap of tricuspid valve are observed and estimated right ventricular meanpressure was 60mmHg. In right heart catheterization, mean pulmonary artery pressure at rest was 43mmHg. We had diagnosed her as overlap syndrome (SLE andsystemic sclerosis localized type) with PH, and started the prescription of sildenafil. [Conclusions] In pediatric patients with rheumatic diseases which may be complicated by PH, it is very important to perform regular screening tests even if without clinical symptoms.

P2-199

A 14-year-old boy with juvenile ankylosing spondylitis successfully treated with infliximab

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Conflict of interest: None

Juvenile ankylosing spondylitis (JAS) is a representative of the spondyloarthropathies with strong association with HLA-B27. A 14-year-old boy was referred to our hospital because of low back and buttock pain that gradually worsened over last 6 months. Upon admission, he had reduced mobility of the spine without any sign of enthesitis. Laboratory data were negative for rheumatoid factor and antinuclear antibody. Serum C-reactive protein level was 2.3 mg/dl and erythrocyte sedimentation rate was 71 mm/hr. HLA typing test was positive for B27 antigen. MRI study showed bilateral sacroiliac arthritis. He was diagnosed as juvenile ankylosing spondylitis (JAS) according to the modified New York criteria, although few JAS cases initially present with axial symptoms in children. Treatment with NSAIDs did not improve the patient's symptoms and administration of infliximab induced a substantial and rapid improvement in all parameters of disease activity.

P2-200

Treatment with adarimumab in a patient with psoriasis arthritis-associated organizing pneumonia

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Conflict of interest: None

We report a case of a 62-year-old man with a 5-years history of psoriasis referred to hospital because of fever, aggravated pulmonary symptoms and polyarthralgia. Chest X-ray showed infliltration shadow. Although he was treated with anti-bacterial agents, the symptoms and X-ray finding became worse. He underwent bronchoscopy, The bronchoalveolar fluid lavage (BAL) findings were 95.5% of macrophage, 1.0% of neutrophil, 3.0% of lymphocyte and 0.5% of eosinophil. He was diagnosed of organizing pneumonia. On the other hand, Psoriatic arthritis was diagnosed as arthritis with enthesitis and fulfilled with CASPER classification. Because of risk of pustular psoriasis by steroid therapy, We initiated treatment with adalimumab, subcutaneously injected once two weeks. Following 2 weeks of therapy with this agent, his symptom such as arthralgia, fever, dyspnea and cough improved immediately. The improvement was confirmed by reduced lung shadow on chest radiography and high-resolution CT scan. This report suggests adalimumab may be effective in the treatment of psoriatic arthritis-associated organizing pneumonia.

P2-201

Two RA cases of high KL-6 during MTX+adalimumab therapies

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Conflict of interest: None

[Objectives] We have measured KL-6 of the rheumatoid arthritis(RA) patients for the purpose of detection of pulmonary lesions. We report two RA cases of high KL-6 during the use of methotrexate (MTX) and adalimumab (ADA). [Case1] 56 years old. Male. RA disease duration: 10months. Past history: Osteonecrosis of rt knee. Laboratory data of his initial visit : CRP 5.54 mg/dl, ESR 63mm/1h, MMP-3 371.8 ng/ml, KL-6 443 U/ml. MTX (8mg/week) was prescribed. KL-6 was 575U/ml after 4 weeks of initiation of MTX, and 760 U/ml at 8 and 12weeks. SD-A and SP-D were 28.0 ng/ml and 55.8 ng/ml, respectively. There was no pulmonary and malignant lesions by the examination of HRCT and whole body FDG-PET/CT. Therefore, because of the inadequate response to MTX, ADA was started. The highest KL-6 was 1861 U/ml, and SP-D was 232 ng/ml. [Case2] 71 years old. Female. RA disease duration: 14 months. Past history: Hypertension. Laboratory data of her initial visit :CRP 0.47 mg/dl, ESR 59 mm/1h, MMP-3 58.3 ng/ml, KL-6 467 U/ml. Because of the inadequate response

to MTX(8mg/week), ADA was added. After 3 months, KL-6 was 901 U/ml. Hence, MTX was withdrawn. There was the reduction of KL-6. After 6 months, KL-6 was 464U/ml. From HRCT of this patients at the initiation of ADA, we suspected Chronic bronchitis.

P2-202

Thee cases of MTX pneumonitis in whom MTX was reintroduced

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Conflict of interest: None

Allergy or hypersensitivity is widely accepted as the mechanism of MTX pneumonitis. However, the clinical feature of MTX pneumonitis is heterogeneous and the mechanism of acute and subacute types may be different. We have been thinking that the mechanism of subacute type of MTX pneumonitis is non-allergic. We present 3 cases of MTX pneumonitis in whom MTX was reintroduced.. The first case is a 65 year-old man who had 10mg MTX/week with 3 -5 mg PSL/day. In May, 2009 abnormal shadows on CXR were pointed out and chest CT revealed consolidations and GGOs compatible with MTX pneumonitis. Two months after cessation of MTX, the shadows disappeared and 6mg/week of MTX was reintroduced because of flare up of RA. The second case is a 29 year-old woman in whom the shadows compatible with NSIP worsened after the dose escalation of MTX to 12mg /week. Two months later 6mg/week of MTX was reintroduced. The third case is a 63 year-old woman, in whom MTX pneumonitis developed after the dose escalation of MTX to 8mg /week. One month later 6mg/week of MTX was reintroduced. In all cases relapse of MTX pneumonitis has not been observed. We think that in subscute type of MTX pneumonitis MTX can be reintroduced without complication, and this finding is against the allergic mechanism.

P2-203

A study of Pulmonary arterial hypertension with connective tissue diseases in Kagawa

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Conflict of interest: None

Pulmonary arterial hypertension (PAH) with connective tissue diseases (CTD) is progressive, life-threatening. Definite diagnosis of PAH requires right heart catheterization that is essential for therapeutic decisions. CTD-PAH should be differentiated from other forms of pulmonary hypertension (PH) in patients with CTD usually include PH due to interstitial lung disease, left heart and/or thromboembolic disease. Treatment of patients with CTD-PAH is based on complex strategy consisting of the evaluation of severity, assessment of vasoreactivity and combination of drugs and interventions tailored according to patient's clinical status and response to therapy. Since the efficacy of these therapies in CTD-PAH is due to retardation of clinical deterioration rather than reversal of the disease early treatment is of key importance for improving long-term outcome in CTD-PAH. There are some reports that immunosuppressants (IS) is effective for early stage CTD-PH. We focused on the efficacy of IS combined with several pulmonary vasodilators (PV) on CTD-PAH in Kagawa PAH study group. We examined 18 CTD who was diagnosed of PAH. PAH who is deteriorated rapidly, were treated with a combination of IS and PV, who responded well to the treatment. We discussed about the treatment for CTD-PH.

P2-204

Bronchiolitis with Rheumatoid Arthritis

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Conflict of interest: None

The rheumatoid arthritis (RA) patient examined five cases in which spraying of the nodular shade in alignment with a bronchus, the cavitary shade, bronchiectasis, etc. were accepted, on the chest CT, The microbiological inspection which carries out bronchoscopy inspection enforcement at all the examples is netative, after that, bronchiectasis got worse and one example has taken the progress stabilized on the picture without four respiratory symptoms. When the above bronchioles pathological changes are accepted by the chest CT in RA medical examination especially at the time of biological therapy introduction, in accordance with the diagnostic criteria of non-tubercular myocobacteia (NTM), an examination of sputum and the detection of which carries out bronchoscopy inspection enforcement are not obtained, but it may hesitate the medical treatment introduction by biological therapy as NTM doubt. Those seem to the noninfectious lung pathological change like follicular bronchiolitis is suspected. In RA, the bronchioles pathological change has been reported to 60%, and it is pointed out that many lymph fault formation to a rheumatoid arthritis patient of a lung is accepted. Bibliographic consideration is added and it advocates that it may be a bronchioles pathological change of RA.

P2-205

Repeated Alveolar Hemorrhage during the active phase of Takayasu's Arteritis: A case report.

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Conflict of interest: None

【Case】34 years-old woman, with chief complaint of cough and right back pain. She was admitted to our hospital for antibiotic-resistant pneumonia. Chest X-ray showed consolidations of the right middle and lower lobes. She underwent bronchoalveolar lavage (BAL) and was revealed to have hemosiderin-laden macrophages. She was first treated as having idiopathic alveolar hemorrhage with prednisone (PSL) starting at 30 mg/d, which improved the laboratory findings. The PSL dosage was gradually decreased to 10 mg/d as the symptom was worsening. She had the diminished pulse and the claudication in left upper extremity and the bilateral subclavian bruits. Pulmonary angiogram demonstrated complete occlusion of the right middle and lower branches. These findings suggested having Takayasu's arteritis. After the methylprednisolone pulse therapy performed, PSL 38 mg/d was administrated and gradually reduced. The serum inflammation reaction was slowly promoted and the alveolar hemorrhage reoccurred at 24 mg/d, which was reconfirmed by BAL After the pulse therapy was reperformed and methotrexate was administered, the laboratory findings gradually improved.【Results】It is rare to confirm the repeated alveolar hemorrhage by bronchoalveolar lavage, in Takayasu's arteritis during its active phase.

P2-206

Two cases of alveolar hemorrhage during Methotrexate therapy for rheumatic disease

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Conflict of interest: None

Case1:91-year-old man with rheumatoid arthritis had treated with Methotrexate(MTX) 4mg/week for 4 years. In May 2011, he complained of cough, and was treated by antibiotics. Ground-grass opacities with chest X-ray were appeared. He was admitted to our hospital, and complained of hemosputum and dyspnea, at the next day. Chest CT showed ground-grass opacity, and bronchoalveolar lavage fluid(BALF) showed bloody fluid and predominance of lymphocytes. He was diagnosed with alveolar hemorrhage, and treated with methylprednisolone(m-PSL) pulse therapy followed by oral prednisolone(PSL). Case2:62-year-old woman with ankylosing spondylitis, was administrated with MTX in March 2010. Six months later, she was hospitalized for fever, cough, dyspnea, and hypoxemia. There were ground-grass opacities with chest X-ray, and BALF was bloody and showed predominance of lymphocytes. She was diagnosed with alveolar hemorrhage, and treated with m-PSL pulse therapy followed by oral PSL. Both cases were well responded to the steroid therapy and PSL was tapered. Although MTX is known to induce interstitial pneumonia, there are few literatures of alveolar hemorrhage during MTX therapy. Alveolar hemorrhage was expected rare complication of MTX.

P2-207

The features of the fracture in patients of Rheumatoid Arthritis of our hospital.

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Conflict of interest: None

[Objectives] To examine characteristics of rheumatoid arthritis patients with bone fracture. [Methods] Bone mineral density (BMD) of lumbar spine was measured with dual-energy X-ray absorptiometry. Relationships of BMD with patient backgrounds, locations of fracture and prescribed drugs were analyzed. [Results] In 2,300 patients with rheumatoid arthritis in our hospital, 166 cases (7.2%) were complicated with fracture. Mean age of cases with fracture was 69.9+-10.9 y/o (73.8 in male, 69.5 in female). Ninety-eight patients (59.0%) had spinal compression fractures. Bisphosphonate was prescribed in 45 cases (27.1%). In 84 cases (50.6%), any drugs for osteoporosis was not prescribed through unavoidable circumstances. Corticosteroids were administrated in 123 cases (77.7%). Mean dose of corticosteroid was 5.0 mg/day (1.0-18.0 mg/day). Young adult mean (YAM) of BMD was 76.1% in patients with compression fracture. Compared with age-matched normal population, BMD of male patients over 70 y/o with spinal compression fracture was 79.4% and with fractures other than spine was 135.0%.

P2-208

Analysis of clinical aspects of incident fracture in glucocorticoid-induced osteoporosis (GIO).

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Conflict of interest: None

Objective) To clarify clinical factors committed to incident fracture in GIO. Subjects & Method) Patients (136) with rheumatic diseases (without rheumatoid arthritis) were recruited for this two years prospective study. Incident fracture was defined with the FIT study protocol. Result) The mean of age, %YAM, rate of prevalent fracture, predonisolone dosage were 60, 81%, 43%, 8.2mg/day, respectively. The incident fracture was seen in 25% in Bis treated group, 80% in D3, 50% in K2, 62% in non-Tx. Multivariate analysis showed Bis (OR 0.03) and K2 (0.08) Tx, prevalent fracture (5.9), prednisolone dose (2.2/5mg), age (1.3/5y), BMD (1.3/5%) were shown as independent factors for the incident fracture. Conclusion) In GIO, the rate of fracture was high. Other than dosages of glucocorticoids, prevalent fracture, age, BMD were contributed to incident fracture. Treatment with Bis and K2 were effective.

P2-209

Effects of teriparatide therapy on bone markers and bone mineral densities in glucocorticoid-induced osteoporosis in rheumatic diseases

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Conflict of interest: None

[Background and purpose] The purpose of this study was to evaluate short-tem effect of teriparatide herapy on bone markers in patients with rheumatic disease. [Subjects and methods] The subjects were 38 patients (36 females and two males) with rheumatic disease. They have been taking glucocoriticoid and a history of bone fracture. The mean of age, bone mineral density (BMD) of the lumbar spine, and BMD of the femoral neck were 72.5 years old, 72.4%YAM, and 65.7%YAM, respectively. The previous therapies were 31 patients with bisphosphonates (Bis-group) and eight patients with others (Other-goup). Bone markers (ucOC, TRACP, PINP, BAP, BMD, etc) were monitored longitudinally from the base line (0W) to 24 months (24M) at most. [Resulsts] In all the patients BAP was changed from 15.4 (0W) to 17.5(1M), 17.0(3M), and 21.4(6M) (*, $p<0.05$). BMD of the lumbar spine altered from 75.6(0W) to 81.0(3M), 79.8(6M). [Conclusion] It took several months to detect significant alternation of bone markers after the therapeutic change from bisphosphonates to teriparatide. BAP may be a good marker as BAP demonstrated early significant responses.

P2-210

P2-211

The analysis of cases with bone fractures and utility of teriparatide in patients with rheumatoid arthritis

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Conflict of interest: None

[Objectives] To determine the clinical feature of bone fracture

in patients with Rheumatoid arthritis (RA) and effectiveness of teriparatide therapy for bisphosphonate ineligible cases. [Methods] 109 patients with RA fulfilled the ACR criteria 1987 and/or 2010 in our hospital were investigated retrospectively with their charts and analyzed the risk factors with bone fragility fractures, gender, age, numbers and location of bone fracture, history of glucocorticoid therapy, bone mineral density and bone metabolism markers. [Results] 16 cases had bone fragility fractures including 14 vertebral compression fractures,1 femoral and 1 rib. Their sex ratio is 0.23, their mean age is 70.2 y/o. 9 cases received low dose glucocorticoid therapy (2 to 7.5 mg daily) with bisphosphonate and/or activated vitamin D. In 2 bisphosphonate ineligible cases, teriparatide injection could attenuate their symptoms. [Conclusion] Glucocorticoid could be a risk factor with fracture in patient with RA, even low-dose especially in elderly cases, thus bisphosphonate therapy should be necessary. Teriparatid could be alternative in bisphosphonate ineligible cases.

P2-212

Investigation of clinically amyopathic dermatomyositis

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Conflict of interest: None

[Objectives] We investigated clinically amyopathic dermatomyositis(CADM). [Methods] 18 patients, who were diagnosed with CADM at our hospital between 1998 and 2011, were included. Survivors and deaths were compared, classified by the presence of interstitial lung disease(ILD) and cancer. For cases with complications of ILD, differences in treatments were also compared. [Results] The result shows 10 cases with the complication of ILD, and 8 cases without ILD. In cases with ILD, the survivors were 7, 3 patients died, showing the mortality rate of 30%. 4 patients received only steroids as an initial therapy, and immunosuppressive agents were added at the time of exacerbation of ILD. 2 cases of acute-exacerbation of ILD died, and 2 cases of subacute were alive. And, triple therapy (PSL, IVCY, and CyA) from the initial treatment was performed in 5 patients, 4 cases survived, and 1 died, representing the mortality of 20%. Prediction of progression of ILD is uncertain, thus triple therapy from the beginning is considered preferable for patients associated with ILD. On the other hand, in cases without ILD, 4 had associated cancer and 4 had no cancer. The former all died, all of the latter survived, suggesting patients who were not complicated by ILD nor malignancy to be a good prognosis.

P2-213

Clinical features of dermatomyositis (DM) with Mechanic's hand.

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Conflict of interest: None

[Objective] To derive clinical significances by comparing clinical manifestations of DM with and without Mechanic's hand. **[Methods]** We compared clinical differences between 7 patients with Mechanic's hand and 27 patients without Mechanic's hand who visited our clinic. **[Results]** There was no significant difference between patients with and without Mechanic's hand in female rates (with Mechanic's hand 71 vs. without Mechanic's hand 78%), mean values of creatine phosphokinase (1467 vs. 1299 IU/l), positive rates of anti-Jo-1 antibody (14 vs. 11%), maximum doses of prednisolone (40±13 vs. 40±13 mg/day), methylprednisolone pulse therapy (57 vs. 42%), treatments with immunosuppressants (71 vs. 38%), cancer diagnosis rates in 3 years after onsets (0 vs. 7%), 3-year survival rates (86 vs. 89%). DM patients with Mechanic's hand had significantly high concomitant rates of interstitial pneumonia (IP) (100 vs. 44%) and mean age of onsets (51±6 vs. 39±12 years). **[Discussion]** Patients with Mechanic's hand have a high prevalence of IP. This is consistent with the previous report (1). **[Conclusion]** DM with Mechanic's hand related to IP and elderly onset. Reference: 1. Stahl NI, Klippel JH, Decker JL. A cutaneous lesion associated with myositis. *Ann Intern Med* 1979;91:577-579

P2-214

A case that could identify a muscle biopsy region and diagnose it as dermatomyositis by muscle echo

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Conflict of interest: None

Female at age 60 became aware of polyarthritis from March 2009. The symptom was diagnosed as rheumatoid arthritis by orthopedist in June due to anti-CCP antibody positive, and a complication of interstitial pneumonia was also pointed out. Since her arthritis improved within about three months with oral administration of salazosulfapyridine 500mg/day and prednisolone 2.5mg/day, she discontinued thease medicine from September 2010. In June 2011, dermatomyositis was suspected due to a sign of Mechanic's-hand, Gottron and the CK increase at 2000 level. She visited our department in August. Although typical skin manifestation and increase of myogenic enzymes were recognized, clear muscle ache and weakness were not recognized, anti-J0-1 antibody was negative, and active myogenic change was not detected in needle electrode examination. Slight inflammation findings were detected at a portion of triceps brachii muscle with MRI. We conducted muscle biopsy by identifying a region after confirming the portion with ultrasonic wave. We made a definite diagnosis of dermatomyositis from inflammatory cell infiltrate around blood vessels in biopsied tissue and necrotic reconstruction image of muscle cells. We report the usability for muscle ultrasound examination in diagnosis of dermatomyositis.

P2-215

Utility of serum macro-CPK in the diagnosis of inflammatory myositis

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Conflict of interest: None

【Objectives】 Macro-CPK, an isozyme of CPK, is known to be associated with malignancy and with collagen diseases. We examined the positive association of macro-CPK serum level with disease. 【Methods】 In the present study, 40 patients with high levels of serum CPK (>150 IU/L) were included (7 with dermatomyositis, 8 with polymyositis 7 with rheumatoid arthritis, 3 with polymyalgia rheumatic, 3 with vasculitis, and 13 with other diseases). The level of macro-CPK was measured by agarose gel electrophoresis. 【Results】 1) Among the 40 patients, 13 patients (32.5%) were positive for macro-CPK. The positive rate of macro-CPK

among patients with inflammatory myositis was 80% (12/15). Only one patient in the 'other diseases' category was positive for macro-CPK. 2) Macro-CPK was positive in all cases with polymyositis. Serum CPK levels tended to be lower (<600 IU/L) for patients with dermatomyositis who were negative for macro-CPK and higher (>700 IU/L) among patients with inflammatory myositis who were positive for macro-CPK. These results suggest that macro-CPK may represent a marker of inflammatory myositis, which could help to diagnose this disease.

P2-216

Detection of myositis-specific autoantibodies by a line blot assay

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Conflict of interest: None

[Objectives] Anti-aminoacyl tRNA synthetase (ARS) antibodies have been known as myositis-specific autoantibodies and are useful for the diagnosis of myositis. However, it is very cumbersome how to detect those antibodies, because the immunoprecipitation is the only method to detect anti-ARS antibodies except for anti-Jo-1 antibody. [Methods] In this study, we have screened for autoantibodies using a line blot assay about serum samples which were obtained from 50 patients with polymyositis and 29 with dermatomyositis. The test strip coated with parallel lines of highly purified antigens react on autoantibodies in sera of patients. [Results] Our results indicated the detection of many autoantibodies: 7 patients of anti-Mi-2; 7 of anti-Ku; 4 of anti-PM-Scl100; 13 of anti-PM-Scl-75; 12 of anti-Jo-1: 22 of anti-SRP; 23 of anti-PL-7; 23 of PL-12; 7 of anti-EJ; 1 of anti-OJ; 53 of anti-Ro-52. Although it is rare for anti-PM-Scl antibodies in Japanese patients, the numbers of patients positive for them were more than the numbers reported previously in Japanese, suggesting that the false-positive may come from this method. It is necessary to improve the specificity of this line blot assay by comparing with the immunoprecipitation.

P2-217

A case of amyopathic dermatomyositis and rapidly progressive interstitial lung disease that was successfully treated using anti-CADM-140 antibody for the evaluation of disease activity

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Conflict of interest: None

This 52 year-old woman had polyarthralgia and dyspnea on exertion in April 2011. She saw a primary medical doctor and was diagnosed as rheumatoid arthritis (RA) SASP(1000mg/day) and PSL(5mg/day) was started for RA. However, her respiratory symptom was getting worse rapidly in June and she was hospitalized emergently for further investigation. On referral to our hospital, she had Gottron's sign that were consistent with dermatomyositis(DM). However, there was no muscle weakness and the creatine kinase level was within the normal range. Her respiratory symptom was severe and progressive. Therefore, we suspected amyopathic DM(ADM) accompanied with rapidly progressive interstitial lung disease (RP-ILD). Autoantibodies were analyzed by enzyme-linked immunosorbent assay and anti-CADM-140 antibodies were detected. Treatment with 40 mg PSL and intravenous cyclophosphamide pulse therapy and 100mg of CyA daily was initiated, followed by methyl-PSL pulse therapy. Respiratory symptoms gradually improved and the titer of anti-CADM-140 autoantibody decreased in parallel by enzyme-linked immunosorbent assay. We here report this suggestive case that showed the usefulness of anit-CADM-140 antibody for the evaluation of disease activity in patients with ADM and RP-ILD.

P2-218

A case of anti-CADM-140-antibody-positive amyopathic dermatomyositis with non-progressive interstitial lung disease

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Conflict of interest: None

Anti-CADM-140 antibody is associated with clinically amyopathic dermatomyositis (CADM) and rapidly progressive interstitial lung disease (RPILD). We report a 74-year-old female patient with CADM who was positive for anti-CADM-140 antibody (anti-MDA-5 antibody) but presented with non-progressive interstitial pneumonia. Chest CT scan showed several areas of triangular subpleural opacities. The patient was treated with oral prednisolone and immunosuppressants including tacrolimus, azathiprine, and cyclosporine, but all immunosuppressants were soon withdrawn due to adverse effects and inefficacy. However, with only medium dose of prednisolone, the finding of interstitial pneumonia was rather improved. Detection of anti-CADM-140 antibody in CADM patients generally indicate RPILD involvement with a poor prognosis, but our patient so far showed relatively benign clinical course.

P2-219

A Case of dermatomyositis with successful delivery despite acute exacerbation of interstitial lung disease in early pregnancy period.

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Conflict of interest: None

A case is 37-year-old woman with rheumatoid arthritis diagnosed in 2005. She had been commenced on SASP 1g and PSL 6mg/day due to wish for gestation. Asymptomatic interstitial lung disease (ILD) was detected by chest X-ray in July 2010. She got pregnant by in vitro fertilization and embryo transfer in March 2011. In May, she was admitted for emerging dyspnea and desaturation of SpO2 88% with elevated CK and KL-6. On admission, she was at 8 week of pregnancy. Mechanic's hands and periungual erythema were present with no muscle weakness, and myogenic changes in needle EMG and positive anti-PL12 antibody confirmed as diagnosis of dermatomyositis (DM). Oral PSL 50mg/day (0.6mg/Kg) was introduced and monitoring was carried out with chest X-ray under abdominal shielding. Ground-glass opacity of the lower lung was improved without exacerbation during the course of treatment. Fetus growth was good despite gestational diabetes on insulin treatment, but she delivered a healthy baby by caesarean section because of premature rupture of the membranes at 35 weeks of pregnancy under treated with oral PSL 22.5 mg/day. Since there are few reports concerning with the case of DM with successful delivery despite acute exacerbation of ILD, we report

this case with discussion.

P2-220

A case of dermatomyositis with anti-PL-12 antibody who presented myocarditis and interstitial pneumonia

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Conflict of interest: None

A 46-year-old woman presented interstitial pneumonia and polyarthritis with rheumatoid factor in 1997. She was diagnosed as rheumatoid arthritis and prednisone and tacrolimus improved her symptoms. In 2010, she developed Raynaud phenomenon and Gottron's papules and her interstitial pneumonia was deteriorated. In 2011, her creatine kinase was elevated, electrocardiogram showed multifocal VPCs, and cardiac posterior wall motion was hypokinetic on echocardiogram. Cardiac catheterization revealed no ischemic heart disease. We estimated myocarditis was due to dermatomyositis, although she did not suffer from muscle weakness, and electromyogram was normal. Anti-PL-12 autoantibody was proved later. Large amount of prednisone and azathioprine ameliorated her interstitial pneumonia. Her cardiac function was no more damaged after initiation of therapy, and the level of troponin T decreased smoothly. Anti-PL-12 antibody is a kind of antisynthetases autoantibody against transfer RNA synthetase, and is detected in about 1 percent of inflammatory myositis. Our case presented typical skin lesion, interstitial pneumonia, and cardiac involvement, but no muscle weakness. Anti-PL-12 antibody was very useful to confirm our diagnosis.

P2-221

An autopsy case of acute interstitial pneumonia with antisynthetase syndrome positive for anti-EJ and anti-PL-7 antibodies

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Conflict of interest: None

A 81-year-old man transferred to our hospital because of acute respiratory failure. The chest CT images showed non-segmental diffuse interstitial changes in the bilateral lungs and the serum level of myogenic enzymes were elevated (CK 589 IU/l, aldolase 86.4 U/l), The diagnosis of acute interstitial pneumonia with myositis was made. We started the steroid pulse therapy, but his conduction was not improved. During the course, he complicated hemophagocytic syndrome and on the 5th hospital day he died. Results of histopathological findings in the lung tissue showed the diffuse alveolar damage pattern with alveolar hemorrhage and hyaline membrane formation, and the chronic interstitial lesion with the fibrosis under the pleura. Meanwhile, results in the muscle tissue showed no active myositis. The anti-ARS autoantibodies were proved to be positive (anti-EJ and anti-PL-7 antibodies), therefore this case diagnosed the acute exacerbation of interstitial pneumonia with antisynthetase syndrome (AS). AS is characterized by myositis, interstitial pneumonia, polyarthritis, Raynaud's phenomenon, fever, mechanic's hands and so on. Anti-ARS antibodies except anti-Jo-1 antibody are not detected so much, we reported the case with two anti-ARS antibodies.

P2-222

An autopsy case of amyopathic dermatomyositis (ADM) complicated with diffuse alveolar damage (DAD) and hemophagocytic syndrome (HPS).

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Conflict of interest: None

[Objectives] We herein report an autopsy case of amyopathic dermatomyositis (ADM) complicated with diffuse alveolar damage (DAD) and hemophagocytic syndrome (HPS). [Methods] A 63-year-old female was referred to us for fever, arthritis and skin rash lasting for 4 weeks. She presented with heliotrope rash and gottron sign, and her muscle symptoms were not evident with normal CK levels and negative anti-Jo-1 antibody, which were suggestive of ADM. Other laboratory findings showed elevated liver enzymes; serum ferritin, 1324.3 pg/ml; and serum KL-6, 603 U/ml. Radiological studies revealed the features of interstitial pneumonia (IP) in her lung and showed no evidence of malignancy. High-dose corticosteroid, oral cyclosporine and intravenous cyclophosphamide did not ameliorate the progression of IP. Furthermore, the development of pancytopenia was seen during the treatment, and it was inferred as the result of HPS. Blood transfusion and G-CSF increased the blood counts. On the 79th therapeutic day, she was died of respiratory failure due to IP. By the result of autopsy, the case was histopathologically diagnosed as having ADM complicated with DAD and HPS. [Results] HPS is rarely complicated in ADM. We herein discuss the case of HPS in ADM, and review of the literature.

P2-223

A case of steroid-refractory dermatomyositis complicated with autoimmune hepatitis and pericarditis

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Conflict of interest: None

We reported a case of dermatomyositis (DM) with liver and heart disturbance in a 22-year-old female. In August 2010, she was admitted to our department with a 7-month history of pain on the shoulders, elbows, hands and foots and with a 3-month history of fever, malaise, progressive pain on symmetric muscle, and dermatitis on the face, hands, elbows, neck and knees. On clinical and serological examinations, the liver impairment was diagnosed as autoimmune hepatitis (AIH) by a histological study. Finally, she was diagnosed as having DM with AIH and treatment with oral prednisone (1mg/kg/day). Her weakness worsened over the next 1 months and CK did not improve, although liver enzyme levels decreased. She was then initiated on intravenous immunoglobulin (IVIg) and oral methotrexate (8mg/w). Two weeks later, she had a pain in her chest and was diagnosed as pericarditis. She was added pulsed methylprednisolone followed by high-dose corticosteroids(1.5mg/kg/day). After the treatment, her involvements of heart, muscle, liver and skin improved. Liver and heart involvement in patients with polymyositis (PM)/DM has not been well described and is considered to be uncommon. We report the

relatively unusual case with a review of the literature.

P2-224

Case of hemophagocytic syndrome associated with active dermatomyositis: an autopsy case

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Conflict of interest: None

We report a case of dermatomyositis (DM) with hemophagocytic syndrome (HPS). The patient is a 63-year-old female admitted to our hospital with muscle weakness, high fever and thrombocytopenia. On physical examination, proximal muscle weakness, polyarthralgia and skin rash on the hands were noted. Laboratory data revealed elevated serum levels of muscle enzymes, liver dysfunction, coagulopathy and elevated ferritin. Serum levels of M-CSF, TNF-alpha, soluble IL-2 receptor were remarkably increased. Bone marrow aspiration showed histiocytosis with prominent hemophagocytosis. Although she was treated with methylprednisolone pulse therapy (1 g/ day x 3 days) followed by 100 mg/day intravenous prednisolone, she was not responded to the treatment and laboratory data got worse. She was administered repeated therapeutic plasmapheresis with total plasma exchange by fresh frozen plasma and IVIG, these were not effective for improving her symptoms and laboratory abnormalities. However, she suffered from septic Enterobacter cloacae infection and finally died of sepsis. Autopsy revealed liver necrosis and hemophagocytosis. HPS is a rare complication of DM and only few cases have been documented so far in the literature.

P2-225

Liver damage in polymyositis and dermatomyositis

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Conflict of interest: None

【Objective】 Serum levels of creatine kinase (CK) and other muscle enzyme, such as aspartate aminotransferase [AST] and alanine aminotransferase [ALT], are elevated in patients with polymyositis (PM) and dermatomyositis (DM). Elevations of serum levels of AST and ALT in PM/DM results not only from liver involvement associated with PM/DM but also from various other causes. Our aim is to evaluate liver involvement in PM and DM. 【patients and methods】 We selected patients with PM and DM from Jan. 2006 to Oct. 2011 in our hospital. Serum levels of AST, ALT, and CK at diagnosis were analyzed using multivariate analysis of variance method. 【results】 Serum levels of AST, ALT and CK in 42 patients (PM:14, DM:28) were 150.0±30.6 IU/L, 102.9±15.8 IU/L, 2105.6±424.2 IU/L, respectively. Serum levels of AST, ALT, and CK were 98.47IU/L, 71.48IU/L, 545.3 IU/L in patients with DM. In contrast, serum levels of AST, ALT, and CK were 87.03 IU/L, 65.50IU/L, 1342.30 IU/L in patients with PM. These profiles of serum levels of enzymes between DM and PM patients were significantly different ($p<0.005$). 【conclusion】 Our results suggested that liver involvement is found in patients with both PM and DM, especially in patient with DM.

P2-226

A case of dermatomyositis with carcinoma of unknown primary

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Conflict of interest: None

the patient was 57-year-old man. Eyelid edema appeared from January 2011. In march, joint pain in his limbs and loss of muscle strength of proximal line predominance, elevated CK(5000) have also appeared. So we diagnosed it as dermatomyositis. While he has merged the interstitial pneumonia, we started treatment with prednisolone70mg/day. Then muscle weakness and interstitial pneumonia improved remarkably and CK also decreased. At the same time we recognaized cervical lymph node swelling. ClassV, squamous cell carcinoma was detected by the biopsy of the lymph nodes. Althouh neck and chest-abdominal enhanced CT and PET were enforced, the primary tumor was unclear. In addition, we consider the possibility of the metasatasis from pharyngeal cancer and performed randam biopsy of the pharynx under general anesthesia. But there was no malignant findings. So we treated with transvenous chemotherapy. Cervical lymph node dissection surgery underwent in june, only to find squamous cell carcinoma in one lymph node. Primary cancer remains unknown. Afterwards continuing oral chemotherapy and prednisolone7mg/day do not allow worsening of sympotems. It is considered extreamely rare that dermatomyositis can be deveroped due to carcinoma of unknown primary as this case.

P2-227

Two patients with dermatomyositis and peritoneal serous papillary carcinoma

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Conflict of interest: None

Patient 1: A 63-year-old woman had a fever and edematous erythema of both hands and upper arms. The CPK level was 6862 U/L, with decreased muscle strength. The patient was admitted with a diagnosis of dermatomyositis. Bilateral pleural effusion was present. Cytologic examination revealed class V adenocarcinoma. Primary tumor could not be identified. Symptoms of myositis improved after treatment with prednisolone (60 mg). After 8 months, she was readmitted because of ascites. Cytologic examination of the ascitic fluid showed class V adenocarcinoma. After 10 months, the patient died of ileus. Autopsy revealed peritoneal serous papillary carcinoma (PSPC). **Patient 2**: A 64-year-old woman had edematous erythema of the face, dysphagia, decreased muscle strength of extremities, and increased myogenic enzyme levels. Dermatomyositis was diagnosed. An abdominal mass measuring 5 cm in diameter was palpated, and a peritoneal tumor was suspected on CT. After symptoms of myositis responded to treatment with prednisolone (60 mg), a laparoscopic biopsy was performed, leading to a diagnosis of PSPC. The tumor was resected after 3 courses of chemotherapy. The patient is receiving a maintenance dose of prednisolone (7 mg), with no flare-up of rash.

P2-228

A fatal case of non-occlusive mesenteric ischemia (NOMI) developed in dermatomyositis (DM) patient with lung carcinoma.

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Conflict of interest: None

A 73-year-old female had rash on her face and extremities with pruritus, heat and swelling. One month after, she had muscle weakness and got dysphagia and was finally hospitalized. Her skin rash was typical of DM, distributing also on her neck, and chest, and edema was severe in her face and extremities. Manual Muscle Testing was 3/5 on extremities. Creatine kinase was 3672 U/L. Right sided pleural effusion was observed. Her hypoxemia gradually worsened, abdominal distention was developed severely, and metabolic acidosis progressed despite administration of sodium bicarbonate. She was admitted to the intensive care unit and was intubated and continuously hemodiafiltrated. She died on the fifth hospital day. Abdominal pain was absence thoroughly in the course. The autopsy revealed intestinal necrosis thoughout from small to large intestine, without clear thrombi or emboli in mesenterium, and non-occlusive mesenteric ischemia (NOMI) was the diagnosis and considered as the cause of death. Although bronchioloalveolar carcinoma was found in the left lung, it was considered not fatal. NOMI complicated with dermatomyositis is scarce in the literature, however, it could be a complication of DM which frequently involves vasculatures.

P2-229

A case of amyopathic dermatomyositis with intracranial malignant lymphoma diagnosed from generalized seizures.

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Conflict of interest: None

A 48-year-old male was pointed out the rise of CRP and RF by a medical examination in May,2009. He presented skin rashes in bilateral fingers, and visited our hospital in September. Gottron's signs were observed. He showed no myalgia and no muscular weakness. There was no rise of myogenic enzyme and anti-Jo-1 antibody, but KL-6 and SP-D were increased. Tumor markers, including sIL-2R, were normal. Chest CT demonstrated the findings of interstitial pneumonia (IP). He was diagnosed as having amyopathic dermatomyositis (ADM), complicated with IP. General examination revealed no malignancies and other complications. We proposed him to take medical therapy, but he refused to take that because of having no symptoms. On January 22, 2010, he developed sudden generalized seizures. Head CT and MRI revealed space-occupying lesion in the right frontal lobe. Brain biopsy was performed, and the specimen was histopathologically compatible with malignant lymphoma (ML). The diagnosis of intracranial ML (Stage IA) was made. Radiotherapy and 4 courses of chemotherapy were done. It has been reported that approximately 50% of PM/DM cases are complicated with malignancies, but this case is rare. Moreover, our case implies that the chemotherapy may also have a preferable effect on IP comorbid with ADM.

P2-230

A case of polymyositis in a patient with HTLV-1 associated myelopathy and anti-centromere antibody-seropositive Sjögren's syndrome

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Conflict of interest: None

A 57 year-old woman was admitted to our hospital complaining of bilateral leg weakness in August 2011. She was diagnosed with polymyositis (PM) because of electromyogram findings, a high titer of serum muscle enzymes, and histological evidence of lymphocytic infiltration in the the muscle biopsy specimen. In addition, the diagnosis of HTLV-1 associated myelopathy (HAM) was also established based on increased tendon reflex, abnormal reflex and positivity for liquor anti-HTLV-1 antibody. A medical interview revealed that the patient had history of dysphagia due to xerostomia. Sialography revealed apple tree pattern and minor salivary gland biopsy specimen showed lymphocytic infiltration, which were compatible with Sjögren's syndrome (SS). The results of tests to detect autoantibodies revealed positiveness of anti-centromere antibody (ACA). We started administration of 30 mg/day of prednisolone and muscle symptoms immediately improved. This was an interesting case of PM accompanying HAM and ACA-seropositive SS.

P2-231

A case of dermatomyositis accompanied by generalized subcutaneous edema.

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Conflict of interest: None

We describe a 58-year-old woman with dermatomyositis (DM) accompanied by generalized subcutaneous edema. She had suffered from low-grade fever, anorexia, Gottron's papules, proximal muscle weakness and tenderness, and lower limbs subcutaneous edema prior to admission. Her laboratory findings revealed elevation of serum skeletal muscle enzymes, and negative tests for antinuclear antibody and anti-Jo-1 antibody. Muscle biopsy specimen showed myopathic change. These findings were compatible with DM. Her disease was marked worsening after admission and subsequently developed dysphagia, generalized edema and oliguria. The absence of other causes indicated that the generalized edema was associated with DM. Steroid pulse therapy accompanied by oral administration of prednisolone (PSL) with continuous hemodiafiltration improved her disease. Her disease-muscle weakness, dysphagia and anasarca relapsed when PSL was gradually reduced and reached 40 mg/day. Treatment with steroid pulse therapy again and oral methotrexate controlled the generalized subcutaneous edema and the DM again. Generalized subcutaneous edema is a very rare manifestation of DM, and we report the clinical features of DM accompanied by generalized subcutaneous edema adding review of the literatures.

P2-232

Cutaneous polyarteritis nodosa associated with HLA-B39-positive undifferentiated spondyloarthritis in a Japanese patient: a case report

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Conflict of interest: None

We present a 43-year-old man diagnosed with HLA-B39-positive spondyloarthritis who developed cutaneous lesions consistent with cutaneous polyarteritis nodosa (CPN). Previous studies indicated an elevated incidence of HLA-B39 in HLA-B27-negative Japanese patients with spondyloarthritis. This case suggested that CPN may also occur in association with forms of HLA-B39-positive spondyloarthritis. The rarity of this association is emphasized. Therapy with corticosteroid and methotrexate improved both cutaneous lesions and clinical symptoms of spondyloarthritis.

P2-233

A case of sensorineural hearing loss with myeloperoxidase antineutrophil cytoplasmic antibody (MPO-ANCA)-associated vasculitis.

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Conflict of interest: None

[Objectives] We report the case of a 64-year-old man with MPO-ANCA positive who presented with hearing loss. [Methods] The patient presented with a month history of right hearing loss. He was diagnosed otitis media and treated with antibiotics by otolaryngologist, but it was not effective for hearing loss. Ocular hyperemia was pointed out at that time. He complained of weight loss of 10 kg over the past two months, so he was referred to our hospital. He was confirmed to have right sensorineural hearing loss. Furthermore, ophthalmologic examination revealed bilateral episcleritis. No renal involvement was found and chest computed tomography revealed no evidence of lung involvement. The MPO-ANCA level was 129 IU/ml. Although no findings of vasculitis were revealed in histology, we diagnosed this case as MPO-ANCA-associated vasculitis clinically. The patient was started on methylprednisolone therapy at 60mg/day and methotrexate 8 mg/week, which resulted in marked clinical improvement but hearing loss continued. [Results] We report a case of MPO-ANCA-associated vasculitis that seemed to be related to the otitis media and sensorineural hearing loss. In cases of signs of ear involvement and fever, vasculitis should be considered as differential diagnosis.

P2-234

A case of rapidly progressive glomerulonephritis with anti GBM antibody complicated by thrombotic microangiopathy

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Conflict of interest: None

A 61-year-old woman was admitted to our hospital because of high fever and macro hematuria. Her serum creatinine level was elevated as 2.8mg/dL, though she had never detected renal dysfunction until admission. Her serum CRP was elevated as 29.8mg/dL, too. Renal biopsy was performed and it showed crescent glomerulonephritis. In addition, anti GBM antibody was detected, so she was treated with metylpredonisolone pulse therapy followed by oral predonisolone. Three weeks after admission, her platelet count was decreased as 8000/mL and diagnosed as thrombotic microangiopathy. In addition of steroid, she was received plasma exchange. She could recover from thrombotic microangiopathy and leave hospital though she became end stage renal failure and had to undergo hemodialysis. Conclusion: rapidly progressive glomerulonephritis with anti GBM antibody was rarely complicated thrombotic microaniopathy. In spite of such sever complications, if patients recovered life threatening crisis, they could pass relatively stable course.

P2-235

Two cases of C-ANCA-negative Wegener's granulomatosis

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Conflict of interest: None

It is useful for early diagnosis of Wegener's granulomatosis (WG) to measure the level of C-ANCA. This time we report, with bibliographic considerations, two cases of C-ANCA-negative WG throughout clinical course. A 68-year-old male presented with general fatigue, nasal congestion and rhinorrhea. Then he occurred with dysphagia due to multiple cranial nerve palsy by basilar invasion of granuloma. He was diagnosed conclusively by histopathological findings of the sinus tissue. But his renal biopsy did not show any characteristic findings. Next, 66-year-old female presented with fever, weight loss and severe bilateral hearing loss. She was P-ANCA-positive and then was diagnosed by sinus histopathological findings. Her pulmonary specimens by transbronchial lung biopsy showed non-specific inflammatory lesions. But renal biopsy was not done because of normal urinalysis. Both patients got the therapy with prednisolone (PSL) and cyclophosphamide (CPA), but showed bone-marrow suppression due to CPA in-mid course. The former died of acute cholecystitis after that. The latter achieved a remission once and then had a relapse, in dose reduction of PSL, without the elevations of all of serum ANCA levels. She successfully achieved a remission again, and was treated by PSL alone.

P2-236

A case of ANCA associated vasculitis diagnosed by the necrotizing angiitis in the breast cancer.

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Conflict of interest: None

A 62 year-old female was admitted to our hospital complaining

arthralgia and fever. She was diagnosed interstitial pneumonia and received corticosteroid 5mg/day. The arthralgia was getting worse, it is difficult to walk for pain. Clinical findings showed increased levels of C-reactive protein and MPO-ANCA. Computed tomography showed breast mass. Needle biopsy revealed the breast cancer. The operation of this cancer was performed on the15 th day. Therefore we consider, this case was paraneoplastic syndrome. But, after the operation fever had remained and C-reactive protein increased again. The tissue showed the necrotizing angiitis in the breast. Polyneuropathy was appeared gradually on foot. As a result, she was diagnosed ANCA associated vasculitis, and started the therapy. To our knowledge, many cases reported that ANCA associated vasculitis and malignant tumor. However, the case was very rare that tissue of cancer revealed the angiitis. We report this case with some considerations.

P2-237

A case of splenic rupture associated with granulomatosis with polyangiitis

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Conflict of interest: None

A 47 year-old woman was suffered from fever, sinusitis, and refractory uveitis. She was positive for PR3-ANCA. She was clinically diagnosed as having a granulomatosis with polyangiitis (GPA; Wegener granulomatosis). Her clinical symptoms improved rapidly by treatment with oral prednisolone at a dose of 30 mg/day. However, in November 2010, when tapering the steroid dose, she presented with abdominal pain and fever. Ultrasonographic study detected cystic lesion in the spleen. Although the symptoms disappeared once, she had experienced exacerbation of abdominal pain in February 2011. A computed tomographic scan revealed that rapture of the cystic lesion in spleen. Splenectomy was performed and pathological findings showed necrotizing granuloma with infiltration with various inflammatory cells. We report the present patient as a rare case of GPA complicated with splenic rupture.

P2-238

A case report of Churg Strauss Syndrome with Systemic sclerosis

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Conflict of interest: None

We experienced the case of a 46-year-old woman with mononeuritis multiplex. She comorbided bronchial asthma, eosinophilia and erythema on her limbs. A skin biopsy of the *lower limb* lesions showed perivascular diffuse eosinophilic infiltration in the dermis. So we diagnosed her as Churg Strauss Syndrome(CSS). While, she have developed skin pigmentation, depigmentation, and Raynaud's phenomenon for 10 years. Her laboratory data showed positive anti-centomere antigen and negative myeloperoxidase antineutrophil cytoplasmic antibody. Since skin thickening was not present on the trunk, she was considered to have a limited type of systemic sclerosis. Rodman's modified Total Skin Score was 5 / 51. Few reports about CSS comobid with SSc have been published. We report a case of CSS with SSc and some literature reviews.

P2-239

A case of Takayasu arteritis complicated with multiple hepatic abscess and Pyoderma Gangrenosum

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Conflict of interest: None

36-year-old woman presented with a 3-weeks history of fever and painful erythema on her legs. Since they were resistant to antibiotics and NSAIDs therapy, she admitted our hospital. Physical examination showed neck pain, weakness of right radial pulse, and *laterality* of brachial artery *blood pressure*. Radiological test revealed inflammatory stenosis of the brachiocephalic artery, the right carotid artery, and the arch of aorta. Labolatory test showed elevation of CRP level. Then, we diagnosed her as highly active Takayasu arteritis(TA). In erythema lesions, abcess formation was emerged. Skin biopsy was performed and diagnosed as pyoderma gangrenosum(PG) by dermatologist. In addition, liver abscesses were comorbid. We couldn't exclude the possibility of infectious disease, we administered antibiotics and 10mg prednisolone(PSL). After finished adequate antibiotic therapy, we increased PSL to 40mg. Owing to medication, her temperature and CRP level was reduced, and skin symptoms and liver abscess were improved promptly. These findings suggested that PG and liver abcess were associated with TA. We experienced a rare case of TA complicated with multiple hepatic abscess and PG, so we report this case followed by some literature reviews.

P2-240

2 cases of Wegener granulomatosis with pituitary involvement

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Conflict of interest: None

[Case1] The patient is a 25-year-old woman who was diagnosed as Wegener granulomatosis(WG) with gingivitis, skin ulcer, sinusitis, multiple lung nodules and positive PR3-ANCA when she was 23. After given high-dose corticosteroid(CS) and IV cyclophosphamide(IVCY), she had rituximab for her refractory lung nodules and pachymeningitis, and was treated with azathioprine for maintenance. Two years after, pachymeningitis was flared and CS was increased. Two months later she developed headache, polydipsia and polyuria. MRI of the head revealed a pituitary tumor and water restriction test showed central DI. Infliximab was added and increased CS and nasal dDAVP improved her symptoms. [Case 2] A 65-year-old woman developed bilateral exudative otitis media 6 months prior to admission. Otolaryngologists gave her multiple treatments such as CS and antibiotics, but her symptoms remained. After stopping CS, she developed fever and was referred to us. She had a tumor in nasal root, scleritis, sinusitis, diffuse bronchial membrane thickening, lung nodules and positive MPO-ANCA other than persistent fever. She also had polydipsia, polyuria and a pituitary tumor found on MRI of the head. She was diagnosed as WG with DI, and high-dose CS, IVCY and nasal dDAVP were given. Her symptoms are improving.

P2-241

A Case Report on eosinophilic myocarditis Complicated by Central Retinal Artery Occlusion

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Conflict of interest: None

[Objectives] To describe a left central retinal artery occlusion(CRAO) in a patient with eosinophilic myocarditis. [Methods] case report [Results] A 45-year-old women was admitted with dyspnea. She showed eosinophilia and Cardiac hypofunction recognized at arrival. As a result of myocardial biopsy, the patient was diagnosed as eosinophilic myocarditis. Despite being MPO-ANCA positive, skin biopsy of a purpura did not indicate vasculitis. Hypereosinophilic syndrome or Churg-Strauss syndrome(CSS) was suspected, which resulted in the commencement of steroid pulse therapy. On the sixth day of hospitalization, it was discovered that the patient had been affected by visual deterioration in the left eye since several days before hospitalization, leading to a diagnosis of left CRAO after funduscopy. Carotid ultrasound, MRAngio, antiphospholipid antibody, transthoracic ultrasonography, transesophageal ultrasonography and Holter electrocardiography resulted free from any abnormal findings, and was diagnosed as central retinal artery occlusion complicated by eosinophilia. As far as researched, 12 cases have been reported complications of hypereosinophilia that diagnosed CSS and CRAO. Coexistence of CRAO and eosinophilia is an extremely rare case, therefore I would like to report this case.

P2-242

A case of granulomatosis with polyangiitis associated with abdominal periaortitis

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Conflict of interest: None

The case is a 70-year-old woman. Six years ago, she developed ANCA-associated vasculitis with fever, bilateral femoral myalgia and MPO-ANCA elevation and was successfully treated with prednisolone (PSL). Three years later, the disease became exacerbated with similar symptoms to initial onset. She was retreated with PSL 40mg/day, then her symptoms again ameliorated and PSL was tapered. At the age of 70, she suffered from fever, left side facial pain. CT scan revealed soft tissue masses in left maxillary and ethmoidal sinus, pulmonary infiltration, and wall thickness of abdominal aorta. Since infectious aortitis could not be ruled out, she was treated with antibiotics, but not effective. Histological findings obtained by the biopsy of the sinus revealed necrosis accompanied with vasculitis, which led to the diagnosis of granulomatosis with polyangiitis (GPA) associated with periaortitis. The treatment with PSL 10mg/day plus ST mixture and cyclophosphamide 50mg/day was initiated and fairly effective. Although the manifestation of GPA is usually small sized vasculitis, several lines of evidence demonstrated GPA cases complicated with aortic involvement. The present case might be compatible to the same etiology.

P2-243

A case of polyarteritis nodosa with giant cell arteritis diagnosed by an arteria temporalis superficialis biopsy

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Conflict of interest: None

A 74-year-old woman reported experiencing edema and pain in both legs starting in 2008. Upon examination, we observed multiple mononeuritis and purpura that were restricted to the lower limbs; thus, we diagnosed the patient with skin-type polyarteritis nodosa (PN) and started treatment with 30 mg prednisolone. After the patient began taking the medication, the observed skin eruptions subsided; however, the peripheral neuropathy persisted. After we reduced the dose of PSL, the patient returned to the hospital with a fever and severe inflammation. During a follow-up hospitalization, a thorough examination revealed numerous microaneurysms in the celiac artery. Thus, we diagnosed the patient with systemic-type PN and initiated treatment with 48 mg PSL (1 mg/kg) and 500mg intravenous cyclophosphamide starting in January 2010. The fever subsided after the therapy was initiated, but the severe inflammation persisted. Additionally, the patient reported experiencing restiform eminence with tenderness on the left head. So, we performed an arteria temporalis superficialis biopsy. The biopsy revealed invasion of multinucleated giant cells, leading us to diagnose the patient with pathological giant cell arteritis.

P2-244

First case report: isolated testicular vasculitis in a 25-year-old man with IgA nephropathy

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Conflict of interest: None

A 25-years old man presented with an acute right testicular pain. He was noted to have microscopic hematuria and proteinuria for several years. With presumptive diagnosis of a testicular tumor, orchidectomy was performed. The pathology showed vasculitis with fibrinoid necrosis. CRP, ESR and other serological tests were normal. Angiography did not show evidence of systemic vasculitis. IgA nephropathy was diagnosed by renal biopsy. IgA nephropathy almost exclusively involves young adults and predominantly affects the kidneys only. In contrast, HSP affects mostly children and involves skin, gastrointestinal tract, joints, and scrotum as well as the kidneys. This case is the first case of isolated testicular vasculitis in a young adult patient of IgA nephropathy. We speculate Henoch-Schonlein purpura (HSP) as an underlying pathophysiology.

P2-245

A case of pituitary involvement in Wegener's granulomatosis

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Conflict of interest: None

A 51-year-old man, who complained nasal obstruction and nasal discharge, came to our hospital in 2007. His blood test was elevated of CRP and PR3-ANCA. He diagnoted Wegener's granulomatosis by nasal septum biopsy. He was treated with prednisolone and oral cyclophosphamide (CPA). In September 2008, the total given dose of CPA was set to 15g, and it stopped, and changed into azathioprine(AZA). In April 2009, he complained visual field defect and MRI showed a mass in pituitary gland. In the pathology, it was showed glanulomatosus inflammation. It judged that AZA was ineffective and started methotrexate. In April 2010, he experienced

disturbance of vision. MRI showed an increased mass in pituitary gland, moreover CT showed a mass in the lung. In May 2010, he was treated with rituximab. However, in July 2010, he experienced dysarthria and right hemiplegia, diagnoted left cerebral infarction. In Angiography, left internal caroid artery was blockaded by the mass in pituitary gland. Since the effect in immunosuppressive therapy was not expectable, the surgical removal of the tumor was enforced. The new mass in pituitary gland was not seen after the operation. The report of Wegener's granulomatosis which forms a mass in pituitary gland is rare, considers a precious case, and reports.

P2-246

Three cases of hypertrophic pachymeningitis associated with vasculitis

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Conflict of interest: None

Hypertrophic pachymeningitis (HP) is an uncommon disorder, characterized by chronic, inflammatory thickening of dura matter. We present three cases of HP associated with vasculitis: two granulomatosis with polyangiitis (GPA) and one microscopic polyangiits (MPA). In all three cases, headache and cranial nerve involvements were observed, and HP was diagnosed after disease flare. Both GPA cases were positive for PR3-ANCA, and MPO-ANCA was positive in a MPA case. Clinical symptoms and MRI findings responded to immunosuppressive therapy in three cases. Although HP has been reported in 2-8% in GPA patients, its frequency may have been underestimated. Since headache and facial pain are common manifestications between HP and upper respiratory tract involvement of GPA, HP may be missed unless contrast enhanced MRI is performed. We should be aware of HP at the time of GPA diagnosis.

P2-247

A case of sensory ataxic dominant neuropathy associated with microscopic polyangitis

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Conflict of interest: None

A 70 years-old woman was admitted to our hospital on July 27,2011 because of gait disturbance. She had back pain and neck pain suddenly before 1 week, and then had skin eruptions and numbness of upper and lowerextermites. Neurological examination revealed severe degree of disturbance of deep sensation and mild muscular weakness in the extremities. She was diagonosed as microscopic polyangitis (MPA) on the basis of symptoms of mononeuritis multiplex, acute renal failure and by the positive of myeloperoxidase-antineutrophil cytoplasm antibody (MPO-ANCA). The treatment with predonisolone and azathioprine improved unsteady gait, renal dysfunction and decreased the titers of MPO-ANCA. Sensory ataxic dominant neuropathy associated with MPA is rare, although peripheral neuropathy is a common complication of MPA.

P2-248

A case of aortitis syndrome associated with polycythemia vera and focal segmental glomerulosclerosis.

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Conflict of interest: None

A 66-years-old woman had general malaise from June, 2010, she was diagnosed polycythemia vera and treated with bloodletting and hydroxycarbamide. At the same time, she presented urinary protein and occult blood. Physical finding showed a persistent slight fever. Laboratory findings revealed elevated levels of C-reactive protein. Thoracoabdominal computed tomography (CT) scan showed wall thickening of ascending aorta, aortic arch and bilateral carotid arteries. Ultrasound examination of temporal arteries displayed no sign of wall-thicking of temporal artery. In serologic test, infections such as tuberculosis and syphilis were not found, consequently we diagnosed aortitis syndrome. We thought that aortitis syndrome was not related to urinary protein and occult blood, because of no sign of renal artery stenosis in CT scanning and Ultrasonography. Thereby we practiced renal biopsy and this specimen displayed focal segmental glomerulosclerosis (FSGS). We treated with 45mg/day predonisolone to these diseases. Subsequently, wall-thicking of carotid arteries in Ultrasonography, and proteinuria and occult blood were improved. A case of aortitis syndrome associated with FSGS is rare, and thereby this leads us to think about an immunologic mechanism.

P2-249

Two interesting cases mimicking IgG4-related systemic disease

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Conflict of interest: None

[Background] Recognition of IgG4-related systemic disease (IgG4-RSD) has grown and expanded to specific disease entities across most medical specialists, yet most practitioners are probably still unaware of this disease spectrum. Clinicians should understand the broad range of findings associated with IgG4-RSD and know "IgG4-RSD mimickers". We encountered two cases mimicking IgG4-RSD that gave us an important lesson. [Case1] A 35-year-old man presented with cervical, auricular, and bilateral hilar lymphadenopathies. Serum levels of IgG4 were elevated: 171 mg/dl (9.2%). Lymph node biopsy from the neck revealed the pattern of sarcoidosis, but finally resulted in a positive culture of *M. tuberculosis*. Diagnosis of tuberculous lymphadenitis (TBL) was made. [Case2] A 75-year-old man presented with multiple subcutaneous nodules. He rarely manifested constitutional symptoms of fever or weight loss. Although serum levels of IgG4 were low, PET study showed high FDG-uptakes not only in subcutaneous nodules, but also in bilateral submandibular gland, mesentery, and periaortic lesions, which partially resembled IgG4-RSD. Subcutaneous nodule biopsy revealed marginal zone B-cell lymphoma (MZL). [Conclusion] In diagnosing IgG4-RSD, the possibility of TBL and MZL should be considered.

P2-250

A case of sclerosing mesenteritis presenting with a single discrete abdominal mass

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Conflict of interest: None

Sclerosing mesenteritis (SM) is a rare idiopathic primary inflammatory and fibrotic disease that affects the mesentery. It was recently described an association with elevated serum IgG4 and/or autoimmune pancreatitis in some patients with SM, suggesting a possible role for IgG4-related immunopathologic processes in the pathogenesis of this disease. Here we report a case with possibly IgG4-related SM. 75 years-old male was referred to the other hospital due to palpable abdominal mass. As the combination findings of CT and PET scanning suggested that his abdominal tumor was malignant lymphoma, he was referred to our hospital. Although accurate pathological diagnosis was not obtained from initial biopsy at laparotomy, repeated exploratory abdominal surgery was performed and he was diagnosed with SM. Additional immunohistochemical study revealed abundant tissue infiltration of IgG4-positive plasma cells in the biopsy specimen, in spite of the lack of serum IgG4 elevation. He was treated with prednisone for eight months and moderate response was obtained. Further analysis of similar cases with solitary MS should be necessary to delineate a disease spectrum of IgG4-related autoimmune disease.

P2-251

A case of IgG4-related disease complicated by tumor in piriformis muscle

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Conflict of interest: None

A 67-year-old male complained of the left submandibular in Octobar 2010. The mass was resected at Osaka Medical Collage. Histopathological findings was as follows; 1) infiltration of lymphocytes and plasma cells in the submandibular grand 2) fibrosis and sclerosis in the interstitial tissue 3) obstructive phlebitis 4) the percentage of IgG4 positive cells in plasma cells was 30%. The serum levels of IgG4 was 128ng/dl. He was diagnosed as IgG4-related disease (Mikulicz disease). He was referred to our department. PET/CT image revealed increased activity in the right submandibular grand, the abdominal aorta, bilateral iliac artery, lymph nodes in the pleural and peritoneal cavity, and the left piriformis muscle. He had a dull pain in his stomach and felt slight nausea in March 2011. The serum levels of amylase and lipase rose to 230U and 603U, respectively. CT and MRI of the abdomen showed the swelling of the pancreas and tumor in the pancreas head. Endoscopic ultrasound-guided-fine needle aspiration biopsy of the pancreas revealed no histological picture of malignancy. Prednisorone 40mg/day was initiated, and clinical and laboratory findings were improved. PET/CT image 6 month after the treatment showed decreased activity in the "hot" lesions including the left pirimormis muscle.

P2-252

Five cases of IgG4-related disease without pancreatic lesion

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Conflict of interest: None

[Background] Although IgG4-related diseases have been recognized as a new entity of autoimmune diseases, their diagnosis and treatment have yet to be determined. [Objectives and Methods] We examined clinical courses and pathologies in 5 patients with IgG4-related disease and 1 RA patient with elevated serum IgG4 levels. [Results] Case1: 77 years female with hypoalbuminemia and tubulointerstitial nephritis was diagnosed by lip and kidney biopsy. Case2: 67 years male with hypopituitarism and prostatitis was diagnosed by prostate biopsy. Case3: 62 years male was diagnosed by kidney biopsy, which was performed because o! f positive gallium scintigraphy. Case4: 54 years female with Mikulicz disease was diagnosed by lip and submandibular biopsy. Case5: 67 years female was diagnosed by typical organ involvement such as salivary gland enlargement and periaortitis without pathological studies. In contrast, infiltration of IgG4 positive cells was not observed in the joint biopsy in RA patient. All cases had organ involvement other than pancreatic lesions and were effectively treated by glucocorticoid. [Conclusions] IgG4-related disease should be considered even in atypical cases, including other rheumatic diseases may be important for further understanding of IgG4-related diseases.

P2-253

A case of IgG4-related acute interstitial nephritis following remitting retroperitoneal fibrosis

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Conflict of interest: None

85 year-old man with remitting retroperitoneal fibrosis was admitted for rapidly progressive kidney injury. He had no family history of rheumatic or collagen vascular diseases, however, he had remote history of tuberculosis. He was diagnosed as IgG4-related retroperitoneal fibrosis because of elevation of serum IgG4 (396 mg/dl) 1 year ago. Because risk of tuberculosis reactivation was considered, administration of corticosteroid was avoided. Though left hydronephrosis disappeared by itself, rapidly progressive kidney injury occurred again. Renal biopsy was not performed because of renal atrophy. He was diagnosed as acute interstitial nephritis by elevation of urinary β2MG and Gallium scan. Methylpredonisolone pulse therapy followed by 20 mg/day oral predonisone was started with improved renal function. Acute interstitial nephritis was considered to be IgG4-relate.

P2-254

A case of IgG4-related retroperitoneal fibrosis with deep vein thrombosis in the right leg

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Conflict of interest: None

61-year-old man was admitted to the hospital with a month history of the swollen right leg accompanied with sharp pain. The former doctors repeated the ultrasound but not found the thrombosis in the lower extremities. Serum level of D-dimer slightly elevated to 1.6 μg/ml after admission and deep vein thrombosis was detected by ultrasound and CAT scan. The patient was treated with anticoagulant and the swollen leg shrunk. Also we found retroperitoneal mass on the right side that involved right femoral vein, and

ureter that resulted in hydronephrosis. The right kidney was not functioning in the renal scintigraphy and a ureteral stent was inserted. The histology of the retroperitoneal mass was diagnosed as retroperitoneal fibrosis which showed fibrotic changes with massive fibroblasts with the infiltration of lymphocytes and plasma cells. The serum level of IgG4 was 150 mg/dL and almost all of the plasma cells were positive for IgG4 by immunostaining. We diagnosed the IgG4-related disease caused the retroperitoneal fibrosis initiated oral prednisone at the dose of 60mg daily. The retroperitoneal mass also shrunk after 2 weeks of prednisone therapy but the right kidney did not resume working in the renal scintigraphy.

P2-255

A case of IgG4-related disease fulfilling criteria of sarcoidosis

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Conflict of interest: None

A 39-year-old man who had uveitis, BHL, elevation of serum lysozyme and negative of TST was diagnosed as sarcoidosis 9 years ago and was treated with glucocorticoid. The uveitis flared in March 20XX and was improved by glucocorticoid therapy. He was aware of swelling of lymph nodes on his neck in May, the biopsy revealed non-specific inflammation. FDG-PET showed swelling and FDG accumulation in bilateral lachrymal, salivary glands, lymph nodes in mediastinum. Contrast-enhanced CT showed diffusely interstitial pattern in the lungs, and multiple defect lesions in the kidneys. He was referred to our hospital in August. We confirmed elevation of serum IgG4 level and infiltration of IgG4-positive plasma cells in the lymph node and sublingual gland, and finally diagnosed him as IgG4-related disease. On the other hand, non-caseating epithelioid granulomas with giant-cells were found in the sublingual gland and lung obtained by TBLB. Oral prednisolone (1 mg/kg/day) treatment improved dramatically swelling of the salivary glands, pulmonary and renal lesions on CT. This case fulfilled criteria of both Mikulicz disease/IgG4-related disease and sarcoidosis. Our interesting case should be diagnosed as IgG4-related disease because of markedly elevated serum IgG4 level.

P2-256

Clinical examination in 5 patients with IgG4-related disease

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Conflict of interest: None

[Objectives] IgG4-related disease, which has shown infiltration of plasmacytes in various organs such as pancreas, salivary gland and lachrymal gland, firstly reporting from our country. It is characterized by IgG4-positive cells infiltrations and increased serum IgG4 levels. We have examined 5 patients with IgG4-related disease. [Methods] We assessed the clinical feature of five patients with IgG4-related disease (male:female=3:2, ave. age:56.3) visited in the outpatient clinic of General Internal Medicine (GIM). Secretary capacity of salibary and lachrymal glands, serum examinations were performed. Three of them were diagnosed as Mikulicz disease. We checked serum amylase, auto-immuno antibodies (Ab) and serum fraction of protein, immunoglobrin and IgG4. All patients were examined by MRCP and salivary glands by MRI. [Results] Secretary capacities of salivary and lachrymal glands were decreased in four of 5 patients. The positive rate of anti nuclear Ab and anti SS-A Ab were each 20%. The MRCP showed no abnormal findings in five patients. The average primary predonine doses were 29mg and all patients were cured containing one case of recurrence. There were no pancreatic and lung abnormalities in patients with IgG4-related disease showing salivary and lachrymal glands swellings.

P2-257

Clinical features and radiological assessment in IgG4-related disease

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Conflict of interest: None

[Objectives] To analyze clinical features and imaging of IgG4-related disease with involvement of multiple organs. [Methods] We retrospectively investigated 7 patients with new-onset IgG4-related disease, who admitted to our division between August 2006 and May 2011. [Results] Average patient age [mean±S.D.] was 72.3±10.5 years at diagnosis. Patients included 5 males and 2 females. Diagnoses included autoimmune pancreatitis in 3 cases, sialadenitis in 4, hypertrophic pachymeningitis in 3, hypophysitis in 1, interstitial pneumonia in 2, pulmonary inflammatory pseudotumor in 1, interstitial nephritis in 1, renal tumor in 2, retroperitoneal fibrosis in 2, and multiple lymphadenopathy in 5. Laboratory data were as follows: serum IgG4 (725.9±856.7mg/dl), IgG (3090.4±2261.0mg/dl), IgG4/IgG ratio (20.1±11.1%), and CRP (0.25±0.25mg/dl). Brain MRI in 5 cases revealed pachymeningitis in 3 cases, but no symptoms in 2 cases. FDG-PET in 6 cases revealed multiple regions of high FDG accumulation. FDG-PET after treatment in 1 case showed decreased FDG uptake. Almost all of the patients responded well to moderate steroid therapy. In conclusion, FDG-PET could be useful for evaluation of disease activity, while brain MRI was helpful for identifying hypertrophic pachymeningitis in IgG4-related disease.

P2-258

Three cases of IgG4-related orbital disease

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Conflict of interest: None

We here report three cases of IgG4-related orbital disease. (Case 1) A 69-year-old man noticed a mass lesion in right upper eyelid and received an operation for the removal of the mass. A histopathological examination revealed the accumulation of IgG4 positive plasma cells (IgG4/IgG ratio:40%). The serum level of IgG4 was 178mg/dl. (Case 2) A 75-year-old man received an enucleation of right orbital mass because of right upper eyelid swelling. A histopathological finding revealed an accumulation of IgG4 positive plasma cells (IgG4/IgG ratio:40%). The serum level of IgG4 was 666mg/dl. Gallium scintigraphy showed hot spots in right parotid gland, bilateral submandibular glands, neck and hilar lymph nodes. (Case 3) A 64-year-old-man received an excision of right orbital mass because of right upper eyelid swelling and dou-

ble vision. A histopathological feature showed IgG4 positive plasma cells (IgG4/IgG:51.1%). The serum level of IgG4 was 539mg/dl. Gallium scintigraphy showed an accumulation in bilateral hilar lymph nodes, right side of thoracic vertebrae and ileocecum. We suggested that a histopathological examination and serum IgG4 concentration were important for the diagnosis of IgG4-related disease in orbital mass lesions.

P2-259

An elderly case of chronic active Epstein-Barr virus infection with mixed cryoglobulinemia

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Conflict of interest: None

A 76-year-old female was admitted to our hospital due to sustained fever, anemia, numbness of lower limb and liver dysfunction. In July, 2006 elevated of atypical lymphocytes was found together with EBVCA-IgM negative, VCA-IgG positive and EBNA-IgG negative when she was admitted to treat for chronic sinobronchial syndrome. In October, 2007 liver dysfunction and low grade fever appeared. We found coldness and purpura in bilateral foot, elevated rheumatoid factor and cryoglobulinemia. Moreover, the titer of EB virus antibodies were EBVCA-IgG x10240, EA-DR IgG x2560 and EBNA-IgG x10, respectively. The EBV-DNA level of peripheral blood was $4.7x10^4$ copies/ml. EBV infected not only B cells but also T cells and NK cells. Southern blotting confirmed the monoclonal proliferation of EBV-infected cells. We diagnosed as chronic active Epstein-Barr virus (CAEBV) infection with mixed cryoglobulinemia. We did not choose intensive therapy using steroid, immunosuppressant and anti-cancer drug, because the risk of infection should be considered. In July, 2008 she was suffered from recurrent hemosputum with severe respiratory failure and thrombocytopenia caused from CAEBV infection and she finally died. Here, we present a rare case in elderly patient of CAEBV infection with cryoglobulinemia.

P2-260

The septic elbow arthritis caused by *Candida albicans* in a patient with SLE; a case report

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Conflict of interest: None

A 45-year-old woman presented with painless swelling on her left elbow in Nov. 2009. She was diagnosed with systemic lupus erythematosus (SLE) on 1976, and she has continued to take corticosteroids for 34 years. Several times of arthrocentesis was performed for the painless tumor of her elbow. As the examination of the culture of the joint fluid was negative for bactria and mycobacterium infection, we continued to make arthrocentesis on the assumption that it might be caused by chronic synovitis. Because the symptoms become worse, surgical debridement with complete excision of her bulky tumor was performed eight months after the emergence of symptoms. Specimens of the joint fluid obtained at surgery showed growth of *Candida albicans.* After surgery, treatment with oral fluconazole was started. One month later she is completely asymptomatic. We reports an unusual case involving bulky tumor of the elbow joint caused by infection with *Candida albicans.* This case was obtained complete remission by the combination of surgical resection of bulky tumor and drug therapy. In the case of atypical arthritis lack of acute inflammation, we need to consider fungal infection as well as mycobacterium infection as differential diagnosis.

P2-262

Pathogen associated molecular patterns (PAMPs) of gram positive coccus can alter immune response

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Conflict of interest: None

[Oblectives] Septic arthritis due to gram positive cocci is a very harmful destructive joint disease and may occur in the patients with rheumatoid arthritis (RA) under immune-suppressive status. Toll-like receptor (TLR) can sense lipoteichoic acid (LTA), a lipoprotein derived from the pathogens, and induce inflammation via activation of macrophages. This study was designed to clarify the molecular mechanism of LTA-mediated response of macrophages. [Materials and methods] Bone marrow-macrophages were stimulated by soluble LTA (sLTA) (1μg/ml). Total RNA was isolated after 0, 1, 3 hours of exposure and reverse transcribed into cDNA. mRNA of cytokines, TLRs and TLR-associated molecules was amplified with the use of its primer at each times and quantified by real-time qPCR. [Results] sLTA increased significantly mRNA levels of TNF-α and IL-1β ($p<0.05$). mRNA levels of TLR2 in stimulated cells was higher than in control cells and mRNA levels of TLR6 in stimulated cells were not differ from in control cells. [Discussion] Although TLR2/6 heterodimer mainly can act as the receptor of LTA, discrepancy between mRNA level of TLR2 and TLR6 after stimulation by LTA may imply the inhibitory mechanism relating of self-protective mechanism of immune system in arthritis and the allied conditions.

P2-263

Quantitative evaluation of periprosthetic infection by real time PCR: a comparison with conventional methods.

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Conflict of interest: None

[Objectives] Recent several studies have demonstrated the limited accuracy of conventional culture method for diagnosing periprosthetic infection. We have applied real-time PCR assay for a rapid bacterial identification around implant, and reported its utility. On the other hand, a capability of quantification is also useful feature of this assay. The aim of our study was to validate the usefulness of quantitative analysis using real-time PCR of clinical periprosthetic infection cases in comparison with more established tests such as CRP, microbiologic culture, and histopathology. [Methods] 49 cases of suspected infection or aseptic loosening that had undergone surgery were reviewed retrospectively. Universal PCR assay was used for quantitative analysis. The difference of threshold cycles between clinical samples and negative control (ΔCt) in each case was calculated. [Results] We confirmed that quantification by universal PCR based on the ΔCt correlates with the preoperative CRP level, and is associated also with the microbiologic culture results and pathological severity. In cases of sus-

pected infection, quantitative evaluation by intraoperative real-time PCR should provide useful information that would assist with decision-making, i.e. whether to conduct a one or two-stage revision.

P2-264

The efficacy of measurement of CD64 on neutrophils in perioperative patients with RA (The evaluation in single-instituition; the second report)

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Conflict of interest: None

[Objectives] To evaluate the efficacy of CD64 measurement on neutrophils in perioperative stage in RA patients. [Methods] 15 RA patients received orthopaedic surgery in Niigata University Medical and Dental General Hospital were selected. Surgeries were 7 in TKA, 3 in THA, 1 in femoral head replacement, 1 in toe plasty, 1 in debridement after chronic infection in hip, and 2 in debridement after knee purulent arthritis. Eight cases were treated with biologics. Blood samples were sujected to measure CD64 on neutrophils before and 1, 2, and 3 weeks after surgery and each value and ratio of change was analyzed. The cutoff value was determined 2000 molecules/cell. [Results] Ten cases were negative, 2 in false negative, 1 in positive, and 2 in false positive. The average of CD64 except positive 1 case were 1036 before surgery, and 1280, 1068, 1007 after 1, 2, and 3 weeks after surgery. The ratio of change was 1.23, 1.07, and 0.99 after 1, 2, and 3 weeks after surgery. Three cases (5 samples) exceeded cut ff value and 2 cases of them were observed 1 week after surgery, but the ratio of change was less than 2.5. The others were observed in 1 positive case (purulent knee arthritis). [Conclusion] Our data suggest that the monitoring of CD64 is useful to determine postoperative infection.

P2-265

Study in patients with rheumatic disease (RD) complicated with infection who required hospitalization

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Conflict of interest: None

[Objectives] 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 pts with RD complicated w/ infection from July 2010 to June 2011, we assessed disease states, immunosuppressive therapy, & pathogenic microorganisms. Pneumonia accounted for ca. 60% of the cases, ca. 30% of which were atypical pneumonia, the 2nd most case following bacterial pneumonia. Therapy w/ a single steroid or MTX was more often performed than that w/ potent biologicals. The infection rate was relatively high for ETN among biologicals. [Results] Therapy w/ oral steroids or MTX, mainly controlled by pts, was associated with higher infection risk than that w/ biologicals adequately controlled at the hospital. Similarly, there were relatively more pts using self-injected biologicals among those using biologicals. Very high infectious complication rate among pts using a single steroid was noteworthy. The recent rapid advance of 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.

P2-266

Infectious disease in the patients with rheumatoid arthritis and connective tissue disease in our hospital

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Conflict of interest: None

[Objectives] [Methods] To evaluate the clinical features of infectious diseases in patients of our department, we retrospectively analyzed clinical data of 51 hospitalized connective tissue disease patients who had developed infections from 2006 to 2010. [Results] The mean age was 61.9 years old (36 female and 15 male). RA is 27 cases (mean age was 58.0), SLE was 7 cases (mean age was 47.7), polymyositis (PM) / dermatomyositis (DM) is 3 cases. Corticosteroid was used in 43 cases (average dose of prednisolone was 6.1mg for RA and 5.1mg for SLE), the other immunosuppressive agents was used in 33 cases, and biologic agents was used in 12 cases. The average level of albumin value was as follows; RA: 2.91 mg/dl and SLE: 3.0 mg/dl. The average lymphocyte counts of RA was 756.7/μl and those of SLE was 1157/μl. Diabetic complications were observed in 8 cases of RA and none of SLE. The profile of infectious diseases are as follows; pneumonia: 30 cases, sepsis: 10 cases, gastroenteritis: 10 cases, peritonitis: 1 case, and cellulitis: 1 case, and so on. 10 cases of the infectious disease-related death were observed.

P2-267

The assessment of the severe infection risk in patients with connective tissue diseases

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Conflict of interest: None

[Objective] Many patients who have trouble with connective tissue diseases die because of infection. We research our ambulatory patients who got hospitalized with infection. [Subjects and Methods] 171 patients got hospitalized from September 2010 to September 2011 and 50 of them (9 male, 41 female) result in hospitalization with infection. We analyzed their focus of infection, base disease, therapy, and laboratory data (WBC, Lym, CRP, and IgG). [Results] 50 cases are 16 RA, 10 SLE, 9 angitis, 4 PMR, and 11 others. 2 patients died. 23 had respiratory infection, 8 had urinary-tract infection, 7 had digestive tract infection, 4 had skin infection, and others. 48 took steroid, 17 took immune suppressor, and 3 took biological drug. 27 had CRP over 10 and all of 27 took

steroid. 28 took steroid over 7.5mg/day. [Conclusions] The first reason of infection was respiratory infection and the second was urinary-tract infection. Especially, we need to pay attention to the patient who takes PSL over 7.5mg/day with infection.

P2-268

Analysis of infectious events in connective tissue diseases. Effects of corticosteroids and glucose intolerance.

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Conflict of interest: None

[Objectives] To clarify effects of corticosteroids and glucose intolerance on infectious events in connective tissue diseases. [Methods] Patients (1170) with various connective tissue diseases in our department were studied retrospectively. [Results] 1, One hundred fifty seven cases had infections (pneumonia 23%, urinary tract infection 24%, herpes infection 13%, cellulites 5%). 2. Patients with infection showed higher doses of corticosteroids, higher rates of immunosuppressive agents/glucose intolerance/renal insufficiency/pulmonary damage than those without infection. 3. Patients with more than 15mg/day of prednislone revealed had significantly higer infection rates. Conclusion) The rate of infection in connective tissue diseases are still high. Patients with higher age, renal/pulmonary damage, and glucose intolerance should be monitored frequently.

P2-269

The factors of infection in microscopic polyangiitis patients with induction therapy

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Conflict of interest: None

[Objectives] We report the risk factors of infection in microscopic polyangiitis (MPA) patients with induction therapy. [Methods] We assessed whether clinical and laboratory findings correlate to number of days during the treatment of antibiotics, antimycotic agents or anti-cytomegalovirus agents in 33 MPA patients. ⊿IgG was a parameter defined as the difference of serum IgG between before induction therapy and at the nadir level during the therapy. [Results] The mean of age and initial PSL dose were 69.7±11.5years old, 50±12mg, respectively. Remission rate was 87.9%. The percentage of steroid pulse therapy, immunosuppressive therapy, and γ-globulin supplementation therapy were 34.4%, 45.5%, 62.5%, respectively. Mean days with antibiotics, antimycotic agents and anti-CMV agents were 20.8±22.2days, 18.4±27.1days, 7.6±13.1days, respectively. The number of days during the treatment of antibiotics was correlated to serum albumin (Alb) and ⊿IgG(p=0.0042, p= 0.0227, respectively). The number of days during the treatment of anti-CMV agents also correlated to serum Alb and ⊿IgG(p=0.0049, p= 0.0072, respectively). Our data suggested that serum Alb and ⊿IgG were risk factors for bacterial and CMV infection in MPA patients with induction therapy.

P2-270

A case of Goodpasture symdrome complicated with thrombotic microangiopathy (TMA)

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Conflict of interest: None

A 58-year-man visited his home doctor with complaints of fever, diarrhea, cough and sore throat. Because of high-fever and oliguria, he was referred to our hospital. Hemodialysis was started urgently because of sever renal failure and anuria (serum Cr 10.5mg/dl). His consciousness was alert. MPO-ANCA and anti-glomerular basement membrane antibody (anti-GBM antibody) were both positive. Culture tests were all negative. Renal biopsy showed diffuse glomerular necrosis. On day 6 after admission, he complained of dyspnea and chest CT revealed bilateral ground glass opacity compatible with alveolar hemorrhage. Therefore, we diagnosed Goodpasture syndrome. Laboratory data showed thrombocytopenia and fragmentation of red blood cells, and elevated serum LDH without decrease in-ADAMTS 13 level. Under the diagnosis of TMA, he was successfully treated with steroid-pulse, intravenous cyclophosphamide and plasma-exchange. After 12 times of plasma-exchange for 2.5 month, his symptoms resolved, however, he needs to continue hemodyalisis. Both MPO-ANCA and anti-GBM antibody antibody prominently declined. We report this case because it is rare that GPS is complicated with TMA.

P2-271

A case of methotrexate-associated pneumonia in a rheumatoid arthritis patient; discrimination between pneumocystis jiroveci pneumonia and drug-induced pneumonia

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Conflict of interest: None

A 78-year-old female was diagnosed with rheumatoid arthritis (RA) based on the presence of polyarthritis and a positive finding for rheumatoid factor and anti-citrullinated protein antibody in early May 2011. Her articular symptoms gradually improved with 8 mg/week of methotrexate (MTX). However, pyrexia and cough developed about 3 months after the start of MTX. A chest X-ray revealed diffuse ground-glass opacity in the middle to lower lung fields, and she was immediately hospitalized. Elevated serum β-D-glucan levels suggested the possibility of pneumocystis pneumonia (PCP). On the contrary, bronchoalveolar lavage fluid findings were compatible with drug-induced pneumonia. High-dose oral prednisone (PSL) and sulfamethoxazole trimethoprim were thus started. The patient's clinical symptoms thereafter significantly improved and the dose of PSL was decreased gradually without relapse. Patient assessments must be based on various factors such as blood samples, image findings and bronchoscopic examinations for a differential diagnosis of pneumonia in a patient with RA treated with MTX.

P2-272

A case of refractory polymyalgia rheumatica that markedly responded to methotrexate (MTX) and etanercept (ETN)

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Conflict of interest: None

[Objectives] Polymyalgia rheumatica (PMR) reportedly follows a good clinical course. We report about a patient with relapse after steroid-related adverse reactions and dose reduction, interfering with long-term steroid use. This patient treated with MTX and ETN was able to successfully withdraw from steroid and have his disease clinically well controlled. [Methods] A 71 year old man had been in good health by nature without any oral medications. In late Nov. 2009, pain occurred in the neck, both shoulder joints and upper arms, back and both femurs. On Nov. 20, an examination at our department of orthopedics revealed positive inflammatory reaction with CRP 3.14, WBC 11200 and ESR 56(/h); the patient was referred to our department on Dec. 14. [Results] With a diagnosis of PMR he started taking prednisolone (PSL) 20 mg/day but developed dyslipidaemia and moon face. Despite early PSL dose reduction, PMR relapsed; MTX and then ETN started. Even after discontinuation of PSL treatment, the disease was well controlled with MTX and ETN.

P2-273

An atypical case of polymyalgia rheumatica (PMR) with marked elevated inflammatory markers in the absence of proximal muscle pain at presentation

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Conflict of interest: None

A 64 year old man developed fever (39°C or higher) and left shoulder pain since November 2010. He visited our hospital in December 2010. Physical examination revealed frozen left shoulder. At this time he had no proximal limb girdle symptoms. His blood test showed elevated levels of WBC (10,000/μl), CRP (19.2 mg/dl) and ESR (156 mm/hour). Systemic investigation did not reveal any malignant or infectious disease. Various autoantibodies including ANCA were negative. In March 2011, as he complained fever, anorexia and weight loss, he was admitted to our hospital. He developed pain on the bilateral shoulders and neck, morning stiffness and proximal muscle pain. FDG-PET showed FDG aggregation around the left shoulder joint, bilateral hip joints and right sternoclavicular joint. FDG-PET did not detect any signs of tumor or inflammation of large vessels. He was diagnosed as PMR. The symptoms responded to treatment with 30mg of prednisolone per day promptly. We report an atypical case of PMR who presented with high fever, unilateral shoulder pain, and marked elevated inflammatory markers without the typical limb girdle features associated with PMR over a 4-month period.

P2-274

A case of reactive scapulohumeral periarthritis which was difficult to distinguish from polymyalgia rheumatica

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Conflict of interest: None

【Case】 The patient was 62 years old male. He attended a local hospital due to hypertension treatment. Right shoulder pain appeared from mid July in2011. The pain progressed to bilateral shoulder and upper arm on late July in 2011. He was given nonsteroidal anti- inflammatory drugs, but he felt ineffective. He went and admitted to our hospital on August 2nd. Laboratory data on admission showed that CRP level was 11.99 mg/dl, ESR was 53 mm/hr, ANA and RF were negative. Contrast MRI showed bilateral scapulohumeral periarthritis. So we considered that his diagnosis was polymyalgia rheumatic, and planned to give adrenocorticosteroid. But he contracted upper respiratory inflammation before admission. Therefore we prospected existence of infection, and gave 2g of azithromycin to him. His symptom disappeared immediately, and CRP level decreased to negative range. He discharged from hospital on August 15th.【Consideration】We experienced reactive arthritis after infection frequently, but case of reactive scapulohumeral periarthritis was rare. In this case, antibiotic was useful, so we could avoid to give adrenocorticosteroid. We felt keenly that enough judgment was important before use of adrenocorticosteroid, because same case may erroneously diagnosed as polymyalgia rheumatic.

P2-275

Clinical, laboratory, and radiological assessment in six patients with mimicking PMR

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Conflict of interest: None

[Objectives] We found out 6 patients with mimicking polymyalgica rheumatica about clinical, laboratory, and radiological assessment. [Methods] Six patients whose PMR diagnosis was confirmed at onset were recruited. When their polymyalgia symptom flared up during tapering of PSL treatments, we examed clinical, laboratory, US, and MR data and reconsider their diagnosis. [Results] 2 of 6 patients were classified with ACR/EULAR2010 Rheumatoid Arthritis criteria. Each of 1 patient were classified with dermatomyositis and SAPHO. 2 patients were not classified with ACR/EULAR2010 RA criteria, but showed characteristic findings of MRI and US for RA. They achieved remission with treatment as rheumatoid arthritis. We needed to reconsider PMR diagnosis when polymyalgia symptom flared up during tapering of PSL treatments.

P2-276

Case Report: Manubriosternal Joint Arthritis Associated With Psoriatic Arthritis- Disease Activity Evaluation By Diagnostic Imaging-

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Conflict of interest: None

46-years-old man who was diagnosed as Psoriasis at the age of 26 years old visited our hospital because of anterior chest pain and multiple arthralgia especially in distal interphalangeal joint. His first symptoms was started as the sharp pain of both lower limbs and arthralgia was continued more than ten years. Despite he received investigations, the diagnoses was not confirmed. Although he treated as intercostal neuralgia with nonsteroidal anti-inflammatory drugs(NSAIDs), his anterior chest pain was increased within the last three months. He admitted our hospital in October 2011.

He showed slightly positive rheumatoid factor(RF) in blood test and distal interphalangeal joint space narrowing in X-ray. We suspected psoriatic arthritis and examined joint ultrasound. Power Doppler signal was found around the manubriosternal joint(MSJ). Association of MSJ arthritis is rarely reported, so we reported this curious case.

P2-277

A case of refractory psoriatic arthritis successfully treated with ustekinumab.

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Conflict of interest: Yes

[Case] A 53-year-old man, diagnosed with psoriatic arthritis (PsA) by a characteristic skin rash and polyarthritis nine years ago. He was treated with SASP and MTX, which showed poor efficacy. IFX was started five years ago and skin lesion ameliorated rapidly. After the 14th administration of IFX, infusion reaction appeared and psoriasis (Ps) was gradually recurred. IFX was switched to ADA two years ago, then Ps was improved again. After the 37th administration of ADA, skin lesion and bilateral ankle joint swelling reappeared. The dosage of MTX was increased from 6mg to 8mg, but his symptom was not improved. Following skin biopsy which confirmed Ps, ADA was switched to ustekinumab (UST). PASI improved (27.1 to 14.2) after its 2nd administration. [Discussion] Recently, it has been suggested that Th17 and Tip-DC (TNF-alpha and inducible nitric oxide synthase producing DC) are involved in the pathogenesis of Ps. Because the differentiation of Th17 as well as Th1 is inhibited by UST, it is reasonable to predict Ps is a target of UST. As UST has just approved for PsA, it may be a first Japanese case report showing efficacy of UST against TNF-I-failure-Ps.

P2-278

Prevalence of psoriatic arthritis in patients with psoriasis: ultrasonogaphic study

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Conflict of interest: None

Background/Purpose: The existing data on prevalence of psoriatic arthritis (PsA) among patients with psoriasis in the literature vary between 5.8 and 40%. Method: To determine the arthritis with ultrasonograply in psoriasis without arthritis. Results: Seven cases among 14 cases are detected with arthritis.

P2-279

A case of knee pustulotic arthro-osteitis treated by total knee arthroplasty

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Conflict of interest: None

Joint destruction with palmoplantar putulosis is rare. A 67-year-old woman presented with 20 years history of skin eruption on the palmar and plantar. Multiple arthritis of the patient rapidly progressed during the past one year, and the patient was diagnosed as pustulotic arthro-osteitis. MRI showed marked increased synovitis in the left knee joint. Consistent with Arthroscopic examination showed massive synovitis in left knee joint. The pathological diagnosis was nonspecific chronic synovitis. An effect was not accepted although treated with biological drags for one year after arthroscopy. Knee joint destruction progressed, and total knee arthroplasty was performed at right side.

P2-280

Successful treatment of TNF inhibitor induced palmoplantar pustulosis with Cyclosporine: A report of 2 Cases

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Conflict of interest: None

【Objectives】 TNF inhibitors are playing a major role in the management of psoriatic arthritis, however paradoxical development of palmoplantar pustulosis (PPP) has been well documented. Although majority of the PPPs are mild and subside with or without discontinuation of TNF inhibitors, some lesions occasionally remain refractory and there is no established strategy to treat this problem. **【Methods】** We report on 2 patients with TNF inhibitor induced refractory PPP successfully treated with cyclosporine. One patient was a 51-year-old woman with psoriatic arthritis treated with methotrexate and infliximab. Seventy months after the initiation of TNF-α inhibitor therapy, she developed PPP. The other patient was a 45-year-old woman with a psoriatic arthritis who developed PPP. Despite discontinuation of infliximab and treatment with topical steroids were tried, their skin eruptions remained and joint diseases flared. Other TNF inhibitors were also tried, but no apparent improvements noted over months until cyclosporine was finally instituted in each case. **【Results】** Cyclosporine is effective in the treatment of TNF inhibitor induced refractory PPP. **【Conclusion】** It is necessary to perform a larger study to confirm the effect.

P2-281

Two cases of SAPHO syndrome with spondylitis who were successfully treated by the use of adalimumab

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Conflict of interest: None

For SAPHO, rather rare seronegative spondyloarthritis, no established therapy has been described yet. We experienced two cases of SAPHO, who obtained immediate pain-relief by adalimumab (ADM). Case 1 is 68 years female. She presented with palmoplantar pustulosis (PPP) at age 45 and had backache from 52. At age 66, she was diagnosed as SAPHO with spondylitis. MRI showed the inflammatory change in lower thoracic spine. Her backache was not relieved by MTX or steroid. In 2011, ADM was started and her VASDAI improved from 72 to 17. Case 2 is 66 years female. Sternocostclavicular hyperostosis (SAPHO) was pointed out at age 38. She developed PPP at age 42 and spondylitis at 58. Sulfasalazine and MTX were not effective. Infliximab started at age 59 was effective for chronic pain for 3 years and then became ineffective. In 2011 ADM was started and her VASDAI decreased to 15 from 71. MRI showed disappearance of STIR high signal between Th 5-6. One third of SAPHO patients have spondylitis.

Chronic axial pain restricts ADL and even cause metabolic syndrome. For such patients, new effective therapy is eagerly needed. Both patients became able to exercise and travel soon after starting ADM, showing the efficacy of biologics for SAPHO with spondylitis that has been rarely reported so far.

P2-282

A case of SAPHO syndrome accompanied with nephrotic syndrome

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Conflict of interest: None

62-year-old man admitted to our hospital with a pain and swelling of left clavicle on July, 2010. He had been diagnosed as SAPHO syndrome on January, 2008, who presented with acne, pustulosis, and hyperostosis, and an oral admission of Methotrexate was perfomed, but he immediately stopped this admission by himself. On admission, he was discharged the pus produced in left clavicle and was perfomed an admission of teicoplanin. On nine days from admission, he was accompanied with nephritic syndrome. Renal biopsy was performed and revealed diffuse mesangial proliferation with IgA deposition. Oral admission of prednisolone (30mg/day) was performed, and the clinical symptom of SAPHO syndrome and nephritic syndrome was improved. In previous reports, renal manifestations are rarely occurred in SAPHO syndrome. In this case, the development of diffuse mesangial proliferative glomerulonephritis with nephrotic syndrome may be related with the abnormalities of immunity of SAPHO syndrome.

P2-283

A case of HLA-B27 negative Ankylosing spondylitis accompanied with optic neuritis

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Conflict of interest: None

[Objectives] A case of ankylosing spondylitis accompanied with optic neuritis. **[Methods]** Case is 37 year-old male. He has no history of sexually transmitted disease and food poisoning. He has no specific family history. In Dec. 2010, he was suffered from neck and back pains, exacerbated at rest. He was referred to the department of rheumatology in May 2011. Physical examinations revealed right elbow and right knee joints were tender and swollen, the left shoulder and left jaw were tender. BASFI, BASMI and BASDAI was 6.1, 3, 3.1, respectively. The modified schober test and the chest expansion test indicated 3.5cm, 1.3cm, respectively. Laboratory data showed that the inflammatory reactions were elevated, chlamydia DNA and antibodies were all negative. The HLA typing showed A2/A26, B7/B62. CT of pelvis revealed bilateral sarcoilitis. MRI of spines revealed syndesmophytes on some vertebrae. The funduscopy showed reddish optic disc bilaterally, and the examination of visual field revealed enlargement of Marriott's scotoma. **[Results]**As Modified New York criteria was fulfilled, NSAID was commenced. However his disease was not enough improved. Thus infliximab (5mg/kg) was introduced. Although the symproms of joints were almost resolved, the ophthalmological findings were not changed.

P2-284

A case of ankylosing spondylitis who needed long time for diagnosis with the main symptom of pyoderma gangrenosum

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Conflict of interest: None

Pyoderma gangrenosum (PG) can be overlapped with RA, hematologic malignancies, Crohn's disease and ulcerative colitis, but the overlapping with ankylosing spondylitis (AS) is rare. We report a case of AS with the main symptom of PG who needed long time for the diagnosis of AS. A 68 year-old woman visited dermatology service in 2006 because of skin ulcer, and was biopsied with the skin resulted in the diagnosis of PG. In December 2007, because chest and back pain worsened in response to decrease of the dose of PSL, she visited rheumatology service suspicious of RA but the diagnosis of only OA was given. In August 2011, Takayasu arteritis was suspected because of BP difference between bilateral extremities and continuous elevation of inflammatory biomarkers, when she visited us. Precise anamnesis revealed back pain since 18 year-old which worsened at the age of 48. Uptake was found at cervical and thoracic vertebrae by FDG-PET and ossification and spur formation at C45, ossification and cube formation of lower thoracic vertebrae, sclerosis of sacroiliac joint, and of facet joints of lumbar vertebrae by CT, which led us to the diagnosis of AS. In conclusion, we reported a case of AS with PG who needed long time for the diagnosis. Precise anamnesis was most important.

P2-285

FDG-PET/CT for detection of enthesitis: A case report of spondyloarthritis

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Conflict of interest: None

The patient was a 52-year old woman with a 30-year history of inflammatory back pain and a 4-year history of polyarthralgia and pain in the planta pedis. On physical examination, no arthritis, psoriasis or tender point of fibromyalgia was noted. Schober test was 2.5 cm, chest expansion 3.3 cm and Mander enthesis index 2. No tenderness in either Achilles' tendon nor planta fascia enthesis was noted. CRP, rheumatoid factor and anti-CCP antibody were normal. Neither X-ray nor foot MRI showed sacroiliitis or enthesitis. She did not meet the European spondyloarthropathy study group classification criteria, modified New York criteria, Amor criteria or CASPER criteria. Only PET/CT detected enthesitis in the planta fascia, hip joints and ischial tuberosity. Patients with chronic pain and negative inflammation including spondyloarthritis tend to be diagnosed with undifferentiated arthritis. PET/CT may be a more useful tool for detection of enthesitis than physical examination, CRP, X-ray and MRI.

P2-286

A case of ulceratve colitis complicated with pyoderma gangrenosum, aseptic subcutaneous abscess and genital ulcer successfully treated with glucocorticoid and infliximab

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Conflict of interest: None

[Objectives] We present a case of ulcerative colitis (UC) which developed pyoderma gangrenosum (PG), aseptic subcutaneous abscess and genital ulcer accompanying flare of UC, which were successfully treated with glucocorticoid and infliximab. [Methods] The patient was 41 years old female who had remitting and exacerbating UC. Her colitis had gradually exacerbated with neck pain, low back pain and chest wall pain for several weeks before visiting us. On her first evaluation, spondylarthritis associated with colitis was suspected. Non-steroidal anti-inflammatory drug was prescribed, which didn't prevent disease progression and she was admitted. On admission subcutaneous fluid of 5 cm in diameter was felt over her sternoclavicular joints, suspected PG of 2 cm in diameter was on her head, and small genital ulcers were seen. Treatment with glucocorticoid and temporal antibiotics were started, and infliximab was introduced with successful tapering of glucocorticoid. [Results] PG is a known complication of UC, with which development of purulent lesions in various parts of the body is seen. In this case disease progression was effectively controlled with glucocorticoid and infliximab.

P2-287

A peculiar image of Gallium-67 scintigram in cutaneous sarcoidosis

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Conflict of interest: None

A 65-years-old man with uveitis was admitted to our hospital in October 2010 due to appear multiple red nodular lesion on the forehead and scalp extensively for 3 months durations. No other skin lesions were ditected any parts other than forehead and scalp. In laboratory findings, CRP was negative, but soluble interleukin-2 receptor (1682 IU/ml), angiotensine converting enzyme (34.4 IU/l) and the lysozyme (24.4μg/ml) were high level. Nodular lesion was biopsied and revealed non-caseating granulomas with epithelioid cells. The chest computed tomography(CT) scan revealed lymph node enlargement on an aorta, we gave him a diagnosis of sarcoidosis. For refer to the leasion of sarcoid, Gallium-67 scintigram was performed. The image of head demonstrated intense Gallium-67 uptake in the scalp matching exactly the skin lesion, it was an interesting image which it look like putting on helmet. When therapy with predonisolone (30mg/day) was started, the eruption and accumulation image of Gallium-67 on the forehead and scalp disappeared.

P2-288

Nasal sarcoidosis as a rare etiology of saddle nose

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Conflict of interest: None

Case report: A 42-year-old woman presented with migratory arthritis and nasal congestion. Nineteen years ago, sarcoidosis was diagnosed by migratory pulmonary infiltrates with histopathologic evidence of non-caseating epithelial granuloma and resolved spontaneously in several years without recurrence. The initial physical examination showed tenderness in the bilateral shoulders. Her nasal appearance was normal. Initial CRP was 3.13mg/dl. Serological studies including ANA, RF, MPO-ANCA, PR3-ANCA and TPHA were all negative. Chest CT showed bilateral trabecular shadows. Gallium scintigraphy showed uptake in the bilateral lower lung field, right supraclavicular and upper mediastinum lymph nodes. Bronchoscopic specimens showed granulomatous infiltration. CRP improved without treatments. However, nasal congestion persisted with progression of saddle nose deformity over 2 months. The anterior rhinoscopic examination exhibited hypertrophic nasal mucosa and histopathology revealed inflammatory granulation. In both specimens, immunohistochemical study of monoclonal antibody against *Propionibacterium acnes* (PAB) were positive, consistent with sarcoidosis. Conclusion: Nasal sarcoidosis is a rare but important etiology of saddle nose.

P2-289

A case of sarcoidosis diagnosed based on renal biopsy, presenting with chronic renal dysfunction and mononeuropathy multiplex.

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Conflict of interest: None

A 77-year-old woman with past history of uveitis was referred to our clinic for renal dysfunction (serum creatinine level 1.3mg/dl) 9 months before admission. She had been suffering from dysesthesia in her distal portion of the extremities for 6 months. She had also noticed lower extremity muscle weakness. She was admitted to our hospital because her renal function progressively declined (serum creatinine level 3.3mg/dl). With the renal biopsy, the diagnosis of granulomatous interstitial nephritis was confirmed. The findings of the nerve conduction study were compatible with mononeuropathy multiplex. The chest CT showed interstitial shadow in the both lung. BALF revealed increase in lymphocyte of 32.0 % and CD4/8 ratio of 13.7. Hyperccalcemia (serum calcium level 10.9 mg/dl) was also documented. With these findings, we confirmed the diagnosis of sarcoidosis and began prednisolone 40 mg/day (0.8 mg/kg/day). Her muscle weakness and renal function gradually improved. Her creatinine level was 1.5 mg/dl three weeks after. Generally, renal and neurologic involvements are reported to occur in less than 5% and 5-10% among sarcoidosis patients, respectively. We report this case because it is rare that kidney and nervous involvements occurred without typical findings for sarcoidosis.

P2-290

A case of muscular sarcoidosis with thymoma and myasthenia gravis

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Conflict of interest: None

We report a rare case of muscular sarcoidosis with thymoma and myasthenia gravis. A 69-year old woman presented with bilateral leg pain and flexion contracture of her fingers. Serum CK level was elevated and muscle magnetic resonance imaging showed high intensity signals on T2 weighted images. Histological studies of gastrocnemius muscle showed non-caseating granulomas, compatible with muscular sarcoidosis. She also had thymoma and myasthenia gravis. After thymectomy she was treated with prednisolone (30mg/day), and her symptoms and MRI imaging improved.

P2-291

A case of refractory adult onset Still's disease (AOSD) successfully treated with etoposide and tocilizumab (TCZ)

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Conflict of interest: None

A 38-year-old woman had suffered from fever, arthralgia, sore throat and skin rash since January 2011. The laboratory findings showed increased levels of serum ferritin and liver damage. She was diagnosed with AOSD and treated with steroid pulse therapy (methylprednisolone 1000 mg/day×3days×2), followed by prednisolone (50 mg/day) and cyclosporine (150 mg/day). However, her symptoms continued and serum ferritin level increased to 10000 ng/ml. She was referred to our hospital and treated with intravenous immunoglobulin, plasma exchange and intravenous cyclophosphamide (500 mg/day) with unfavorable response. After obtaining her informed consent, a pulse therapy of etoposide (200 mg) followed by TCZ (4 mg/kg/2 weeks) were performed. Her conditions and laboratory findings improved. Serum ferritin level decreased to 215 ng/ml.

P3-001

Clinical and Pathological characteristics of rheumatoid arthritis associated with malignant lymphoma: a single center experience.

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Conflict of interest: None

Objectives: We summarize our experience of RA patients accompanied with ML including MTX associated lymphoproliferative disorder. **Methods:** The clinical data of 13 patients with RA associated ML treated at our hospital from 1990 to 2010 was retrospectively analyzed. **Results:** There were 4 males and 9 females with a mean age at ML diagnosis of 62.7years (range: 31 to 85years). The disease durations of RA before the onset of ML were 24 to 420 months (average: 167 months) and 6 patients received MTX. Of these 6 patients, two patients were treated with biological agents (abatacept and tocilizumab, respectively). The histological types were DLBCL in 7 patients, FL in 1 patients, CHL in 2 patients, NK/T-cell lymphoma in 1 patient, subcutaneous paniculitis-like T-cell lymphoma (SPTCL) in 1 patient and NOS in 1 patient. EBV infection was confirmed in 3 patients by means of in situ hybridization. Spontaneous lymphoma regression was observed in 4 patients by discontinuation of MTX alone. Among these cases, two patients were still alive in CR without chemotherapy. Of all patients, 9 patients were alive and experienced long-term CR. **Conclusions:** Our experience was similar to that of other reported series. However, rare histological lymphomas such as SPTCL and NK/T-cell lymphoma were observed.

P3-002

9 cases of lymphoproliferative Disorders in Rheumatoid Arthritis

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Conflict of interest: None

[Objectives] We aimed to know the backgrounds and outcome of lymphoproliferative diseases, which occured during the courses of RA treatments. [Methods] We analyzed retrospectively the data of 9 patients, who were diagnosed as LPD at department of hematology in our hospital since 2006 until 2011. [Results] Patients contain 7 females and 2 males. Their average onset age was 63.6 years old. 8 were diagnosed by pathology, and one was diagnosed clinically. 6 had extranodal lesions at several organs, such as stomach, lung, salivery gland, skin and spine. The average RA history was 8.9 years. 6 were Stage III or IV, and 3 experienced TKA. However three were early RA. At the onset, 7 were treated with MTX, with SASP only, 1 with CsA, and 4 with biologics(4IFX, 1ETN, 1TCZ). All cases were treated with low dose PSL. The average time of follow up was 19 months. Among 3 who were followed only by discontinue of immunosuppressants, 2 kept CR and one kept PR. 3 were treated with R-CHOP, 2 only with ritximab and one with radiation. All treated group kept CR. One could discontinue RA treatment. 8 were treated with low dose PSL, 3 with TAC, 4 with SASP and 3 with BUC.

P3-003

Characterization of lymphoproliferative disorder in 8 rheumatoid arthritis patients.

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Conflict of interest: None

[Objectives] Rheumatoid arthritis (RA) is a risk factor of malignant tumor including malignant lymphoma. Methotrexate (MTX) is a key drug in treatment of RA, but a portion of patients treated with MTX may develop lymphoproliferative disorder (MTX-LPD). [Methods] We analyzed the data of 8 patients with RA and LPD, who were admitted to our hospital from January 2010 to July 2011. [Results] All patients were administrated with MTX and 4 patients were received biological DMARDs. Mean age was 65.8±8.3-year-old, mean disease duration of RA was 15.5± 12.9 years, mean total dose of MTX was 1120.5±472.3 mg, and mean duration of MTX treatment was 2.8±1.5 years. The pathological diagnoses were 5 diffuse large B cell lymphomas, 1 Hodgkin lymphoma, 1 T cell-rich large B-cell lymphoma and 1 undifferentiated LPD. In 4 out of 7 patients analyzed, the presence of Espstein-Barr (EB) virus was detected in LPD. Treatment was chemotherapy in 7 patients and withdrawal of MTX in a patient. All patients obtained good responses with treatment. MTX−LPD is classified as other iatrogenic immunodeficiency-associated LPD in WHO classification 2008. It is difficult to determine the relation between LPD and MTX, because clinical symptoms of MTX-LPD are not differed from other lymphoma.

P3-004

The clinical feature of Organizing Pneumonia with RA

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Conflict of interest: None

[Aim] Organizing pneumonia(OP) developed frequently in patients with rheumatoid arthritis(RA). It is important to differentiate OP from infectious pneumonia. Clinical features of OP in RA were not fully clarified. The aim of this study was to clarify clinical features of OP in RA. [Method] We retrospectively reviewed medical records of 499 RA out-patients at Dokkyo Meddical University Hospital. OP was diagnosed based on radiographic images, clinical course including response to antibiotics or corticosteroid and pathological findings. [Result] Among 499 RA patients, 19 RA patients (3.8 %) developed OP. (7 male, 12 female, age; 61±8(mean ±SD)). One Patient was diagnosed as RA after OP occurred. Three patients developed OP after infection. Half of OP in RA patients had low disease activitiy of RA when OP was developed. Therapies for RA at the onset of OP were predonisolone, MTX, SASP, biologics in 10, 11, 2 and 5 cases, respectively. Notably, some patients developed OP during successful treatment for RA with biologics, and re-administration of the agents did not induce OP. [Disscussion] OP is a frequently developed pulmonary complication in RA, which developed in approximately 4 % patients regardless of RA activity.

P3-005

Analysis of predictors of progressive RA-related interstitial pneumonia in early elderly-onset RA (EORA) by Chouju registry of Rheumatoid Arthritis on Non-biological and biological DMARDs for Elderly patients (CRANE)

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Conflict of interest: Yes

[Objective] To evaluate clinical predictors of exacerbation of IP associated with early EORA. [Methods] We analyzed early EORA(<3 years from onset) by records of CRANE, a monocentric prospective cohort of EORA. [Result] 80 early EORA were analyzed for mean period of 96 months. Mean age was 74 years old, disease duration was 0.9 years, DAS-28 score was 6.49, and HAQ score was 1.23. At the enrollment, 22.5% had existing IP, and 58.8% had high (>15) titer of ACPA. 7.5% exhibited exacerbation of IP and required administration of glucocorticoids. The mean duration from onset of RA to exacerbation of IP was 18 months, and mean DAS28 score at that time was 5.77. In the exacerbated group, all had high titer of ACPA. Existing IP was seen in 83% and they were refractory to glucocorticoid therapy, required immunosuppressant or biological DMARDs. Among the baseline characteristics, significantly more patients had existing IP and high titer of ACPA in the exacerbated group than non-exacerbated group. Univariate analysis (Kaplan-Meier method) showed these two factors predict the exacerbation of IP significantly. [Conclusions] Existing IP and high titer of ACPA indicate risk of exacerbation of IP with early EORA, especially with high disease activity.

P3-006

Predictive factor of interstitial lung disease in rheumatoid arthritis

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Conflict of interest: None

[Objectives] To investigate predictive factor of interstitial lung disease (ILD) in rheumatoid arthritis (RA) patients. [Methods] 76 patients with ILD in RA were treated at our hospital and followed up at least one year. HRCT parameters and other clinical features were retrospectively analyzed. [Results] All 76 patients had abnormal HRCT findings which were consistent with ILD. In HRCT findings, irregular linear opacities were found in 92.1%, ground-glass opacity 27.6% and honeycombing 18.4%. There were significant differences in honeycombing at the initial presentation between progressive ILD and asymptom ILD (100% vs 16.9%, p=0.0003). In progressive ILD patients, there were no differences in the methods of immunotherapy, however patients started immunotherapy at the earlier phase showed improving of ILD. Conclusion. HRCT focused on honeycombing is a usefil predict factor of the outcome of ILD in RA.

P3-007

Rheumatoid nodules confirmed pathologically by video-assisted thoracic surgical (VATS) biopsy in a woman with rheumatoid arthritis (RA)

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Conflict of interest: None

A 70 years-old woman develop finger arthralgia in 1993. Following diagnosis of RA, treatment with MTX was started on May 2000, which resulted in favorable condition. Lymphadenopathy in the abdominal cavity and the neck appeared on October 2006. Pathological findings showed diffuse large B cell lymphoma, and chemotherapy with R-CHOP was carried out, which resulted in complete remission on January 2008. DMARDs was interrupted in the meantime. Since August 2008, her arthritis flared and treatment including leflunomide, tacrolimus and low-dose steroid, which controlled inadequately her symptoms. The nodular shadow became larger in size on January 2010, and the patient presented cough and sputum. Lung biopsy specimen by VATS revealed typical findings of rheumatoid nodules. Following discontinuation of leflunomide and tacrolimus, 500 mg of rituximab was administered twice. The activity of RA and the nodular shadow in the lung showered improvement, and subcutaneous rheumatoid nodule disappeared concomitantly.

P3-008

Association between atherosclerosis and chronic kidney disease in patients with rheumatoid arthritis; observational cohort study.

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Conflict of interest: None

OBJECTIVE To determine whether the disease activity of RA contributes to arteriosclerotic development via CKD. METHOD We performed a prospective cohort study of the observation period for 12 months in patients who fulfilled American College of Rheumatology criteria for RA. Increments of brachial-ankle pulse wave velocity (baPWV) were measured as primary outcome. Decline of estimated glomerular filteration rate (eGFR) was measured as secondary outcome. As an exposure factor, we analysed Disease Activity Score 28. To correct cofounding among each covariates, we performed logistic regression analysis included age, gender, NSAIDs use and classical risk factors of atherosclerosis. RESULTS Increments of baPWV was significantly greater in the patients with high disease activity of RA and diminished eGFR. The patients with high disease activity had lower eGFR than those of patients with low disease activity of RA. CONCLUSIONS Our data implyed that the disease activity of RA contributes to arteriosclerotic development via CKD.

P3-009

What we should learn from three cases who died during the treatment of rheumatoid arthritis

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Conflict of interest: None

[Introduction] We report three cases who died during RA treatment with reviews of the literatures. [Case reports] Case 1. A 77-year-old man. After one year RA treatment with MTX, he developed acute exacerbation of interstitial pneumonia by respiratory infection. Chest CT showed remarkable diffuse ground-glass opacity and infiltrative shadow in the bilateral lung fields. He was hospitalized immediately, but he died on ninth day. Case 2. A 71-year-old woman. She had been treated with adalimumab and MTX for one year, and was hospitalized due to acute exacerbation of interstitial pneumonia. Chest CT showed ground-glass opacity pneumonia image in almost lung field. The treatment with antibiotics, steroids, the gamma globulin was ineffective and she died on the fifth day. Case 3. A 67-year-old man. At three months after the treatment with adalimumab and MTX, stage 4 gallbladder cancer associated with metastases in the liver and lymph nodes was revealed, for which he underwent chemotherapy for tree months before he died. [Discussion] Alarcon and coleagues reported old-age, diabetes, lung diseases, the use history of the antirheumatic drugs, and hypoalbuminemia are risk factors for pulmonary disorders by MTX. We also need the cautions to the malignant tumor before and after RA treatment.

P3-010

Inhibition of articular destruction in patients with rheumatoid arthritis in remission with non-biological disease-modifying antirheumatic drug monotherapy

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Conflict of interest: None

[Aims&Method] We reported that DAS28-ESR remission of RA was achieved in 84 out of 538 patients with non-biological DMARDs (non-BIO), as monotherapy in 55 and in combined therapy in 29. In this study, we investigated inhibition of articular destruction in RA with remission with non-BIO monotherapy. [Results] Remission was achieved with SASP in 20, bucillamine (BUC) in 17, MTX in 17, and leflunomide (LEF) in 1. The DAS28 score changed from 4.80 to 1.60 in the SASP group, from 4.35 to 2.11 in the BUC group, and from 4.74 to 1.93 in the MTX group, significantly, and yearly modified Total Sharp Score (mTSS) changed from 6.3 to 0.04 ($P<0.10$), from 33.6 to 0.49 ($P<0.01$), from 6.51 to 2.06 ($P<0.05$), respectively. Analysis stratified by duration of disease (≦6 months or >7 months), the ⊿mTSS was shown a greater inhibitory effect in early RA ($P<0.10$). Correlations analysis of backgrounds related to ⊿mTSS in patients with clinical remission revealed duration of disease ($P<0.01$) and swollen joints ($P<0.05$) as significant factors. [Conclusions] Satisfactory inhibition of articular destruction was seen in early RA with remission of RA with non-BIO monotherapy disease. We can anticipate that use of T2T will provide improved remission rates and inhibition of articular destruction in RA.

P3-011

A Multi-Center Study of the Usefulness of DMARDs (Bc) Therapy for Early RA

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Conflict of interest: None

[Objectives] As a first-choice of DMARDs, Bucillamine (Bc) was administrated to early rheumatoid arthritis (RA) patients and the outcome was prospectively studied (Sapporo Non-Biologic DMARDs Therapy on the Window of opportunity for RA Clinical Study: SNOW Study). [Methods] A total of eighty nine patients were enrolled in this study. All patients fulfilled the JCR criteria for the diagnosis of early RA, and were prospectively followed up for 6 – 48 months after starting Bc. And, we analyzed a remission rate using the ACR / EULAR definitions of remission in RA clinical practice settings. [Results] Mean DAS28-ESR values were 4.8 at the baseline, and 2.4 after 48 months of treatment. Remission rate according to the European League Against Rheumatism (EULAR) criteria (DAS28-ESR) was seen in 57.1% of patients after 48 months of treatment. It was similar to the value determined by the ACR / EULAR definitions of remission. Fifty-two percent of patients continued Bc at 48 months, while in some patients Bc was continued in combination with MTX. These results indicate the usefulness of Bc therapy for early RA.

P3-012

Remission of early rheumatoid arthritis by using disease-modifying antirheumatic drugs and evaluation of their efficacy

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Conflict of interest: None

[Objectives] To confirm the efficacy of additional treatment with MTX in patients poor response to SASP or bucillamine(BUC) and to determine its efficacy in early administration. [Methods] We assigned 24 early RA patients to an SASP group(S group) or a BUC group(B group). The patients received monotherapy for 3 months, and those showing a poor response received additional treatment with MTX for 1 year. [Results] The treatment efficacy

was evaluated in 19 patients;5 patients dropped out of the study. MTX was administered to 7 patients. The overall good response and remission rates were as high as 63% and 58%, respectively. In the S group, remission rate with a single drug was 40%, and it increased to 70% with additional MTX treatment, which indicated the efficacy of combination therapy. Patients with a more than 30% decrease in CRP level or its negative conversion after 1 month had a significantly higher remission rate than other patients. Further, patients with a decreased number of or those with >50% improvement in painful and/or swollen joints after 3 months of the treatment had higher good response rate than other patients. [Conclusion] The treatment is useful to achieve remission, and if the joint symptoms show a 50% improvement at 3 months, the treatment should be continued.

P3-013

As study of the efficacy and safety of increased dosage methotrexate therapy for rheumatoid arthritis

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Conflict of interest: None

[Aims] Of 90 patients with RA administered MTX in dosages exceeding 8 mg/w, we investigated the efficacy and safety of increased MTX dosages in 46 patients who continued this treatment for 3 months or longer. [Subjects and Methods] The subjects comprised 9 males and 37 females. With an average age of 56 years, and a mean duration of disease of 92 months. Concomitant medications included PSL in 13 subjects, bucillamine in 14, tacrolimus in 5, other non-biologics in 5, and biologics in 2. The mean observation period following the increase in the MTX dosage was 4.9 months. We evaluated these subjects in terms of the DAS28, serum biochemistry markers, and adverse reactions. [Results] The MTX dosage was initially increased from 8 mg/w to 10.2 mg/w, and 10.6 mg/w by the time of the final assessment. The DAS28 decreased from 4.7 to 4.1. Reported adverse reactions were 24 cases, hepatic dysfunction, stomatitis/gingivitis, leucopenia, shingles, etc. This led to a dosage decrease in 4 subjects, and cessation of MTX in 1 subject. Most adverse reactions were dose dependent, and were dealt with by observation, reducing the MTX dosage, or symptomatic treatment. [Conclusions] Increasing the MTX dosage improved its clinical efficacy. There were no serious adverse reactions.

P3-014

The effectiveness and tolerance of administration of over 10mg methotrexate weekly in patients with rheumatoid arthritis.

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Conflict of interest: None

【Background】In Japan we are permitted to use 10-16mg methotrexate(MTX) weekly for treating with rheumatoid arthritis(RA). The purpose of this study is to confirm whether over 10mg MTX weekly is useful by using the database administrated clinical information.【Material & Methods】17 patients with RA treated withover10mg MTX weekly are included in this study. They are 15 female and 2 men. The average of age is 55.1±14.1 years old. The average of disease duration is 9.71±7.1 years.【Results】In treating with 8mg MTX weekly, DAS28-CRP4 is 3.66. In last observation, DAS28-CRP4 is 3.20 and improved significantly ($p<0.016$). One case is good response; three cases are moderate response of the EULAR response criteria. The proportion of remission and low disease activity increases from 14.3% to 42.9%. An increase of liver enzymes occurs only two cases. Six cases were treated with biologics. In four cases the dose escalation of MTX was performed due to loss of efficacy of biologics. Two cases started biologics after the dose escalation of MTX.【Conclusion】We reported about the effectiveness and tolerance of administration of over 10mg MTX weekly in patients with RA. The dose escalation of MTX contributes to the improvement of effectiveness of biologics.

P3-015

Efficacy and safety of methotrexate at dosages over 8mg/week in patients with rheumatoid arthritis

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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.【Methods】61 RA patients (15 male, 46 female), who are administered MTX at dosages over 8mg/week in our department, were included in this study. We assessed the efficacy of MTX using DAS28-CRP, MMP3, and CRP at initiation of dose escalation and at 3months after dose escalation. Adverse events were also assessed.【Results】Mean age is 57±12 years old. Biological agents were concomitantly administered in 28 patients (46%). Folic acid was administered in all patients. MTX at dosages over 8mg/week is continued for three months in 54 patients (89%). In 3-months continuation group, mean DAS28-CRP, MMP-3 and CRP were significantly decreased. Regarding to adverse events, nausea is occurred in 4 patients, abnormal decrease of WBC is occurred in 2 patients, abnormal increase of hepatic enzyme is occurred in 4 patients, and malaise is occurred in a patient. All cases have improved by discontinuation or decreasing dose of MTX. In this study, the value of hepatic enzyme at initiation of dose escalation over 8mg/week is significantly higher in discontinuation/dose decreasing group than that in 3-months continuation group.

P3-016

Examination of increasing methotrexate dosage more than 8 mg/week in rheumatoid arthritis therapy

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Conflict of interest: None

[Objectives] Treatment with methotrexate (MTX) is highly effective in patients with rheumatoid arthritis (RA). Today, we can choice MTX as first DMARDs and increase up to 16 mg/week. The aim of the present study was to evaluate the effectiveness of increasing MTX dosage more than 8 mg/week. [Methods] Thirty five RA patients (5 males and 30 females; mean age 58.3±15.2 yrs) were involved in this study. MTX was administered orally at a dosage of 4~8 mg/week. All patients underwent physical examinations and blood tests every 1~3 months. The MTX dosage was increased by 2mg/week for patients who did not achieve lower disease activity, after informed consent. The number of swollen joints and tender joints, CRP, DAS28 CRP score and side effects were measured. [Results] All items examined improved significantly. Fifteen patients achieved lower disease activity or remission on 10 mg/week, 4 patients on 12mg/week, and 2 patients on 14mg/week, respectively. Although five patients experienced side-effects in this

study, these patients improved after decreasing their MTX dosage. Nine patients required their DMARDs to be changed. MTX therapy implementing more than 8 mg/week is highly effective and still be adequately safe. We should consider increasing the MTX dosage before choosing biologics.

P3-017

An estimate of recent clinical utility of methotrexate

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Conflict of interest: None

[Objectives] Engaging in community medicine, we have treated patients suffered from rheumatic arthritis. The dosage of methotrexate(MTX) was modified recently, and several biologics came to be used, therefore we examined its resent clinical utility. [Methods] Materials: 108 cases (males 25, females 83). Mean age, 62 (25~93). The cumulative retention rates through three years were calculated by means of Kaplan-Meier analysis. [Results] The rate is 91% (12months), 85% (24months), 75%(36months). These values were higher than those in the past. In 108 cases, 13 cases were ceased due to side effects, which are classified by the organs. The 6 cases (5.6%) of them were so serious to be admitted with low ADL. But no cases in them were ceased because of ineffectiveness. The 7 cases in 8 ones dosed over 8mg, or the 10 cases in 12 ones treated by biologics with it are continued to be administrated. [Summary] In this survey, the high value of cumulative retention rate indicates its clinical utility. No cases were ceased from ineffectiveness, by means of more dosage or biologics with it. Yet, the ceased cases from side effects are not decreased.

P3-018

The impact of approved incremental maximum dose of MTX in Japan for daily practice of rheumatoid arthritis

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Conflict of interest: None

[Background] The approved maximum dose of MTX for RA in Japan was increased from 8 to 16 mg/week on Feb. 23, 2011. [Objectives] The efficacy and safety of more than 8 mg/week of MTX were evaluated. [Methods] The developed computer program linked to the electronic medical recoding system selected 55 RA patients whose dose of MTX was increased to more than 8 mg/week after Feb. 23. Changes of SDAI and ALT as makers of clinical efficacy and adverse effect, respectively, were compared those preceding Feb. 23 and those after Aug. 31. [Results] The average dose of MTX was increased from 9.6 mg/week (range: 6-12) to 13.0 mg/week (range: 10-16). In 26 cases in which calculation of SDAI was possible, the number of patients in remission or low disease activity (SDAI<11) was increased from 57.7% (15/26) to 92.3% (24/26). The abnormally high ALT values after increase were observed in 7 patients (14.6%) among 48 patients whose ALT values were in normal range (5-40 U/L) before increase. The average ALT value of the 7 patients was increased from 28.0 U/L (range: 17-40) to 62.0 U/L (range: 43-91). [Conclusion] MTX up to 16 mg/week was beneficial to control RA disease activity from medium or more to low or less. Elevation of ALT was safely monitored at every 4 week-interval.

P3-019

The efficiency of dose escalation of MTX in RA

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Conflict of interest: None

[Objectives] MTX is an anchor DMARD, the effect of which is dose-dependent. Since 16mg/week of MTX as a maximum dose was officially approved, the efficiency needs to be analyzed. [Methods] Among 845 cases of RA, 689 cases are treated with MTX. One hundred eighty nine cases (27.4% of RA with MTS) are under more than 10mg/week of MTX. [Results] More than 10mg/week of MTX reduced DAS28ESR from 3.53 to2.92, DAS-28CRP from 3.11 to 2.70. The counts of tender joints and swollen joints were also significantly improved. Mild liver dysfunction occurred in 15 cases with being normalized by reducing MTX. Benefits of raising MTX were confirmed in RA.

P3-020

Evaluation of efficasy and the dosage change of methotrexate (MTX) after the approval of over-dose prescription of MTX in our hospital.

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Conflict of interest: None

[Objective] To evaluate the efficacy and safety of over-dose prescription of MTX (≧10mg) in the patients with active RA. [Patients and Methods] 157 outpatients with RA in our hospital were investigated in this study and divided into three groups: Group A (MTX≦6mg) Group B(MTX8mg) Group C(MTX≧10mg). The activity of RA was evaluated by DAS28-CRP score after prescription of MTX≧10mg. [Results] Group A (n=29 66.0±11.9y.o. CRP0.19±0.3mg/dl), Group B(n=93 64.0±13.5y.o. CRP0.34±0.4mg/dl), Group C (n=34 58.7±12.3y.o. CRP0.54±0.5mg/dl). DAS score was decreased from 3.3±0.7 to 2.4±0.6 after increased dose of MTX in Group C. One of four patients (25%) with high disease activity and eleven of twenty-four patients (46%) with moderate disease activity achieved remission. Biologics were newly administered in two patients with high disease activity, but could be discontinued in two. In two patients with nausea and liver dysfunction the doses of MTX were decreased. [Conclusion] Increased dose of MTX≧10mg improved the activity of RA, that seemed to be useful in patients with RA who hesitated the use of Biologic drugs.

P3-021

Is it possible to predict the effectiveness of increased dose of MTX over 10mg/w?

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Fukui Red Cross Hospital

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 first medication (first MTX) and/or increased dose of MTX under 8mg/w (MTX up<8mg). [Methods] Nine patients who took MTX up>10mg were evaluated. The laboratory data of CRP, ESR60min, Hb, RF, and MMP3 were examined before and after the first MTX, MTX up<8mg, and MTX up>10mg. More than 20% decrease of CRP and/or ESR were considered as effective, and less than 20%

decrease as non-effective. [Results] The MTX up>10mg was effective in 6 of 9 patients. The first MTX and MTX up<8mg was effective in 4 and 2 patients, respectively. The MTX up>10mg was effective in 2 of 2 patients for whom the MTX up<8mg was effective. The MTX up>10mg was also effective in 3 of 4 patients for whom both the first MTX and MTX up<8mg were non-effective. It was effective in 1 of 3 patients for whom the first MTX was effective and MTX up<8mg was non-effective. These results indicate the possibility that the effectiveness of first MTX and MTX up<8mg predict that of MTX up>10mg.

P3-022

An analysis of genetic polymorphisms affecting the efficacy of methotrexate

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Conflict of interest: None

[Purpose] We examined genetic polymorphisms related to folate metabolism pathway in RA patients, with the intention of building evidence for implementing individualized drug therapy with methotrexate (MTX). [Methods] The present study examined a patient group with an unsatisfactory response to MTX and undergoing concomitant treatment with biological preparations (BIO) and a patient group who had a stable response to MTX. [Results & Discussion] The results of a polymorphism analysis using the concomitant of BIO as the objective variable revealed a significant association between age and the G80A polymorphism of the folate transporter gene *RFC1*, as an explanatory variable. Compared to patients with the A allele, patients with the G allele had less intracellular MTX uptake and therefore had poor efficacy; a greater number of them were found to be BIO concomitant cases. The results of the present study suggest the possibility that the *RFC1* G80A polymorphism may be a useful marker for predicting MTX efficacy in Japanese patients with RA. We are also currently conducting an additional study on MTX and active substance levels in patients' hematocytes.

P3-023

Classification of pulmonary diseases associated with MTX induced myelo-suppressive state.

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Conflict of interest: None

[Objectives] Three major lethal complications of MTX was myelo-suppression, pulmonary toxicity, and infection. First one was sometimes occurred combined with pulmonary complications. We classified our own cases to draw attention for the future case to make correct diagnosis. [Results of case analysis] Case1:A 83 year-old female complicated with PCP, due to low WBC count, almost no pulmonary shadow was observed in Xp, after recovery of WBC count pneumonic infiltration appeared on Xp. Case2: A 57 year-old male, stopped ingestion of MTX becasuse of myelo-suppression. After discontinuation, he complaint dyspnea and his pulmonary shadow became worse in 2 weeks, This revealed to be exacerbation of RA lung. Case 3: A 69-year-old female stopped MTX by decrease of WBC count, but RA became worse after discontinuation, MTX was restarted by lower dose. She was been to nearest clinic because of dyspnea with pulmonary infiltration which was diagnosed to be MTX pneumonitis. [Conclusion] Pulmonary complications sometimes associated with MTX induced cytopenic condition. This time we try to classify these into 3 patterns. To save the patients from this critical condition, correct diagnosis is mandatory. We believe this classification help to make correct diagnosis.

P3-024

Liver dysfunction during MTX therapy in Japanese patients with rheumatoid arthritis.

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Conflict of interest: None

[Backgrond] MTX plays the essential role in RA treatment as the anchor drug, and recently in combined use with biologics. Dose limit change of MTX was approved on February 23, 2011 in Japan, and use became possible from conventional 8mg/week to 16mg/week in RA treatment. While the efficacy is promising, cautions for an adverse event are required. [Objectives] Lliver dysfunction during MTX therapy in Japanese patients with RA was investigated. [Methods] Six hundred and seventeen patients with rheumatoid arthritis who had treated with MTX in our department from February 23, 2011 to August 31, 2011 were investigated. [Results] With no liver dysfunction (group A), mild liver dysfunction under three times the upper limit of normal (ULN) (group B) and liver dysfunction upper three times the ULN (group C) were 359 (58.7%), 243 (39.7%) and 10 (1.6%) patients, respectively. Although five cases in group C were MTX-induced liver dysfunction, liver damage has improved by addition of folic acid, and cessation or reduction of MTX. Eight of 612 (1.3%) discontinued MTX treatment, however, the causes were not liver dysfunction. [Conclusions] Liver dysfunction is often encounterd during MTX therapy, however, most cases are not too severe to continue MTX therapy.

P3-025

The effect of revised MTX therapy in patients with rheumatoid arthritis in Japan

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Conflict of interest: None

[Purpose] We investigated the effect of revised MTX therapy in patients with rheumatoid arthritis (RA) in Japan. [Methods] We selected randomly a hundred patients with RA receiving MTX therapy at orthopedics as the subject. We also selected other a hundred patients with RA receiving MTX therapy at internal medicine as controls. We evaluated the weekly dose of MTX and folate, value of CRP, ESR, BUN, Creatinine, AST, and ALT. We compared them between before and after the revision of MTX therapy in Japan at 2011. [Results] The mean dose of weekly MTX has in-

creased from 6.4 mg to 7.0 mg after the revision. But, there was no difference statistically between the before and after the revision. On the other hand, the number of high dose MTX user (over 10 mg/w) has increased significantly from 6 to 16. There was no difference statistically in each value of laboratory data between before and after the revision. Furthermore, there were no differences of each value statistically between orthopedics and internal medicine. [Conclusion] We sowed the active MTX therapy for the patients with high disease activity after the revision of MTX therapy in Japan at 2011 than before.

P3-026

A case of MTX associated T-cell lymphoma in liver

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Conflict of interest: None

[Objectives] Investigation about MTX-related T cell lymphoproligerative disorders in liver. [Methods] Case report [Results] Case:64 years old. Femal. Medical treatment to her transduces Infliximab(IFX) 200mg/8ws in not as effective in MTX6mg/w by diagnosis of rheumatoid arthritis (RA). It showed improvement of arthralgia / arthrocele / morning stiffness, and RA maintained remission, but there was action for right upper quadrant pain in on admission of an IFX administration purpose in December, 2010. CT showed mass image in liver S4 100mm, S5 50mm. A metastatic liver tumor was suspected on admission examination clinical course. But we cannot find primary lesion. Therefore MTX-related lymphoproligerative disorders(MTX-LPD) were doubted and canceled MTX administration. We showed sIL2R degradation immediately afterwards, and the image top accepted spontaneous remission of a tumor, too. In pathologic finding by liver biopsy, it is three CD3(+), four CD4(-), eight CD8(+). We showed a monoclonal multiplicative T-cell lymphoma image. Discussin:It is the lymphoproliferative disorder that it is thought that MTX-LPD is caused by immunologic inhibition of MTX. T-cell lymphoma is rare and MTX-LPD in liver is not typical.

P3-027

Reactivation of hepatitis B virus in a hepatitis B surface antigen-negative patient with Felty's syndrome treated with low dose predonisolone and methotrexate

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Conflict of interest: None

Immunosuppressive therapy can induce viral reactivation in patients with chronic hepatitis B virus (HBV) infection and, more rarely, in patients with resolved HBV infection who are HBs antigen negative, HBs antibody positive or HBc antibody positive, called de-novo hepatitis. We report the case of a 66-year-old Japanese woman with Felty's syndrome who developed de-novo hepatitis B virus-related hepatitis during therapy with low dose prednisolone (0.5mg/day) and methotrexate (MTX) (4mg/week). She had been complicated with fever for two weeks in September middle, 2011. She was admitted to our hospital on October 4, 2011. Laboratory data showed pancytopenia (WBC870, Hb8.4, Plt8.3) and slight liver dysfunction (AST90, ALT36). HBs antigen was positive which was negative 1 year before. HBV-DNA and anti-HBc antibody were positive. Entecavir was administered and her pyrexia, pancytopenia, liver dysfunction recovered. But some cases of HBV reactivation in patient with RA, including de-novo hepatitis, have been reported. Considering these conditions, more attention should be paid in patients with RA. And more studies are needed to determine who needs screening of HBV (HBs antigen, HBs antibody, HBc antibody), monitoring of HBV-DNA, and prophylaxis with chemotherapy(Lamivudine or Entecavir).

P3-028

The usage and effectiveness of tacrolimus for treating rheumatoid arthritis patients at a hospital

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Conflict of interest: None

[Objectives] To evaluate the usage and effectiveness of tacrolimus (TAC) for RA at a hospital [Methods] We studied 115 RA patients for whom TAC use was initiated/continued during 2009 Follow-up was conducted until December 2010. Effectiveness was evaluated by considering CRP levels and a physician's opinion [Results] In 2009, 94 cases continued TAC use and 7 were transferred, 4 had complications, and 10 were invalid). In 2010, 6 patients were transferred, 3 developed complications, 3 discontinued TAC by choice, 1 did not visit the hospital, and 5 were shifted to biologics. Finally, TAC was continued for 76 cases. Biologics were introduced for 9 and 3 cases that showed no and inadequate response, respectively, in 2009 and for 8 more cases in 2010. Characteristics of patients who continued TAC use were as follows: age, 64 ± 13 years; and amount of TAC used, 1.6 ± 0.7. CRP levels before and after TAC use and at last follow-up were 2.5 ± 2.2 mg/dl, 1.0 ± 1.2 mg/dl, and 0.6 ± 0.9 mg/dl, respectively. In the physician's opinion, TAC yielded good, moderate, mild, and no effects in 15%, 44%, 28%, and 13% cases, respectively [Discussion] Biologics were introduced for 20 of the 115 patients who received TAC at our hospital within 2 years. We think that TAC is becoming a gateway to biologics

P3-029

Comparison of three rheumatoid arthritis disease activity scores in treatment with tacrolimus

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Conflict of interest: None

[Objectives] To objective of this study was to evaluate the three disease activity indices for rheumatoid arthritis (RA). In late years, the Clinical Disease Activity Index (CDAI) and the Simplified Disease Activity Index (SDAI) were developed in order to provide a quantifiable measure of RA activity in added to the Disease Activity Score including a 28-joint count (DAS28). [Methods] From 2005.4 to 2011.3, the clinical courses of 45 patients who received tacrolimus(TAC) were analyzed retrospectively and compared of three rheumatoid arthritis disease activity scores. [Results] 31 patients remained on TAC therapy for 12 months. After TAC therapy, low disease activity and remission rate(%) was changed from 0% to 12.5% (DAS28-CRP), from 0% to 31.3%(CDAI), and from 0% to 31.3% (SDAI) respectively. DAS28-CRP were found to be more stringent in defining low disease activity and remission than SDAI and CDAI.

P3-030

Positioning of Tacrorimus in treating Rheumatoid Arthritis (RA) at rheumatology clinic

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Conflict of interest: None

[Objective] Analyze the positioning of Tacrorimus(Tac) in treating RA at rheumatology clinic. [Methods] One thousand and 637 patients with RA were analyzed in this study. Ninety seven point three percent of them(1,592 patients) were treated with DMARDs, such as MTX(859 patients), Bucillamine(631), SASP(193), Tac(101) and LF(36). [Results] 1. Eighty one patients were treated with Tac. Among them, 35 patients were monotherapy with Tac, 25 patients combined with MTX and 21 patients also combined with Biologics. 2. The reason of Tac monotherapy was because of the presence of MTX intolerable patients. 3. The reasons of combined therapy with MTX. 1) Insufficient effect of MTX as first DMARD, then added Tac afterwards. 2) Intolerance of high dose of MTX in elderly patients. 4. Combined therapy with Biologics: Twenty one patients were treated with Biologics along with Tac. Which includes 11 patients for TCZ, 6 for ETN, 3 for INF and 1 for ABA, respectively. INF is the only one Biologics which needs MTX combined therapy. So, the number of patients was low in INF group because of the presence of MTX intolerable patients. [Conclusion] This preliminary study suggests that Tacrorimus has its unique positioning in treating RA at rheumatology clinic.

P3-031

Low-dose Tacrolimus therapy in patients with RA

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Conflict of interest: None

[Objectives] Effectiveness of Tacrolimus (Tac) on patients with RA was evaluated. [Methods] Tac was administerated to total 239 RA patients in our hospital since 2007. Tac+MTX group (low-dose Tac with MTX) was 134 cases. Tac alone group (TAC without MTX) was 105 cases. Effectiveness of Tac was evaluated by symptoms and the change of DAS28 score. [Results] Background of these two groups were compared as follows, average age was 72.0 y.o in Tac alone group and 61.6 y.o. in Tac+MTX group, average dose of Tac was 1.7mg/day in Tac alone group, and 1.26mg/day in Tac+MTX group. In Tac alone group, MTX intolerant patients and those who have lung disease were included in highly percentage. Tac alone group showed that Tac was useful even in advanced/elderly RA patients who were intorelant to MTX. Tac+MTX group showed that additional use of low-dose Tac to MTX had excellent effect not only in early RA but also established RA. [Conclusion] Low-dose Tac is a useful additional therapy for elderly patients with RA who are intolerant to MTX, or those who has complication such as lung diseases.

P3-032

The boost effect of low dose Tacrolimus (LD-Tac) on secodary loss of reaction with TNFα inhibitor and methotrexate therapy.

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Conflict of interest: None

Objectives: Treatment with biologics for rheumatoid arthritis, there exist certain cases with TNFinhibitors (TNF-I) which may response to biologics from the first, but gradually loss the effectiveness(secondary loss of response:SLR). Differ from the non-responders, SLR patients tend to stick to the first biologics. Recently, low dose addition of tacrolimus(1mg/day:LD-Tac) gives us some promising data when combined with methotrexate. Here, we observed the boost effect of LD-Tac to SLR of TNF-I Methods: Evaluated with DAS28, low disease activity was established from the first, with TNF-I and MTX. SLR was defined as DAS28 above 3.2. These patients were adviced to select other biologics or addition of LD-Tac. 8 cases of etanercept(ETN), and 12 cases of infliximab(IFX) were recruited, dosages of MTX and the administration of biologics were fixed and LD-Tac were intoroduced. The activity were evaluated with DAS28 and switch to another biologics is an endpoint. Results: 1 cases of ETN, 5 cases of IFX were dropped out for tocilizumab, 7 cases of ETN still on this therapy, averageDAS28, went down from 3.65 to 2.53, for IFX 7 cases, averageDAS28 from 4.43 to2.84. Conclusion: For SLR of TNF-I, before switching to another biologics, consideration of LD-Tac addition may be a acceptable choice.

P3-033

Effectiveness of low dose Tacrolimus (LD-Tac) and Methotrexate treatment for active rheumatoid arthritis patients with nontuberculosis mycobacterium complication

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Conflict of interest: None

Objective: Disease-modifying antirheumatic drug(DMARD) treatment requires intensive evaluation against mycobacterium infection. We have no conclusive strategy for nontuberculosis mycobacterium(NTM) infection. Including corticosteroid(CS), DMARD selection is very difficult for these condition. Low dose tacrolimus 1mg/day(LD-Tac) plus methotrexate(MTX) reported to have more efficacy, showed no elevated risk with infection, compared with MTX monotherapy. Method and conclusion: Two RA patients, treated with MTX and TNF inhibitors, developed pulmonary symptoms, a positive culture for M.avium, and worsening of chest-CT appearance. We quit the TNF inhibitors, sustained MTX, and provided LD-Tac. RA activity got worse transiently but returned to low without biologics. 6-month of interruption of TNF inhibitors, we observed diminishing of cough and sputum, CT presented no worsening of NTM. Furthermore, as we scanned chest CT in recruiting patients for biologics administration, in 6 cases have come to conclude having NTM infection. These patients received LT-Tac with MTX, but no biologics. A year later, average DAS28 down from 3.59 to 2.22 and no case showed progression of CT, and no retardation of pulmonary symptoms. LD-Tac with MTX is desirable choice for RA patient with NTM complication.

P3-034

Myelosuppression and folic acid deficiency under salazosulfapyridine medication for a rheumatoid arthritis patients

Masahiko Miya
Komoro Kosei General Hospital

Conflict of interest: None

[Objectives] The myelosuppression under salazosulfapyridine (SASP) medication for rheumatoid arthritis is considered. [Methods] 101 rheumatoid arthritis patients were medicated with SASP.

Three of them produced erythrocytopenia, macrocythemia, or leukocytopenia. SASP checks the folic acid absorption in an intestinal tract, and causes myelosuppression. It was examined whether the improvement of the myelosuppression by folic acid replenishment would enable continuation of SASP medication. [Results] A patient who caused erythrocytopenia and macrocythemia had SASP medication stopped, so that her erythrocytopenia and macrocythemia had been improved. A patient who caused leukocytopenia had SASP medication stopped. A patient who caused erythrocytopenia and macrocythemia considered SASP as the medication stop, and was re-medicated with SASP by folic acid combined use. Although he produced macrocythemia, erythrocytopenia did not arise. He had salazosulfapyridine medication continued. Folic acid replenishment was effective. Although myelosuppression by MTX is known widely, myelosuppression by the folic acid absorption prevention under SASP medication is seldom known. If leukocytopenia or anemia are produced during SASP medication, don't forget folate deficiency.

P3-035

Efficacy of high-dose mizoribine therapy in combination with MTX in rheumatoid arthritis patients: Relationship between efficacy and its effective factor.

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Conflict of interest: None

[Objectives] The aim of this study is to evaluate the efficacy of high-dose mizoribine therapy in combination with MTX in MTX-resistant rheumatoid arthritis (RA) patients and to clarify the relationship between efficacy and its effective factor. [Methods] Mizoribine was orally administrated to thirteen RA patients (3 males, 10 females, mean age; 50.6 years, mean duration of disease; 8.7 years, mean doses of methotrexate and prednisolone; 8 mg/week and 2.5 mg/day) at a dose of 150 mg/day once a day for 12 weeks. When efficacy of mizoribine was insufficient for RA patients at 12 weeks, mizolibine was singly administrated at a dose of 300 mg/day every other day for additional 12 weeks. [Results] DAS28-ESR was significantly decreased from 5.2±0.8 to 2.7±0.6 in 150 mg/every day, 3.4±0.6 in 300 mg/every other day. Four patients found adverse events which were not severe. 61.5% of patients achieved significant improvement of DAS28-ESR and 38.5% of patients achieved clinical remmision. In addition, the efficacy of mizoribine is related to the body weight, renal function, serum peak concentration of mizoribine and RA activity. The combination therapy of single administration of high-dose mizoribine every other day and weekly MTX was effective for RA patients.

P3-036

A study of the efficasy and safety of mizoribine for rheumatoid arthritis patients with complications

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Katayama Orthopedic Rheumatology Clinic

Conflict of interest: None

[Objective] Patients with rheumatoid arthritis (RA) poorly responding to or exhibiting diminished responses to antirheumatic therapy were treated with mizoribine (MZR) to evaluate its usefulness. [Methods] Twenty RA patients with a mean age of 71.3 years and mean duration of illness of 9.4 years were treated with MZR, and their clinical responses and joint destruction-inhibitory effect of MZR as demonstrated by modified TSS were assessed at 1 year of the therapy. [Results] Of the 20 patients, 18 had concurrent diseases. The mean DAS28-ESR score improved from 5.36 to 4.63. The percentage of patients who continued the therapy was 55% (11/20) at 1 year of the therapy. All the 8 patients with impaired renal function were able to continue treatment for 1 year. Adverse reactions were noted in 6 patients (30%), of whom the treatment was discontinued in 4 patients. Change from baseline mTSS was 2.2(0~13.8, n=8). The progression of joint destruction was inhibited except one patient with rapid radiographic progression following MZR treatment. [Discussion] The usefulness of MZR is thus indicated for the treatment of elderly RA patients with complications such as impaired renal function and suggested that the therapy may inhibit progression of joint destruction in RA patients.

P3-037

Study of effective patient group and treatment regimen of mizoribine

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Conflict of interest: None

While Methotrexate (MTX) is major in RA treatment, we studied effective patient (pt) group & regimen of mizoribine (MZB) that is said to have few adverse effects (AEs). **Methods**: We evaluated treatment response & safety using rates of disease activity score 28 erythrocyte sedimentation (DAS28-ESR) & DAS improvement in 19 patients (pts) not MTX eligible (Group I) & 22 pts receiving MTX (Group II) from 62 pts on MZB. Group I: MZB 150 mg/d w/ concomitant prior antirheumatics; Group II: MZB 300 mg/wk or 150 mg/d w/ concomitant MTX. **Results**: Group I/II, DAS28-ESR at weeks 0, 12, 24, 36, & 48: 5.12/4.71, 4.76/4.73, 4.42/4.35, 4.33/4.32, & 3.37/4.27, respectively; C-reactive protein (CRP) values (mg/dL): 4.23/2.8, 3.71/3.2, 2.47/2.69, 2.16/2.6, & 1.08/1.62, respectively. DAS improvement rate (%) in Group I/II for good, moderate & no response: 21/18.2, 21/13.6, & 58/68.2, respectively. Group I showed DAS28-ESR decrease, DAS improvement, & CRP decrease. MZB was discontinued in 1 pt due to pancreatitis; no serious AE was seen. Group II had lower improvement rate, probably because many pts considered the use of biologicals; MZB 150 mg/d afforded better response than 300 mg/wk. MZB that has few AEs can be considered effective in pts not MTX eligible, or before starting biologicals.

P3-038

Comparative effectiveness of add-on mizolibin or low-dose tacrolimus in RA patients inadequately controlled with methotrexate (MTX)

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Conflict of interest: None

Objective: MTX has been considered to be is an anchor drug in RA treatment. However, some RA patients are treated with MTX unsuccessfully and sometimes it may be difficult to increase MTX dosage because of adverse events such as liver function test abnormality. Although the favorable results of add-on administration of mizoribine (MZR) or low-dose of tacrolimus (Tac) have been reported, comparative effectiveness of MZR or low-dose Tac has not been clarified. Method: Add-on MZR (150mg/day) or Tac (0.5-1mg/day) was administered in RA patients treated with MTX unsuccessfully. Result: Eighteen RA patients had been treated with additive Tac or MZR (n=9 for both group). Compared with MZR group, the ratio of patients who had DAS28 and ACR20 improvement was modestly higher in Tac group. Improvement of CRP level was more frequently observed in Tac group compared with MZR

group. No significant difference was found in swollen joint count or tender joint count between Tac group and MZR group during the study period. The adverse event was not seen in both groups. Conclusion: Our study suggests that low-dose Tac is potentially effective as add-on therapy in RA patients inadequately controlled with MTX.

P3-039

Seven elderly cases of PMR, RA and Pemphigus complicated with steroid withdrawal syndrome

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Conflict of interest: None

Purpose: There have been no fixed criteria for diagnosing steroid withdrawal syndrome (SWS). The direct relationship of doses or periods of glucocorticoid administration and SWS onset is also uncertain. In the present study, seven cases considered to be SWS were retrospectively studied. **Case presentation:** Subjects were aged 76 yrs and over, including 2 cases of RA, 2 of PMR, 2 of pemphigoid, and a complicated case. The period of steroid(PSL) administration ranges 1.5 to 17 yrs; SWS was manifested when 2.5 - 10 mg/day of PSL were used. Except for a case, increased CRP (3.9 - 20.8 mg/dl) and high fever were shown. When SWS was suspected, the alleviation of fever within 24 h was observed in 6 out of 7 cases by additional administration of PSL 5mg/day. **Discussion:** SWS generally occurs within 5 days following cessation of steroid therapy, in which headache, inflammation, nausea and fever are often observed. The mechanism involves increased PGE2 and PGI2 activity at the time of steroid secession. In our cases, a low dose administration of PSL was rapidly effective to improve SWS symptoms. **Conclusion:** Additional administration of a small dose of PSL was effective for the recovery of SWS. The rapid response was clinically helpful to diagnose the complication of SWS at the early phase.

P3-040

A case of rheumatoid arthritis complicated with malignant lymphoma as an initial symptom of knee joint swelling

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Conflict of interest: None

A 73-year-old woman with rheumatoid arthritis(RA) noted the swelling and pain of her left knee joint and the edema of her left lower leg on June 2011. She had been treated with methotrexate(MTX) 8mg/week and etanercept(ETN) 50mg/week since May 2010. Laboratory data showed CRP 2.9mg/dl, an exacerbation of RA was diagnosed and she received enhanced treatment by increasing the dose of MTX to 10mg/week and in addition to prednisolone(PSL) 10mg/day. But her symptom was not improved and her lower leg edema worsened. Therefore her left knee joint puncture was performed, and revealed atypical lymphocytes (10% out of 5300cells/μl) in its synovial fluid. On July 31th, she was admitted to our hospital because of low grade fever, general malaise and swellings and pains of her bilateral inguinal lymph nodes. Laboratory findings showed atypical lymphocytes (13.5% out of 6800 leukocytes/μl), elevated level of CRP (21.1mg/dl) and LDH (653 IU/l). Her right inguinal lymph node biopsy was performed and the diagnosis of diffuse large B-cell lymphoma (DLBCL) was made. After discontinuation of MTX and ETN, her symptom and laboratory abnormalities were improved. It was considered that MTX related DLBCL. We report the case, including literature review.

P3-041

Study of the elderly onset rheumatoid arthritis

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Conflict of interest: None

[Objectives] We investigated the elderly onset rheumatoid arthritis (EORA) about the drug treatment and complications and the sexual distinction. [Methods] We evaluated the 48 patients (12 men, 36 women) diagnosed as RA at the age of over 65 years in the duration of 6 months retrospectively. [Results] The age diagnosed as RA (Age-RA) didn't differ significantly between men and women. Age-RA was significantly lower in the drug combined groups (35cases, 72.9%) and exchange groups (32cases, 66.7%) compared to the drug mono therapy groups ($P<0.001$) and continuation groups ($P<0.01$). The drug exchange groups and the drug combined groups was significantly higher in the men compared to the women ($P<0.01$, $P<0.05$). The drug dose of methotrexate (MTX) and prednisolone (PSL) was higher in the men compared to the women ($P<0.01$). Age-RA didn't differ significantly between the drug complication groups (7cases, 14.6%) and no complication groups. The high frequency of the drug exchange groups and combined groups suggested that we aimed the drug efficacy getting as soon as possible. In addition, higher dose of MTX and PSL suggested that the lower Age-RA men were more difficult to treat in EORA.

P3-042

Tocilizumab as a first line drug for treatment of very early RA

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Conflict of interest: None

[Objectives] The efficacy of Tocilizumab (TCZ) to treat patients with RA was investigated and compared to that of TNF inhibitors. The best use of TCZ was determined. [Methods] Among 27 patients treated with TCZ, seven patients have received TCZ within 6 months of diagnosis of RA (very early RA). Efficacy of TNF inhibitor in 9 very early RA (VERA) among 93 patients treated with those were compared with that of TCZ in 7 with VERA. [Results] Mean WBC counts of 8300 & 8100, and mean thrombocyte counts of $33x10^4$ & $30x10^4$ were not significantly different between group treated with TCZ 7 and ETN 9 at 0 month. However, changing of WBC 5200 and thrombocyte $22x10^4$ in TCZ group were significantly greater than that of WBC 7000 and thrombocyte $26x10^4$ in ETN group at 12 weeks. On the other hand, mean Hb levels of 11.2 and 12.1 were slightly different between treated with TCZ and ETN at 0 month. However increasing of Hb 11.9 in TCZ group were significantly greater than 12.3 in ETN. Remission rate of TCZ 100% was not significantly higher than that of TNF inhibitors 89% [Discussion] TCZ is thought to be a suitable first line drug for patients presenting with leucocytosis and or thrombocytosis in patients with VERA.

P3-043

Comparison of drug survival rates for biologics in patients with rheumatoid arthritis

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Conflict of interest: Yes

[Objectives] The objective of this study is to compare the biologics regarding drug survival rate in patients with rheumatoid arthritis (RA). [Methods] We have studied the cumulative discontinuing rate of the patients with RA who have treated with biologics between April 2003 and September 2011, and the log-rank test was used to compare survival curves. [Results] A total of 216 RA patients started treatment with biologics: 108 with etanercept (ETN), 50 with tocilizumab (TCZ), 36 with adalimumab (ADA), 17 with infliximab (IFX) and 5 with abatacept (ABT). One- and two- year drug survival rates of the ETN was 74.8%, 67.6%, TCZ was 71.6%, 42.3%, ADA was 67.3%, 36.3%, and IFX was 56.3%, 49.3% respectively. Survival was better in ETN compared with TCZ and ADA. [Discussion] Survival rate of ETN with RA is considered better in comparison of biologics used in our department.

P3-044

A study of the persistency ratio of biologicals and related factors in patients with rheumatoid arthritis.

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Conflict of interest: None

In this study, we analyzed the persistency ratio of biologicals and related factors in patients with rheumatoid arthritis treated with biological (etanercept (ETN), infliximab (IFX), adalimumab (ADA), tocilizumab (TCZ)). Persistency ratios are ETN 80.8%, IFX 75.5%, ADA 57.1%, TCZ 75.8% one year later from first administration and 70.6%, 56.3%, 45.0%, 54.1% two years later, respectively. The persistency ratio of ETN is higher than those of IFX and ADA and that of IFX is higher than that of ADA. We examined with factors related to these results. In addition, we considered that it is necessary to analyze persistency ratios of abatacept and golimumab.

P3-045

Comparison the Remission and Continuation Rates of Biologics in the Treatment of Rheumatoid Arthritis−Estimate Efficacy for the First -line Biologics and Second-line Biologics−

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Conflict of interest: None

[Objectives] The aim of this study was to compare the remission and continuation rates among biologics for first-line or second-line. For the strategies of biological treatment for patients with rheumatoid arthritis (RA) biologics, TNF-αantagonists (infliximab: IFX, etanercept:ETN, adalimumab:ADA) were applied for the first-line biologics in our department. [Methods] This study enrolled 74 patients with RA applied biologics (IFX, ETN, ADA, TCZ, ABA). The mean age was IFX; 48, ETN; 60, ADA; 57, TCZ; 64, and ABA; 55 years old. For the first-line biologics and second-line biologics, the remission rate of the new criteria (CDAI, SDAI, Boolean) and DAS28-ESR were assessed at last follow-up period. The continuation rate was assessed by Kaplan-Meier method. [Results] The remission rate of first-line biologics was that DAS28; 47%, CDAI; 33%, SDAI; 26%, Boolean; 26% for IFX and DAS28; 48%, CDAI; 18%, SDAI; 24%, Boolean; 18% for ETN. The remission rate of second-line biologics was that DAS28; 33%, CDAI · SDAI · Boolean; 11% for TCZ. The continuation rate of the first-line biologics was that IFX; 85.1%, ETN; 86.7%, ADA; 53.3% at 1 year and IFX; 66.3%, ETN; 69.7% at 3 years.

P3-046

The effectiveness of tocilizumab therapy on elderly-onset rheumatoid arthritis (EORA) patient

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Conflict of interest: None

[Objectives] Early checkup, treatment have begun to fix the treatment of rheumatoid arthritis (RA), but, on the other hand, advanced age RA patient that the long-term contraction of a disease period passed and the elderly-onset RA(EORA) patient exist. We examined curative effect of TCZ in EORA. [Methods] We gave tocilizumab(TCZ) from June, 2008, and the follow-up of 48 weeks intended for 26 advanced age RA patients 65 years or older. We evaluate it in 10 AORA(adult-onset rheumatoid arthritis) which RA developed under 60 years old, in to 16 EORA(elderly-onset rheumatoid arthritis) that RA developed in to after 60 years old. The effective evaluation of TCZ used disease activity using DAS28-ESR and remission rate that assumed Boolean definition all≦1 as a new remission standard. [Results] As for the change of DAS28, improvement was seen with EORA 2.0±0.7, AORA 1.9±1.0, both groups at time for 48 weeks. The remission rate to assume DAS28<2.6 was 81.3% of EORA, AORA 80.0% in 48 weeks, and there was no difference in both groups(p=1.0000). The remission rate of the new remission standard showed a high tendency 31.3% of EORA toward AORA 20.0%, but was not meaningful(p=0.6680). TCZ showed high curative effect for old RA patient, and the effect was shown to be high regardless of the onset.

P3-047

Rheumatoid arthritis treatment in high risk patients - Patients with cancer

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Conflict of interest: None

[Objective] In Japanese clinical trials, incidence of malignant tumors after treatment of rheumatoid arthritis (RA) with tocilizumab (TCZ) was the same as in RA patients not using TCZ and no clear relation with TCZ was found. It was unclear if TCZ exacerbated malignant tumors. Two RA patients with malignant tumors given TCZ were reported. [Case 1] 76 year-old woman in Stage II, class 2 RA at 2 years after onset. Thyroid papillary carcinoma appeared at age of 56 with postoperative lung metastasis. Pulmonary nodules remained unchanged. From the age of 74, multiple joint arthralgia appeared. After 18 months of MTX 8 mg + TCZ, DAS28-ESR improved by 5.99 -> 3.59. [Case 2] 48 year-old woman in Stage I, class 3 RA at 1 year after onset. At 47 years old, she developed right breast cancer and had breast saving + axillary lymph node surgery. Postoperative chemotherapy was performed for positive lymph node metastasis. Systemic arthralgia appeared

and QOL markedly deteriorated. No improvement occurred after chemotherapy was withdrawn. Early RA was diagnosed from physical, blood and echographic findings. With TCZ treatment, DAS28-ESR improved by 7.10 -> 1.39. [Conclusion] In RA patients with malignant tumors treated with TCZ, tumors were not exacerbated but careful observation is needed.

P3-048

Rheumatoid arthritis patient questionnaire survey about the choice of the biologics

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Conflict of interest: None

[objectives] Recently, biologics have been used in treatment of rheumatoid arthritis (RA) widely. However, about the choice of the drug to an individual patient, the standard is not clear and it often depends on the recommendation of the doctor and choice of the patient. So we performed a questionnaire survey to the patient who used biologics in RA, and we examined problems in conjunction with a factor of the choice of the biologics. [methods] 74 RA patients who used the biologics in our hospital answered the questionnaire. [results] As for the choice reason (multiple answers allowed) of the biologics, “advice of the doctor” is 81.9%, “simple and easy dosage method” is 13.1%, “One treatment time is short” and “long interval” is 11.4% each. On the other hand, “with a little self-pay of the expense “ was 3.2% and a few. The satisfaction rate of the biologics was 7.6/10, the mean self-pay of medical expenses per month was 33,161 yen, and the acceptable upper limit per month was 17,463 yen. [conclusion] There was the dissociation between a real mean self-pay of medical expenses and the acceptable Self-pay cost, biologics forced patients to financially big burden.

P3-049

Which is more effective, TNF inhibitors or IL-6 inhibitor? ~A scoring system for predicting the efficacy of biologics in RA treatment

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Conflict of interest: None

[Objectives] To investigate the possibility of establishing the scoring system for selecting biologics. [Methods] 37 patients given TCZ treatment and 146 patients given TNF inhibitors were enrolled and the correlation analysis between the laboratory data at baseline and the ratio of the DAS28-ESR before treatment and 6 months after treatment was performed. A scoring system was established from the laboratory data correlating to DAS ratio, then the propriety of the system was tested. [Results] The correlation analysis between DAS ratio and each laboratory data before TCZ treatment showed that Plt, Hb, AST, ALT, and Fe had significant correlation to the DAS ratio. On the other hand, those data had less correlation to the DAS ratio in TNF inhibitors therapy group. On the basis of these results, a scoring system was established to predict the efficacy of treatment from the laboratory data before treatment. Then the treatment data of patients in our hospital were scored by this system, and it revealed that the scores tended to be higher in the group above “moderate response” to TCZ, especially in “good response” group in the EULAR response criteria. Adversely, in the “no response” group to TCZ and “good response” to TNF inhibitors, the scores tended to be lower.

P3-050

The drug interval escalation of Tocilizumab in patients with Rheumatoid Arthritis

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Conflict of interest: None

[Objectives] The purpose of this study is to evaluate the drug interval escalation of Tocilizumab in patients with rheumatoid arthritis [Methods] 20 RA patients were allowed the drug interval escalation of Tocilizumab after LDA, we investigated CDAI and SDAI and CRP after the drug interval escalation. But if the disease activity was higher (MDA or HDA) or the patient hope or the CRP is positive, we gave up the drug interval escalation, back to 4weeks. [Results] 6 patients got the successful drug interval escalation of Tocilizumab over 5 - 8weeks with CDAI≦10 and CRP negative.14 patients were failed drug interval escalation, back to 4weeks interval. In conclusion, the patients who maintained CDAI≦10 and CRP negative may be possible to the drug interval escalation Tocilizumab.

P3-051

Therapeutic efficacy of low-dose Tocilizumab

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Conflict of interest: None

Objective: We investigated maintenance of remission and safety after treatment with tocilizumab at a low dose (4 mg/kg) in patients with rheumatoid arthritis. **Background**: Patients often have to stop biologics treatment for financial reasons, frequently resulting in relapse. Reducing the financial burden on patients so that treatment can be continued would help to improve or maintain quality of life. **Patients and Methods**: Nine patients with rheumatoid arthritis who went into low grade activity (DAS28-ESR <3.2) after treatment with tocilizumab were continued on tocilizumab at a reduced dose of 4 mg/kg. The clinical and functional responses were then examined after 12 week. **Endpoints**: We evaluated change in the DAS28-ESR, CDAI and HAQ score after the dose was reduced. **Result** : The clinical respons was maintained (DAS28-ESR: 2.09±1.0 before dose reduction; 2.89±1.1 12 weeks later). Low grade activity was maintained in five of the nine patients. The functional respons was also maintained (HAQ score: 0.29; 0.18). **Conclusion**: Low-dose tocilizumab is useful for treating patients who are in clinical remission. While drug-free remission may be achievable in the future, use of low-dose tocilizumab as a preliminary step could become an option from an efficacy and safety perspective as well.

P3-052

The change of fat and lean of body mass in patients with rheumatoid arthritis treated with tocilizumab

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Conflict of interest: None

[Background] RA patients are often in condition of malnutrition due to catabolic process leading to muscle atrophy and physical inactivity. [Objectives] To assess the change of fat and lean in RA patients treated with TCZ. [Methods] Thirteen female patients with RA were enrolled in this study. Fat and lean of body mass in the patients were assessed utilizing DEXA at week 0 and 24 after TCZ therapy. [Results] Average age and duration were 54 year olds and 9.4 years. Swollen joint count, Tender joint count and DAS28-CRP improved significantly at week 24. Serum levels of ALB, T-chol, TG, LDL-C, HDL-C and Cr increased significantly at week 24. Tocilizumab did not increase fat of limb significantly, while it increased fat of trunk significantly at week 24 (mean ± SD; 7.05 kg ± 2.82 kg at baseline; 7.79 kg ± 2.86 kg at week 24, $p< 0.01$). Lean of limb and trunk did not change significantly. The high correlation between lean of limb and Cr and the moderate correlation between lean body mass and Cr were observed in the patients with RA treated with tocilizumab ($r=0.741893$, $p<0.01$, $r=0.62486$ and $r<0.05$). [Conclusion] This study indicates that TCZ increased fat of trunk comparable to IFX therapy. Serum Cr level is suggested to be an indicator of lean of limb.

P3-053

Effect of biologics on preventing knee joint destruction in rheumatoid arthritis

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Conflict of interest: None

[Objective] We investigated the effect of biologics on preventing knee joint destruction and the correlation between clinical symptoms and joint damage. [Methods] We studied 35 joints who had swelling or tenderness of the knee joint at the time biologics were introduced. The biologics were infliximab, etanercept, and tocilizumab. For 2 years after treatment of biologics, we evaluated the changes of swelling and tenderness of the knee joint, knee joint X-rays (Larsen grade), and progress of disease activity using DAS28. [Results] Twenty-seven of 35 joints showed preventing joint destruction, while 8 joints showed progression of knee joint damage. In the 27 joints with preventing joint destruction, the ratio of loss of swelling and tenderness was 18 joints within 3 months and 21 joints within 6 months after treatment of biologics. In addition, in all 8 joints with joint destruction, there were no changes in knee joint symptoms. [Discussion] This study indicated that biologics were effective treatment for knee joint. We suggest that knee destruction may be mainly related to improvement of clinical symptoms. Therefor, persisting of clinical symptoms of swelling or tenderness, it is possible that even patients with low disease activity show advancement of knee joint destruction.

P3-054

The Effects of Tocilizumab (TCZ) by CDAI Assessment and Bone Destructive Pattern in the patients with Rheumatoid Arthritis

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Conflict of interest: None

We reaffirmed the efficacy of TCZ in 68 RA patients (mean age is 56 years, mean duration is 14 years) by classifying into three categories based on CDAI (44 joints) improved rate (most effective [ME]; not less than 75%, effective [EF]; from 50% to 75% and slightly effective [SE]; from 25% to 50%) and were classified by the joint destructive pattern that is (1) erosive (at least three erosions were present in PIP and MP joint) (ER) or, (2) not erosive (less than two erosions were shown in above area) (NE) or (3) unclassified by hand X ray. Consequently, 20 patients were ME, 32 patients were EF and 16 patients were SE. In these groups, clinical features (age, stage, class and duration) and laboratory data at baseline (c-reactive protein, hemoglobin, platelet and MMP-3) had no difference except age in which ME group was significantly ($p<0.05$) younger in comparison with SE group. Interestingly, 17 of 20 patients with ME group showed NE pattern in contrast, only 6 of 16 patients showed NE pattern in SE group. As in NE group (42 cases) the duration were significantly ($p<0.001$) shorter than ER group (23 cases), the effect of TCZ might due to only the problem of duration. However the possibility that like this bone destructive pattern involved in the effect on TCZ is considered.

P3-055

Tocilizumab suppressed the joint destruction in Rheumatoid Arthritis

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Conflict of interest: None

[Objectives] The objective of this study was to evaluate the suppressive effects of Tocilizmab (TCZ) on the joint destruction in patients with RA [Methods] The patients included 59 cases in which the series of X rays of the hands were available. (The mean age at TCZ: 52 years old, duration of RA: 8.7 years, Bio first: 14 cases, Bio Switch: 45 cases). Genant-modified Sharp score was used for the evaluation. [Results] DasESR improved from 5.44 to 2.25 at the latest follow-up. Yearly progression of Genant-modified Sharp score was also suppressed by TCZ from 9.96 points to 0.56 points. 80% of the petients did not show any progression of joint destruction.

P3-056

The clinical and radiographic effectiveness of tocilizumab in RA patients in real clinical practice

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Conflict of interest: None

【Objectives】To evaluate clinical and radiographic effectiveness of tocilizumab (TCZ) in real clinical practice.【Methods】Among 30 patients treated with TCZ in our hospital, seven patients whose clinical and radiographic data could be followed for a period of 12 months were evaluated the clinical effectiveness by

DAS28, MMP-3 and the radiographic effectiveness by modified total sharp score (mTSS) at baseline and 12 months. 【Results】 The characteristics of the 7 patients were as follow [mean age 59.5 years, disease duration 5.3 years, DAS28 5.7, MMP-3 577.0 ng/ml, stage I/II/III/IV=2/2/2/0, class1/2/3/4=2/3/1/0]. At week 52, mean DAS28 was decreased to 2.8 (one patient achieved clinical remission), and mean MMP-3 was also decreased to 88.3 ng/ml. At week 52, mean mTSS increase no more than 1.0 from baseline, whereas estimated yearly progression of mTSS was 5.5 and three patients (43%) achieved structural remission (⊿mTSS≦0.5). At week 52. Especially, joint space narrowing score at week 52 was significantly decreased from baseline. It was demonstrated the possibility that patients who could not achieved clinical remission with tocilizumab therapy can achieve radiographic non-progression.

P3-057

Changes with time in ultrasonographic findings in weight-bearing and non-weight-bearing joints in patients treated with tocilizumab

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Conflict of interest: None

[Objectives] Ultrasonographic diagnosis is now used mainly for non-weight-bearing joints but seldom for weight-bearing joints. In our hospital, ultrasonographic imaging diagnosis is used on both types of joints in patients given tocilizumab (TCZ). The need for ultrasonographic findings for weight-bearing joints and importance of ADL joint protection guidance for patients including physical therapy (PT) and occupational therapy (OT) are reported. [Methods] Blood flow signals were followed using Grade Point for 12 patients treated with TCZ subjected to ultrasonography five times on both weight-bearing and non-weight-bearing diseased joints. [Results] The results showed different courses. Blood flow signals decreased in non-weight-bearing joints but not always in weight-bearing joints at the same time. Differences in effects between the two types of joints were observed including no changes only in weight-bearing joints and transient increases in blood flow signals.

P3-058

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] Tocilizumab (TCZ) immediately reduces CRP when used in patients with rheumatoid arthritis (RA). On the other hand, there is an impression of slow onset of clinical improvement of the drug. In this study, we evaluated the onset time of TCZ therapy for RA patients using FDG-PET/CT. [Methods] 8 patients (2 men, 6 women; average age: 57.8 years; average disease duration:13.1 years) who underwent TCZ therapies were assessed. Imaging and clinical assessments were performed prior to, 3 and 6 months after the initiation of treatment. The sums of SUVmax (total SUV) of all calculated joints were provided for the evaluation of therapeutic effects. DAS28, SDAI, CDAI and MMP-3 were used for the evaluation of disease activity of RA. [Results] The DAS28 of 3 months (3M) and 6 month (6M) were significantly down compared to the DAS28 at the initiation of the treatment (0M) (p=0.012 and p=0.012). There were also significant decrease of the SDAI /CDAI (3M and 6M) compared to the SDAI/ CDAI (0M). TCZ therapy also reduce MMP-3 (3M) and MMP-3 (6M) compared to the MMP-3 (0M) (p=0.036, p=0.043). The total SUV (3M and 6M) were significantly reduced in comparison with the total SUV (0M). The effect of TCZ therapy for RA patients may express at the time of 3M after initiation of the therapy.

P3-059

Analysis of DAS28, a joint echo and the radiological finding in the Tocilizumab administration example

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Conflict of interest: None

[Objectives] it is understood in Tocilizumab administration example that the findings of DAS28 and the joint echo relatively have much estrangement. We analyzed DAS28, a joint echo, association with joint XP (sharp score) this time. [Methods] In 72 Tocilizumab administration examples, analyzed it about 21 cases that the joint echo was able to observe in 39 at the same time that were able to observe XP for 52 weeks around administration. [Results] there was no progress in 61.1% in 21 with the sharp score (TSS) by the one-year observation. Joint space progressed than bone erosion when we watched contents of the TSS. Also, TSS/y accepted a significant difference in approximately Tocilizumab administration and prevented progress. Presence or absence of biological preparation previous treatment, an in front of treatment MMP-3 level, degree of improvement of SDAI and CDAI showed a significant difference by the comparison between non-progress group (13) and progress group (8). There were no significant differences in the joint echo, but there were many advanced cases for the case which had high value at the administration. Also, the association with the improvement of the echo in eight weeks was unknown probably because we evaluated it with the finger 20 articular total vascularity(%).

P3-060

Predictive marker for the discontinuation of tocilizumab in rheumatoid arthritis with clinical remission

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Conflict of interest: None

[Objectives] To assess the clinical characteristics of rheumatoid arthritis (RA) patients treated with tocilizumab (TCZ) and achieved clinical remission. [Methods] Efficacy was evaluated by CDAI. [Results] 35 (5men, 30women, average age 53.9 years old) of RA patients were treated with TCZ and enrolled in this study. Overall remission rate was 47.4%. 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 remission and without remission. CDAI score at 4 months (remission cases 3.7+/-2.5, non remission cases 13.8+/-7.4) was the predictive marker for the discontinuation of TCZ with clinical remission. Results: CDAI score at 4 months was the predictive marker to achieve clinical remission with TCZ.

P3-061

Characteristics of four rheumatoid arthritis patients achieving biologic-free remission with tocilizumab

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Conflict of interest: None

[Purpose] To analyze the characteristics of four patients with rheumatoid arthritis (RA) achieving biologic-free remission with tocilizumab (TCZ). [Objects and Method] we experienced four biologic-free RA patients, in 11 RA patients who achieved Boolean-based remission using TCZ and methotrexate (MTX) until September, 2011. We clinically analyzed the characteristics of four biologic-free RA patients. The discontinuation timing of TCZ depended on the judgment of the attending physician. [Result] At the start of treatments, the mean duration of four RA patients was 1.6 years, the average of DAS28-ESR was 5.2, and the mean doses of MTX was 7mg/w. Only one patient orally received prednisolone 5 mg/day. The Boolean remission was achieved 4.5 months and the discontinuation of TCZ was achieved 22 months after the treatment with TCZ plus MTX. The mean DAS28-ESR was 0.5 at the time of discontinuation of TCZ. After the discontinuation of TCZ, the Boolean remission was maintained more than six months in all cases. [Conclusion] The combination therapy of TCZ and MTX for RA is effective, and the possibility of discontinuation of TCZ is raised while maintaining the Boolean remission in patients with the early therapeutic intervention.

P3-062

The maintenance therapy of rheumatoid arthritis treated with tocilizmab

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Conflict of interest: None

[Objectives] For safety using of tocilizmab, we tried to innovate the maintenance therapy for RA patients who were initially treated with tocilizmab. [Methods] We eliminate the number of low activity RA outpatients treated with tocilizmab as an initial therapy. The patients group was divided to 3goups; A group: the decrease of the administration dose(4mg/kg), B group : the prolongation of the administration interval and C group: the discontinuance of the administration, then compared among each groups and conventional treatment groups. [Results] The disease activities of RA measured by lab data and clinical manifestation were raised among B and C group, but A group was not shown any overt worsening of RA. The bone erosion and deformity could not be seen in any groups using X-ray test and ultrasonography(US), but increasing of blood flow in some joints were detected by power doppler US in B and C groups. There was no increase of adverse events such as infection in A, B and C groups compared the conventional therapy. In conclusion, it suggests that the decreasing the administration dose of tocilizmab would be beneficial for safety and effectiveness as a maintenance therapy.

P3-063

Discontinuation of biologics and its predictors

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Conflict of interest: None

[Objectives] To analyze predictors of biologics discontinuation. [Methods] 242 RApatients treated with biologics(Infliximab:113, Etanercept: 92, Adalimumab: 22, Tocilizumab: 13) were studied retrospectively using medical records. [Results] An average disease duration from onset to initiation of biologics was 7.5 years. No less than 125 patients (51.7%) have discontinued biologics. Fifty-one patients (40.8%) and 32 patients (25.6%) discontinued because of secondary failure and adverse effects, respectively. Those patents have showed high-disease activity post discontinuation and 53 patients switched to another biologics. Only 4 patients (1.7%) discontinued biologics. A predictor was achievement remission evaluated with Boolean approach. However, one patients had a disease flare after 6 months. [Discussion and Conclusion] Discontinuation of biologics is not easy at the present time. The necessary condition of Bio-free was revealed that patients were in remission and had negative rheumatoid factor.

P3-064

The Perioperative Use of Biologic Therapies for the patients with Rheumatoid Arthritis- About tocilizumab and abatacept Therapies-

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Conflict of interest: None

[Objectives] The guidelines say the surgical operation should be conducted after an interval of 2 to 4 weeks from last treatment of anti-TNF inhibitor. However, there are few reports about Tocilizumab (TCZ) and Abatacept (ABT). So there is currently no clear indication for the perioperative use of those biologics. [Methods] In this study, we report actual use conditions (the interval of the treatment, the concomitant drug and adverse events) of the patients with Rheumatoid Arthritis (RA) treated with TCZ and ABT. [Result] In the case of our 21 cases reported, the average age was 58.9 years old and the average disease duration was 11 years. About the interval of the administration, the average time of preoperative last administration was 22.7 days before the surgical operation and the average time of the postoperative first administration was 25.9 days after surgical operation. Before surgical operation, the combined use rate of MTX was 38.9% and that of PSL was 30.6%. Adverse events was revealed (malignant lymphoma, the delay of wound healing, the postoperative anemia). Treatment was restarted in all 3 cases. [Conclusion] In reported 21 cases, the severe adverse events were not observed when the surgical operation was conducted after intervals of 2 to 4 weeks from last treatment

P3-065

Familial occurrence of two patients with malignant rheumatoid arthritis treated with Tocilizumab

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Conflict of interest: None

[Case1] 62 years-old female. She was diagnosed rheumatoid arthritis in 1985, and treated with PSL and DMARDs. In 1995, She suffered from Myasthenia Gravis induced by Bucilamine. In 1997, episcleritis, **musckle weeknes,** skin rush appeared, and she was diagnosed marignant rheumatoid arthritis(MRA). Treated with Ticilizumab, her arthralgia and vasculitis has improved. [Case2] 60years-old female. She was diagnosed rheumatoid arthritis in 1988, and treated with PSL and DMARDs. However, it was difficult to continue DMARDs because of drug allergy, so ahter that she was treated with PSL, MTX and CyA. In2011, MTX wat stopped because drug induced interstitial pneumonitis was suspected. Then her arthralgia had worsen. We could'nt find any vasculitis, but she revealed hypocomplementemia, and IgG type rheumatoid factor was positive, MRA was suspected. Treated with Ticilizumab, her arthralgia has improved. She was also diagnosed malignant lymphoma of the stomach(DLBCL), mostly MTX-related lymphoproliferative disorders was suspected. [Discussion] MRA is a name for RA complicated with systemic vasculitis or other severe extra-articular manifestations. MRA is found in 0.5-1.0% of inpatients with RA. We discuss about the characteristics of familial occurance of MRA.

P3-066

Successful treatment with tocilizumab for multidrug-refractory rheumatoid arthritis with abnormal surrogate maker

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Conflict of interest: None

We report a case of improvement of clinical manifestations and several abnormal laboratory findings in a patient with rheumatoid arthritis who received tocilizumab. A 73-years-old men with a 18-years history of RA had several DMARDs (bucillamine, salazosulfapyridine, methotrexate, etanercept, and tacrolimus) resistant arthritis and had chronic renal failure, HBV carrier, deep vein thrombosis, past treatment of bladder cancer and past tretmant of Legionnaire's pneumonia. Because of Anemia, hypoalbuminemia and abnormal finding of rheumatoid factor, immune-complex and complement was not controlled by steroid only, in Oct 2010 intravenous administration of tocilizumab was started. After several weeks, his clinical symptoms and laboratory findings were controlled with tocilizumab and we can taper prednisolone to 7mg/day. We have no evidence of vasculitis on histology, but change of these laboratory findings was seemed to be the existence of rheumatoid vasculitis. Tocilizmab is effectiveness of clinical and surrogate maker response and may be therapeutic option for rheumatoid vasculitis.

P3-067

A Case of Rheumatoid Aryhritis complicated by Obstructive Sleep Apnea successfully treated by Tocilizmab (TCZ)

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Conflict of interest: None

The case is an 80 year- old-man suffered from Rheumatoid Arthritis of the onset 1998, and chronic sleeplessness as well. In August 2009, he was introduced to our outpatient clinic for the purpose of arthritic control and insomnia. CRP5.82, DAS28 (CRP) =6.8. We stopped for him to take anxiolytics, Benzodiazepines. The examination for polysomnogram (PSG) showed the electroencephalogram that an alpha wave was carried on at REM sleep, the orthosleep, and also showed the sleep respiratory disorder of AHI=20.1, AI=10.0. In the state that became the sympathetic predominance due to the pain, and the effect on OSA was thought about as well. Because the CPAP treatment, oral appliance therapy were refused, we conducted only TCZ induction. MMP-3 improves from 333 to 112ng/ml, HAQ score from 1.8 to 0.9. In August 2010, Sleep latency shortened with arthritic relief. Insomnia severity questionnaire showed in improvement as well. PSG showed increase of Stage 3, 4 latency, and an alpha wave at orthosleep, REM sleep disappeared. Even frequency analysis by FFT (Fast Fourier transform) showed decrease of amount of alpha wave.. It is thought that contribution of IL-6 in OSA exacerbation Although TCZ do not change respiratory disorder, it improves insomnia, and also electroencephalogram shows improvement.

P3-068

Successful tocilizumab and tacrolimus treatment in a patient with rheumatoid arthritis complicated by systemic lupus erythematosus

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Conflict of interest: None

We report a 37-year-old female of intractable rheumatoid arthritis (RA) complicated by systemic lupus erythematosus (SLE), who was successfully treated with a combination of tocilizumab (TCZ) and tacrolimus (TAC). She was diagnosed with RA at 21 years old, and has been administered oral prednisolone, injectable gold, and salazosulfapyridine, but deformity of her hands gradually developed. She developed high fever and polyarthritis at 35 years old. Renal involvement, thrombocytopenia, pericarditis, positive antinuclear antibody, and high level of anti-double-stranded DNA antibody were found and the patient was diagnosed with SLE. Polyarthritis and immunological abnormalities developed despite aggressive immunosuppressive therapy including high-dose corticosteroids and intravenously administered cyclophosphamide. TAC therapy had only partial improvement of joint symptom. After the initiation of combination therapy with TCZ, not only obtaining a complete remission of RA, but also the serum levels of SLE markers dramatically decreased. Our report suggests the possibility that this combination therapy is effective in treating SLE as well as RA.

P3-069

2 cases of active rheumatoid arthritis exacerbated during tapering of glucocorticoids for treatment of complicated systemic lupus erythematosus with nephropathy successfully treated with tocilizumab

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Conflict of interest: None

[Objectives] We report 2 cases of active rheumatoid arthritis

(RA) exacerbated during tapering of glucocorticoids (GC) for the treatment of complicated systemic lupus erythematosus (SLE) with lupus nephritis (LN) successfully treated with tocilizumab (TCZ). [Case] Case 1; A 69-year-old female has had RA since 1994. She had suffered from rapidly progressive glomerulonephritis (RPGN) in Jan., 2009 and SLE was diagnosed. LN was treated with GC but during GC tapering exacerbation of RA was shown and TCZ was introduced and successfully treated. A little high anti-DNA antibody level and anemia were improved after TCZ treatment. Case 2; A 50-year-old female has had RA since 1980. She had been treated with etanercept since Jul., 2007 and had suffered from SLE in Oct., 2008 (renal biopsy; LN type IV-S(A/C). She was treated with GC and cyclophosphamide pulse therapy. During GC tapering RA exacerbated and TCZ was started. [Comment] A report was shown that suggested TCZ should be effective for repression of anti- DNA antibodies and arthritis in SLE but the safety of TCZ has not yet established. We need to be much careful for using TCZ for patients with RA associated with SLE. [Conclusions] TCZ was successfully used for 2 cases of active RA associated with SLE and no exacerbation of SLE was shown.

P3-070

Biological therapy for Rhupus syndrome 3 cases

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Conflict of interest: None

[Objectives] Rhupus is RA and SLE. This is rare case. We investigate the efficacy of biological therapy in patients with Rhupus. [Methods] We perfomed biological therapy with Rhupus 3 cases. The evidence which diagnosed Rhupus is fulfilled by both RA 2009 criteria and SLE 1997 criteria before biological therapy. We are trouble about treatment in all cases as need high dose steroid. Infliximab is used in Case1. In Case2, we use infliximab at first. After the efficacy is reduced, infliximab is changed for tocilizumab. Etanercept is used in Case3. [Results] In Case1, the joint symptom is improved, but is no remission. After that, biological therapy is off for sever infection. In Case2, the improvement of joint symptom is not related to proteinuria, complement, anti DNA antibody. After change for tocilizumab, low complement, lympopenia, hypothrombocytopenia appered. In Case3, joint symptom is improved and yet raynaud's phenomenon. We can reduce steroid in the two of all cases. [Conclusion] We can improve joint symptom of Rhupus 3 cases for biological therapy. On the other hand, there is not change of SLE organ involvement, but is improvement that partly symptom of SLE. As there is report that improve lupus nephritis for infliximab, we need to think induction of biological therapy for SLE.

P3-071

Abatacept treatment for rheumatoid arthritis complicated by lupus erythematosus - a report of three cases

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Conflict of interest: None

[Background] Abatacept, a CTLA4-Ig fusion protein, is a biologic agent newly approved for rheumatoid arthritis (RA) in Japan. Abatacept is also thought to be a therapeutic option for systemic lupus erythematosus (SLE) by considering its mechanism of action. We report three cases with RA complicated by SLE who received abatacept for their active arthritis. [Patients/ Results] All of three patients were Japanese female with ages ranging from 29 to 66. Disease durations of RA and SLE were 38-183 and 2-565 (months), respectively. Arthritis activity represented by DAS28 ranged from 3.64 to 7.02 and that by CDAI ranged from 19.2 to 39.3 before abatacept treatment. Anti-DNA antibody titers before abatacept treatment ranged from 21.3 to 41.5 IU/mL. After six months with abatacept treatment, a range of DAS28 was from 2.82 to 3.82 and that of CDAI was from 6.7 to 9.6, and all patients achieved moderate EULAR response. On the other hand, the decrease of anti-DNA antibody titers was modest. [Conclusion] Abatacept was efficacious for arthritis but showed only modest effects on serological lupus activity in RA patients complicated by SLE. Possible efficacy of abatacept for SLE will be discussed with a literature review.

P3-072

Smokers with rheumatoid arthritis who could not respond to TNF inhibitors treated successfully with an anti-interleukin-6 receptor antibody: a report of three cases.

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Conflict of interest: None

Patients with rheumatoid arthritis (RA) who smoke are reported less likely to respond to treatment with tumor necrosis factor (TNF) inhibitors. I report cases of smokers who could not respond to TNF inhibitors but were treated successfully with an anti-interleukin-6 receptor antibody (tocilizumab(TCZ)). Case 1. 63-year-old woman whose smoking index was 200, had complained of polyarthralgia since 1996, I could not prescribe methotrexate due to adverse effects. Two years after her first visit, the lateral tibial condyle of the right knee joint collapsed. Therefore, she underwent total knee arthroplasty. She had undergone treatment with eternercept due to high disease activity, but shown no response to her disease for two years. Therefore, I administered TCZ (8 mg/kg monthly), which dramatically improved her symptoms, DAS28 from 4.2 to less than 2.3 and MMP-3 from 405 to less than 59.7. She is in complete remission over 6 months after cessation of the TCZ therapy. Case 2, a 64-year-old man whose smoking index was 1600, and Case 3, a 48-year-old woman whose smoking index was 560 showed resistance to the treatment of the anti-TNF agent, but improved successfully with TCZ. This is the first report of an effective treatment for RA patients who smoke.

P3-073

Therapeutic effect of Tocilizumab on renal AA amyloidosis associated with rheumatoid arthritis: a case report.

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Conflict of interest: None

[Objectives] Recently, some biologics were reported to improve amyloidosis. In this report, we present a case of treatment of reactive AA amyloidosis with Tocilizumab (TCZ). [Case] A 67-year-old woman, suffering from active rheumatoid arthritis without any medication for several years, visited our hospital and endoscopy revealed amyloid deposition in the colon. Firstly we administered Etanercept (ETN) by consideration of her renal dysfunction. After the ETN injection, proteinuria was improved but renal function deteriorated progressively while maintaining a high disease activity. Therefore, we administered TCZ (8mg/kg) every 4 weeks. One month after the first injection of TCZ, serum AA level was normalized and it was kept within normal ranges since then.

[Results] TCZ might be one of a potent drug to be able to treat of AA amyloidosis by suppressing serum AA levels powerfully.

P3-074

Management of pregnant women with Rheumatoid arthritis

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Conflict of interest: None

Improved outcomes of RA may increase RA patients who wish pregnancy. We report three cases of pregnancy with RA. (1) 23 years-old patient. RA appeared at 16 y.o. Remission status was maintained in use of infliximab 4mg/kg and MTX 8mg/w. All drugs were stopped on October 2009 because she wished pregnancy. Pregnancy was revealed on April 2010 and baby was delivered on October 2010. (2) 26 years-old patient. RA appeared at 19 y.o. Control of RA was good in use of Etanercept(ETN) 25mg/w, MTX 6mg/w, SASP 1000mg. MTX stopped on January 2009 because she wished pregnancy. She was diagnosed autoimmune hepatitis, so stopped ETN and SASP. Therapy started at PSL40mg and remission at PSL 2.5mg. Pregnancy was revealed on June 2010 and baby was delivered on February 2011. (3) 30 years-old patient. RA appeared at 19 y.o. Control of RA was good in use of infliximab 4mg/kg, MTX 5mg/w, PSL 2mg and NSAIDs. All drugs were stopped on March 2009 because she wished pregnancy. However, PSL and ETN were started for recurrence of RA on October 2009. ETN was stopped because pregnancy was revealed on March 2011. After that, there was no reactivation and her baby was delivered on November 2011. Conclusion:Further studies are required to establish the standard management of RA patients during pregnancy.

P3-075

New dose limits of Methotrexate (MTX) and Infliximab (IFX) enabled Disease Activity Scoring (DAS) remission of Rheumatoid Arthritis (RA): a case report

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Conflict of interest: None

[Objectives] Recently dose limits of IFX and MTX were increased up to 6 mg/kg every four week and 16 mg a week each in Japan. We report a case that introduced DAS remission after increasing IFX and MTX following the new dose limits. [Methods] Ritchie articular index (RAI), Tenderness joints count (TJC) and Swollen joints count (SJC) were used to measure RA disease activity. [Results] The patient is a 63-year-old man who had joint pains at age 62. He was initially treated with oral PSL (15 mg) and Bucillamine was followed. Three month, when we saw him, Anti-CCP Ab, MMP-3 and HbA1c were elevated, PSL was reduced to 5 mg and 4 mg a week of MTX was started after 1 g of salazosulfapyridine. MTX was increased to 8 mg a week, then he was treated with IFX (3mg/kg) three times, but tenderness joints remained. PSL was finished and IFX was augmented at fourth (300mg), and fifth (6 mg/kg, 384 mg) therapy and MTX was augmented to 12 and 16 mg every month. Twelve month, DAS (1.19) remission was confirmed. Increased limits of IFX and MTX were useful to introduce DAS remission of the RA patient.

P3-076

Nrf2 expression in synovial tissues in patients with rheumatoid arthritis

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Conflict of interest: None

[Objectives] Oxidative stress is involved in rheumatoid arthritis (RA). Nrf2 regulates the response to oxidative stress and its deficiency leads to aggravation of arthritis, increase of oxidative stress. In this study, we investigated nrf2 expression in synovium and effect of biologic agents to nrf2 expression. [Methods] Synovial tissues obtained from thirty-four patients (30 RA included patients treated with infliximab(1), etanercept(4), tocilizumab(1), and adalimumab(1), 4 osteoarthritis(OA)) were analyzed with real-time PCR and immunohistochemistry of nrf2. [Results] Immunohistochemistry of nrf2 showed strong or moderate intensity and diffuse staining pattern in about 80% of RA cases and weak intensity or no positive staining in 3 of 4 OA cases. In real-time PCR, the expression level of nrf2 in RA cases was almost twice as high as that in OA cases and it did not differ between treatment with biologics and non-biologics. [Conclusion] Nrf2 expression level in RA synovium was observed higher than that in OA synovium and it was not seemed to be affected by treatment of biologics. Our findings suggest nrf2 up-regulation as one of antioxidant defense response to strong oxidative stress in RA patients.

P3-077

We estimate the validity that ankles or toe joints are not included in the new ACR/EULAR remission criteria.

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Conflict of interest: None

[Objectives] An ankle or toe joint which is a load joint is not contained in the new ACR/EULAR remission criteria (the new criteria) as well as Disease Activity Score. In 125 RA patients who have been administered biologics in our department, we estimate the validity of the new criteria. [Methods] We examine how many patients reach the new criteria among these patients and evaluate the patients in which the condition of the ankle or the toe joint remains among those achieving remission. Moreover, the factors used as the reason are examined in the patients in which the new criteria was not achieved. [Results] The patients achieving remission and those with ankle or toe joint symptoms were 29 examples and 29 examples, respectively. It was two examples that the condition of the ankle or the toe joint remains among 29 examples which reached the new criteria. Moreover, it was eight examples that only the patient VAS became the reason why they did not achieve the new criteria, and the average patient VAS was 21 mm. One example remained the condition of the ankle or the toe joint, and the patient VAS was 30mm that was the highest value. [Conclusion] There were two patients achieving the new criteria although they had the condition of the ankle or the toe joint.

P3-078

Review of Rheumatoid Arthritis Treatment Based on T2T Strategy

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Conflict of interest: None

(ABSTRACT) (Objectives) To evaluate the treatment in rheumatoid arthritis (RA) based on T2T strategy. (Methods) In our institute, RA patient has been treated based on T2T since 2009. Indices such as DAS28-CRP, CDAI, SDAI, Boolean, and HAQ have been monitored. 237 patients can followed up more than 1 year and have been monitored. (Results) In 237, 105 for StageI, 67 for Stage II, 36 for Stage III, and 29 for Stage IV have been followed up. In these, CDAI remission is 92, 43, 22, and 16 for each Stage. SDAI remission is 92, 43, 22, and 16 for each, and Boolean remission is 86, 39, 20, and 14. Average HAQ is 0.172, 0.338, 0.533, and 1.081 for each. 90.8, 76.7, 60.9, and 41.2% of measured times for each Stage achieved HAQ remission. Disease activity indices such as DAS28-CRP, CDAI, and SDAI are closely correlated for each other (correlation coefficients(C.C.)>0.8), and in zones within LDA, average HAQ is also correlated with each disease activity index (C.C.>0.8). However for StageI and Stage IV have shown that disease activity index did not correlated with HAQ. In StageI, average HAQ is from 0.1 to 0.2, while more than 0.9 in Stage IV. However for Stage II and Stage III, disease activity index is correlated with HAQ (C.C.=0.63). (Discussion) These results have supported the validity of T2T strategy.

P3-079

Comprehensive remission after 2 years of response-driven treatment in early rheumatoid arthritis: T-4 study

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Conflict of interest: None

Objectives: To compare the occurrence of comprehensive remission after 2 years of response-driven treatment according to four different treatment strategies for early rheumatoid arthritis (RA). **Methods:** A total of 243 early RA patients were randomly allocated to one of four strategy groups: routine care (R group); DAS28-driven (D group); MMP-3-driven (M group); or both DAS28- and MMP-3-driven therapy group (Twin; T group). Specifically, medication was started with SASP in all intervention groups. Targets were DAS28 <2.6 for D group, MMP-3 normalisation for M group, and both DAS28 <2.6 and MMP-3 normalisation for T group. If the value in question did not fall below the previously measured level, we intensified medication including MTX, other DMARDs and biologic agents. 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. Comprehensive remission is consisted of the proportions of patients showing clinical remission, radiographic non-progression and normal physical function at 2 years. **Results:** Comprehensive remission at 2 years was achieved by more patients in T group (38%) than in R group (13%; $p<0.0005$) or D group (20%; $p<0.031$).

P3-080

Which region of joints affects remission criteria?: a nationwide study based on the *NinJa* database 2010

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Conflict of interest: None

Objective: To identify effective joint regions on remission criteria. **Methods:** Total Joint indices (TJI) of upper/large (UL), upper/small (US), lower/large (LL), and lower/small (LS) regions were calculated as described previously (1). MTX users from Kurashiki Medical Center were applied to obtain logistic models for predicting the probability of remission, where predictors were TJI, pt and Dr VAS, and CRP. These models were validated using *NinJa* database. **Results:** TJI of all regions except for LS were significant predictors for ACR/EULAR new criteria (A/E), DAS28, and SDAI remission, whereas there was no effective region for boolean remission. The odds ratio of TJI of US for A/E and SDAI was larger than that for DAS28. Overall percentage of correct classification of *NinJa* data were 96% for A/E, 91% for DAS28, 84% for SDAI, and 94% for boolean. Data satisfied A/E were classified into 2 groups: Dr VAS ≦1cm and >1cm. Positive rates of TJI of UL and LL region in >1cm group was significantly higher than those in ≦1cm group. **Conclusion:** Effective predictors for remission depended on criteria. Patients with remission by new criteria still had affected joints in large regions when Dr VAS was bad. **Reference:** 1. Nishiyama S, et al. Rheumatol Int. DOI 10.1007/s00296-011-2058-9, 2011

P3-081

The status of the treatment and its change in Rheumatoid arthritis patients with clinical remission in Ninja (Japanese large cohort database)

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Conflict of interest: None

[Objectives] To know clinical background and therapies in Rheumatoid arthritis patients with clinical remission. [Methods] Data from the large cohort database; NinJa in 2002 to 2010 was analyzed. We examined the clinical backgrounds and the use of NSAIDs, steroid and DMARDs in patients with clinical remission. [Results] 6204 patients data were examined in 2010. SDAI remission was 23.3% and Boolean remission was 17.4%. There was no significant difference in clinical background or treatments between each remission group. The usage rate of steroid was lower in remission group. The usage rates were 33.8%, 31.0%, 57.3%, and 56.2% in SDAI remission, Boolean remission, SDAI non-remission and non-Boolean remission group respectively. The average dose of steroids was lower in each remission group (3.4 mg, 3.3 mg, v.s. 4.4 mg, and 4.3 mg). The usage rate was lower in remission group also about NSAIDs. There was no significant difference in the usage rate of MTX (57.9%, 57.3%, 60.7%, 60.6%) and biologics (19.4%, 18.6%, 19.8%, 20.0%). The average dose of steroids was decreasing and the usage rate of MTX and biologics were increasing year by year in remission group and non-remission group. Especially decreasing rate of steroid dose was higher in remission group than in non-remission group.

P3-082

Poor physical function is a negative predictor for achieving Boolean-based remission in patients with rheumatoid arthritis treated with tocilizumab

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Conflict of interest: None

[Objective] To assess the factors that relate to achieving Boolean remission in patients with RA treated with tocilizumab (TCZ). [Methods] We analyzed efficacy of TCZ in 80 RA patients at 24 weeks by using DAS28 and Boolean remission. We stratified 80 RA patients by medications, age, disease duration and physical function (J-HAQ). We further analyzed predictive factors that influenced on achievement of Boolean remission at 24 weeks. [Results] Among 80 RA patients, 89% were women, median age was 60 years and duration was 8.3 years. The mean DAS28 5.48 at baseline decreased to 2.73 at week 24. DAS28 remission was achieved in 50% and Boolean remission in 12.5%. There was no difference in achieving DAS28 or Boolean remission when stratified by previous biologics use, concomitant MTX use, or age at 65 years. There were significant differences in achieving Boolean remission, when stratified in tertile by duration ($p<0.05$) and J-HAQ ($p<0.05$). The predictive factors for not achieving Boolean remission was worse baseline J-HAQ (OR 3.66) but not duration (OR 1.01), ESR (OR 0.98) or steroid use (OR 2.95). [Conclusion] Poor physical function is a negative predictor for achieving Boolean-based remission in patients with rheumatoid arthritis treated with TCZ.

P3-083

Changes in blood levels of MMP-3 and IL-6 associated with tocilizumab treatment – A washout biomarker?

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Conflict of interest: None

Usefulness as a washout biomarker of blood levels of MMP-3 and IL-6 in rheumatoid arthritis (RA) patients during washout of tocilizumab (TCZ) was examined. TCZ treatment was performed in 76 RA patients. Drug washout was attempted in 18 patients who had achieved clinical remission of DAS28-ESR<2.6. In 8 patients, remission was maintained for 24 weeks after TCZ withdrawal. When mean blood levels of MMP-3 and IL-6 were compared three times until withdrawal of TCZ, MMP-3 values were 52.2±10.0 ng/ml in the remission group and 213.1±164.6 ng/ml in the non-remission group ($p=0.015$) and IL-6 values 27.3±18.8 ng/ml and 96.8±94.1 pg/ml ($p=0.058$) respectively. In the remission group, MMP-3 and IL-6 values remained low and stable after washout. Coefficients of correlation (r) between MMP-3 and IL-6 before (n=66), 24 weeks after (n= 49) and 52 weeks after (n=26) treatment were 0.257483, 0.392341 and 0.9003712 respectively and the *p* values in significant difference testing were 0.0366, 0.0053 and <0.0001 respectively. Correction coefficients became more strongly positive as the number of treatments increased. Measurement of IL-6 is not covered by health insurance but the low, stable values of MMP-3 are important for a biomarker of drug washout in clinical practice.

P3-084

No need for ultrasound findings in the remission criteria with RA patients, treated by infliximab

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Conflict of interest: None

[Objectives] We discuss ultrasound findings add the remission criteria. I think that remission criteria by using methotrexate monotherapy is likely, How about infliximab? [Methods] We investigated the patients with remission (CDAI <SDAI and 3,3 <2,8) by infliximab but existing ultrasound abnormality images (hands and feets, GS and PDUS) We estimated the patients mSHS and ΔHAQ from baseline to 6 months. [Results] 19 cases were included. All paintes were no significant change with mSHS and ΔHAQ. [Discussion) We have no cases over grade 2 abnormality with ultrasoud. We need consider the abnormality

P3-085

Total elbow arthroplasty using Morrey elbow for rheumatoid elbow

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Conflict of interest: None

[Objectives] We retrospectively evaluated the clinical results of rheumatoid elbows replaced with Morrey elbow. [Methods] Twelve rheumatoid elbows of 11 rheumatoid patients (2 males and 9 females) were replaced Morrey elbow and followed up minimum 1 year (mean length: 26.3 months). The average age at the time of surgery was 67.3 years old. The average RA disease duration was 12.2 years. There were 5 initial total elbow arthroplasy (TEA) for mutilating elbow, 5 initial TEA for complicated periarticular fracture (3 comminuted fractures of the humeral distal end, 1 humeral medial condyle fracture, and 1 olecranon fracture), 1 revision TEA for aseptic loosening of Kudo elbow, and 1 re-revision TEA for aseptic loosening of Morrey elbow. [Results] The average range of motion changed from 120 before surgery to 135 after surgery in flexion, - 30 to – 20 in extension, 65 to 74 in pronation, 72 to 82 in supination. Significant improvements were observed in flexion and extension. The averaged JOA score significantly changed from 37.8 before surgery to 82.5 after surgery. There were no major complications. This result has shown that rheumatoid elbow with mutilating change, periarticular fracture, and component loosening can achieved good elbow function by TEA using Morrey elbow.

P3-086

Discovery total elbow replacement for patients with RA: a short time follow-up study

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Conflict of interest: None

[Objectives] The purpose of the present study was to evaluate the results of treatment of rheumatoid elbows with semi-constrained total elbow arthroplasty with Discovery elbow system. Patients: 8 patients (12 elbows) with RA were treated with Discovery elbow prosthesis Larsen gradeIV 1 elbows, gradeV 7 elbow and 4 revision elbow. [Methods] Posterior approach was used in all cases. The implant was cemented fixation. After two weeks casting, ROM exercise was started. The JOA score and the Mayo Elbow Performance Score was used to document the preoperative and postoperative conditions of the elbow. [Results] After surgery, the average arc of extension was -22.5 degrees, and the average arc of

flexion was 134.2 degrees. The average arc of pronation was 70 degrees, and the average arc of supination was 75.8 degrees. The JOA score, were improved from 38.0 points 84.2 points and Mayo elbow performance score were improved from 32.5 to 87.1. One patients had humeral medial epicondyle fracture and another patient had the ulnar nerve paralysis. [Conclusion] Dicovery elbow system improvemed the arc of flexion and pronation, and also improvemed elbow function. However, it was thought that long-term follow-up is needed.

P3-087

Short-term Results of Linked-type Toral Elbow Arthroplasty

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Conflict of interest: None

[Objectives] Recently, linked-type total elbow arthroplasty (TEA) has been widely used for RA or other situations. Short-term results of this procedure in our hospital were evaluted. [Methods] Nine elbow joint could be assessed among the joints treated with linked-type TEA in our hospital from 2007. Age at operation was ranged from 61 to 76 years old (Ave. 70 y. o.). The procedure was applied for the first time operation of RA in 5 joints, the revision for unlinked-type TEA of RA in 2 joints, the revision for unlinked-type TEA after trauma in 1 joint and non-union of humeral distal end fracture in 1 joint. Coonrad-Morrey Total Elbow was used in 6 joints and Discovery Elbow System in 3 joints. Post-operative duration was ranged from 4 months to 4.2 yeas (Ave. 2.5 years). Our indications for RA, unlinked-type TEA will be used for Larsen grade IV or less, and linked-type TEA will be applied for grade V. [Results] The average of elbow JOA score increased from 32 points pre-operatively to 85 points post-operatively. Much improvement was recognized especially in pain and range of motion (ROM). Almost all patient achieved painless joints. Post-operative ROM was 110° (-28° extension and 138° flexion) on an average. There was no joint which needed revision.

P3-088

Total elbow arthroplasty (TEA) using unlinked prosthesis in rheumatoid arthritis

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Conflict of interest: None

[Objectives] Between 2003 and 2007, we undertook 14 total elbow arthroplasties in 11 patients with rheumatoid arthritis. We studied the mid-term results of unlinked total elbow arthroplasty in patients with rheumatoid arthritis (RA). [Methods] A total of 10 patients (13 procedures) was evaluated at a mean follow-up of 6 years (4 to 8). All of 10 patients were women with a mean age of 59 (35 – 73) years. All patients had radiological changes of Larsen grade IV or grade V. According to Kudo's category, eleven elbows had painful instability and two had painful stiffness. [Results] The results, assessed by using the scoring system of Japanese Orthopaedic Association, revealed remarkable improvement in pain and daily activities. The average range of flexion increased by 24 degrees (from 111 to 135 degrees), while the extension lag increased by 3 degrees (from -42 to -45 degrees). [Conclusion] TEA could give good results in terms of relief of pain, mobility and stability. The functional results were good and activities of daily living improved markedly at mid-term follow-up. TEA using unlinked prosthesis is considered to be a valuable procedure for restoring daily living activities of patients with rheumatoid arthritis.

P3-089

Total elbow arthroplasty in patients with RA who had elbow disability and suffered from distal humeral fracture.

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Conflict of interest: None

[Objectives] Osteosynthesis and TEA was reported in patients with RA suffered from distal humeral fracture. These are 2 cases that TEA was performed in patients with RA who had elbow disability before distal humeral fracture. [Results] 81-year-old female, RA onset was 26 years old. About 40 years ago, synovectomy was performed in her right elbow. Before she suffered from transcondylar humerus fracture, her elbow joint was Larsen IV grade in radiological finding and ROM was -40/90. Her hand did not reach to her mouth. TEA with MNSK system was performed to gain her better ADL. After osteotomy in condyle, lateral and medial condyle was fixed using tension band wiring, and prosthesis was placed. There was no dislocation and ROM was -30/130. Current ADL was better than before fracture. 57-year-old female treated with adalimumab, RA onset was 23 years old. Before she suffered from humeral medial condyle fracture, her elbow joint showed Larsen V grade and folk deformity. She wanted to treat without operation and brace was placed. After 1year and 4 months, ROM was -20/140, TEA with PROSNAP elbow was performed due to unstable elbow joint and disturbance of ADL. Two months after operation, instability was disappeared and ROM was -30/140. Her current ADL was better than before fracture.

P3-090

Examination of 2 rheumatoid arthritis patient who underwent radius head resection and distal ulna edge resection in one stage

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Conflict of interest: None

[Objectives] Radius head resection and the distal ulna edge resection are often performed for an elbow joint, wrist disorder in Rheumatoid Arthritis. We evaluate the arms function of 2 cases that operated on the same arms in one stage this time. [Methods] The elbow joint enforced synovectomy after radius head resection. The wrist enforced a Darrach procedure. For the stabilization of the ulna stump, pronator quadratus muscle was fixed to the ulna dorsal part. As for one case, an extensor carpi ulnaris muscle tendon separated to half was putted through the medullary cavity from the back side of the ulna stump and used tenodesis together. None performed the external fixation after operation and admitted an automatic movement exercise from an early stage. [Results] It is for a short-term observation period (up to four months), but the preoperative mean excursion is an improvement trend. The sharp pain was reduced, too, and the satisfaction of the patient was relatively high. Radius head resection and the distal ulna edge resection in the same arms are not generally recommended to spoil stability of the radius ulna interval. However, reduction of the paain, excursion improvement was regarded as a useful method to be provided in the Rheumatoid Arthritis patient without the hard labor.

P3-091

Two case of revision of total elbow arthroplasty with impaction bone grafting method.

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Conflict of interest: None

We report two cases of rheumatoid artritis who had revised total elbow athloplasty with impaction bone graft method.(case 1) Sixty four year old woman was operated primary total elbow athloplasty(TEA) on her left elbow. Four years later we found the humerus component loosening, and we revised the humerus component with impaction bone graft method. (case 2)) Sixty year old woman who was operated primary TEA on her left elbow, was injured distal humerus fracture on left elbow three years after. Seven years later she had the humerus component loosening, and was revised the the humerus component with impaction bone graft method. The used prosthesis of both case was FINE ELBOW(Nakashima Okayama, Japan) which is unlinked type prosthesis. The main factor of the cases loosening was thought of inadequate cement fixation on primary TEA. Therefore we used impaction bone graft method to obtain good fixation.

P3-092

Insufficiency fracture of the proximal tibia associated with the varus deformed arthritic knee

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Conflict of interest: None

Case report: A 73-year-old female, farmer, who had more than 10-year-history of degenerative knee osteoarthritis that had been treated conservatively. She had had severe pain in her right leg without any trauma since June 1st 2007, which came on suddenly. She had severe varus deformity of the bilateral knee. The radiographs revealed severe degenerative arthritis of the medial compartment bilaterally. Precise radiological examination revealed an undisplaced fracture of the one-third of the right tibia. The range of motion of the right knee was 35 to 90 degrees. Using X-ray and CT-scan, we diagnosed the patient to have an insufficiency fracture of the proximal tibia. This was treated in a functional brace for seven months. However, the fracture failed to unite. We then treated her with a modular total knee arthroplasty(TKA) and the fracture united. The pain was relieved and mobility restored. The range of motion was zero to 110 degrees. Discussion 1. The severe varus deformities would have led to repetitive abnormal stress on the proximal tibial metaphysis and caused an insufficiency fracture of the tibia. 2. Modular TKA corrects the deformity, restores normal alignment and converts the abnormal stress to compression force. The long stem tibial component stabilized the fracture.

P3-093

Intramedullary Supracondylar Nail versus Non-contact Bridging Plate for Periprosthetic Femur Fracture after Total Knee Arthroplasty in Rheumatoid Arthritis

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Conflict of interest: None

[Purpose] This study evaluated the clinical and radiographic outcomes of osteosynthesis with intramedullary supracondylar nail: IMSC (Smith & Nephew) versus non-contact bridging plate: NCB-DF (Zimmer) for periprosthetic femur fractures. [Patients] Six periprosthetic femur fractures after total knee arthroplasty were treated with the IMSC, and five fractures were treated with the NCB-DF. All of the patients were women who had rheumatoid arthritis and osteoporosis. All of the fractures were displaced, and none of the knee prostheses was loose at the time of the fracture. [Results] Although periprosthetic fracture is difficult to treat while restoring the malalignment of the fracture and obtaining rigid internal fixation, outcomes in the patients treated by the NCB-DF were superior to those treated by the IMSC. At the time of follow-up, the average knee rating score for all five knees treated with the NCB-DF were almost equal to the prefracture status. [Conclusion] The NCB-DF, which allow for polyaxial screw placement, was quite useful in periprosthetic femur fractures that had insufficient room in the distal fragment for a screw insertion.

P3-094

Fractures in rheumatoid patients treated by surgical procedure

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Conflict of interest: None

Sixty fractures of rheumatoid patients were treated from 2002 to2011 in Okayama city hospital. The mean age at the operation was 72 years old. Forty-five femoral fractures, 8 humeral fractures, 4 forearm fractures, 3 lower leg fractures and one calcaneus fracture were operated. Open reduction and internal fixation was performed for 38 fractures. In the case of joint involvement, we chose total joint replacement for 2 femoral neck fractures, one distal femoral fracture and one distal humeral fracture. As the salvage procedure, four total hip arthroplasty were performed after open reduction and internal fixation in four proximal femoral fractures. Replacement surgery was the choice of treatment in fractures with joint involvement in RA patient.

P3-095

Stress analysis of the acetabular reinforcement ring with hook in total hip arthroplasty

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Conflict of interest: None

[Objectives] An acetabular support ring can be applide during total hip arthroplasty (THA), depending on the areas of bone grafting in rheumatoid arthritis. We evaluated the influence of the support ring on the stress distribution of the bone graft in THA using a finite element method. [Methods] Geometric data were obtained by CT scanning. The bone graft model of the acetabulum and the acetabular reinforcement ring (Ganz ring) was modelled. Fixed restraints were applied to the sacroiliac joint and the pubic symphysis, and the load was applied at the center of the femoral head. [Results] In the cup model, comparatively uniform stress distribution was observed. In the bone graft combination model, the stress of the peripheral area of the acetabulum showed a high tendency. In the Ganz ring model, the hook showed stress concentration, and the stress on the bone graft area tended to be low. These findings suggest that bone grafting with Ganz ring can be expected to provide stress dispersion after surgery.

P3-096

Total hip arthroplasty in juveile idiopathic arthritis

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Conflict of interest: None

Severe destructive joint changes and functional impairments in the patients with juvenile idiopathic arthritis (JIA) often require total joint arthroplasties aimed for functional restoration. The operation seems more complex as for timing, implant choice and impaired joints. We examined pre- and post-operative status of JIA patients who underwent total hip arthroplasty (THA). The patients consisted of one male (2 hips) and 4 female (7 hips) with mean onset of 24.1(17-35) years and 10.5 years of post-operative follow-up. Mean age at operations was 35(30-41) years with body state of 147.7 (126-171) cm in height and 56.6 (39-90) kg in weight. The implants were fixed with cement except for 3 cases in acetabular cementless fixations, and tended to require smaller size. Difficulty at intubation was experienced in one case (2 hips) due to oral disturbance in opening. Two hips occurred dislocations and one had three times revisions followed by infection. All patients had severe hip pain and disability of walking before surgery, but state of pain free and independent gait were possibly achieved. Although THA for JIA was effective restorative approach, careful considerations and assessment for peri-operative status and post-operative follow-up were required.

P3-097

two cases of impaction bone grafting technique

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Conflict of interest: None

[Objectives] [Methods] [Results] Patient 1 : 78 year-old woman with RA who had been taking tacrolimus 3mg/day for 7years presented with gait disturbance, which had gradually worsened. At the mean 20 year-follow-up period after the first operation, loosening of the first endoprosthesis occurred and revision surgeries with Exter stem were performed, using the impaction bone grafting (IBG) with acetabular mesh. Patient 2 : 82 year-old woman with RA who had been taking bucillamin 100mg/day and PSL 2.5mg/day revealed appearance of severe hip pain. Computed tomography (CT) was demonstrated multiple cystic lesion at the subacetabulum lesion and surgery with non Exter stem was carried out by using IBG technique with spongiform bone. There are no complication and satisfactory results with evidence of graft incorporation was observed.

P3-098

Total joint arthroplasty in rheumatoid patients with hemodialysis

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Conflict of interest: None

[Objectives] Total joint arthroplasty for RA patient is widely performed, and good results are reported. However, total joint arthroplasty for RA patient with hemodialysis is limited.. There are extremely few reports of the operation results for such patients. This time, we report the clinical results of TKA and THA which were performed for RA patients with hemodialysis. [Methods] Objects are four hips (four RA patients with hemodialysis who underwent THA) and five knees (three RA patients with hemodialysis who underwent TKA) in our institution. We investigated the volume of blood loss, clinical course, postoperative complication, and JOA score in these cases. [Results] Before the TKA, an average of the JOA score of the five knees was 40 points. And it has improved to 77 points at the time of the postoperative last observation (mean postoperative one year and four months). An average of the JOA score of the four hips (47 points before THA) has improved to 77 points (mean postoperative one year and seven months). As postoperative complications, genu recurvatum was revealed in one case of TKA, and thoracolumbar-vertebrae compression fractures has occurred in one case of TKA and in one case of THA.

P3-099

Treatment of infected joint prostheses with high-dose antibiotic infusion

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Conflict of interest: None

[Objectives] Debridement and continuous irrigation had mainly been performed for the treatment of acute prosthetic joint infections in our institution. However, disadvantage of this procedure is that the patients need to stay in bed during the treatment. To solve the problem, we now treat infected prostheses using debridement and high-dose antibiotic infusion through a Hickman catheter. [Methods] High-dose antibiotic infusion therapy was performed for two RA patients who had infected TKA prostheses and one osteoarthritis patient who had infected THA prosthesis. After open debridement, amikacin (400mg/day), gentamicin (80mg/day), or arbekacin (200mg/day) was infused directly into the joint via a Hickman catheter. On the next day of the operation, the patients could move on the wheelchair. And they could have walking rehabilitation in one week after the operation. [Results] At the final follow-up, the infection was clinically healed in all three patients. The causative organism is MSSA with the two TKA patients, and it was not detected with the THA patient. Patients do not need to stay in bed during this treatment. This high-dose antibiotic infusion therapy might be useful method for the treatment of infected joint prostheses.

P3-100

Single onset of arthritis, RA patients- Efficacy of combination therapy with biologic agents early arthroscopic synovectomy-

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Conflict of interest: None

[Objectives] RA patients with prolonged symptoms after onset monoarthritis sometimes appear to have been treated Appropriately. In our institution we early conduct arthroscopic examination and synovectomy for patients who develop with monoarthritis of the knee, and can lead to a diagnosis of RA, to start of administration of methotrexate, to biological drugs, has been maintain remission now. [Methods] Nine patients with knee monoarthritis first visit to our hospital from March 2011 until August 2008] (two males and seven females). Time from onset to receiving an average 11 months (5 years 3 weeks), patients with other symptoms of arthritis were excluded during the visits. If the symptoms are intense, early arthroscopy performed. Receiving gross synovium, and his-

tological findings, exclude other diseases. After the diagnosis of RA, MTX administration was started 2 weeks after surgery. [Results] The RF-positive patients with serologic testing for initial visit was six cases, anti-CCP antibody-positive was in five. No one meets the diagnostic criteria for early RA patients in Japan College of Rheumatology. Patients with serologic positive prolomged, was introduced into administration of adalimumab in combination biologic drugs, and could be lead maintain remission.

P3-101

Total joint replacement of the first metatarsophalangeal joint with a flexible hinged prosthesis

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Conflict of interest: None

[Objectives] A series of total joint replacements of the first metatarsophalangeal joint with a flexible hinged prosthesis was reviewed clinically and radiographically. [Methods] Between 1996 and 2009, we performed arthroplasty of the first metatarsophalangeal joint for 79 feet of 46 patients with rheumatoid arthritisby using a flexible hinged toe implant. Of these, the patients who were followed up for more than 2 years (32 feet of 19 patients; 18 females and 1 male) were enrolled in this study. The average age of the patients at the time of surgery was 61.5years. [Results] The average age of the patients at the time of surgery was 61.5years. At the average follow-up period of 5 years and 8 months (2–13 years), 29 implants (91%) survived, while 2 required removal. Preoperative radiographs showed a HVA of 43.5°and an M1M2 of 14.2°. At follow-up, HVA and IMA averaged 26.0° and 11.7°, respectively. [Discussions] In case that articular cartilage of MTP joint is not damaged, We believe that total joint replacements of the first metatarsophalangeal joint with a flexible hinged prosthesis is one of the adequate surgical treatment.

P3-102

Hallux valgus for RA report metatarsus osteotomy of five cases.

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Conflict of interest: None

【Objective】Biological agent and methotrexate change rheumatoid arthritis treatment. Hallux valgus for RA report metatarsus osteotomy of five cases.【Patients and methods】Between 2008 and 2011, hallux valgus for RA put into metatarsus oseteotomy. (female 5 cases, average 52 years old) Mann osteotomy 3cases, Mitcell ostotomy 1 case, chevron osteotomy 1case HVA 45 angle over choose Mann osteotomy. HVA45 angle under choose Mitchell or Chevron osteotomy..【Result and conclusions】Before operation was HVA 55 angle. But after operation improve HVA 10 angle. Wouud healing late is 2cases. improve 4weeks. A few of Joint damage of RA vallux hallux was good method in metatarsus osteotomy.

P3-103

Arthroscopic Ankle Arthrodesis in Rheumatoid Arthritis

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Conflict of interest: None

[Objectives] Several techniques for ankle arthrodesis have been described. Many of them are not suitable in patients with severe rheumatoid arthritis because of multiple joint involvement, osteoporosis, and increased risk of infecton caused by poor skin conditions. We present the arthroscopic technique in 3 patients with seropositive rheumatoid arthritis. All patients successfully obtained ankle joint arthrodesis. [Methods] All patients are wemen and stage 4 class 3. The mean age at surgery was 78 (75-80) years old. The mean follow up period was 27.3(11-52) months. We curettaged the cartilage and subchondral bone, and fixed the ankle joint by 2-3 CCS screws. We usually start the PWB in 6 weeks. [Results] The oreoperative JFFS-RA score was increased from 41.6-73 points and JFFS-Hind foot score was increased from 56 to 76.3 points. The average duration for union was 93.7 days. We consider that the ankle arthrodesis for rheumatoid arthritis is minimum invasive and good procedure.

P3-104

The rehabilitation effect on three-patients in the early stage of rheumatoid arthritis (RA) —based on the results of the HAQ analysis—

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Conflict of interest: None

[Summary] For patients in the early stage of RA in our hospital, clinical remission (DAS28<2.6) and structural remission (TSS<0.5/year) were achived. We gave rehabilitations to the clients who didn't achieve functional remission (HAQ<0.5) and in daily life our patients reported about their physical condition. [Results] Three patients were shown to have improved HAQ and to no longer have complaints. Case 1, HAQ=0 after 4 weeks of rehabilitation compared to HAQ=0.3 at the beginning. Case 2, HAQ=0 after 2 weeks of rehabilitation compared to HAQ=1.4 at the beginning. Case 3, HAQ=0.05 after 20 weeks of rehabilitation compared to HAQ=0.65 at the beginning. Two out of three had their HAQ=0 within 4 weeks. The HAQ is high when the ADL level is low. The high level of the HAQ is caused by a limited range of motion, a weak grip, a poor in finger coordination, joint pain and muscle tenseness. [Key point] To rehabilitate, it is important to study the HAQ results fully. We must also avoid excessive use or wrong use to preserve the function of the joint by coaching motion, movement and self control.

P3-105

The Factors Influencing on the Upper Limb Function of the Rheumatoid Arthritis Patients

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Conflict of interest: None

[Objectives] The objedtive of this study was to examine the facotrs influencing on the upper extremity function of the patients with rheumatoid arthritis(RA) using The Simple Test for Evaluat-

ing Hand Function(STEF). [Methods] 90RA patients(20men and 70women) were tested. The average morbidity period was 6 years and 5 months. In all cases STEF was tested in both hands, and the sum of the STEF were compared with the Index of disease activity (SDAI, CDAI, DAS28). The morbidity period was compared with the sum of the STEF. Mann-Whitney's U test and Spearman's correlation coefficient byrank test were statically analyzed by risk 5%. [Results] Significant correlation wasn't seen between SDAI, CDAI, DAS28 and STEF. Negative correlation was admitted between the morbidity period and STEF ($rs=-0.40$, $p<0.05$). All cases were classified by morbidity period with the group within 24 months and the group over 24 months and two groups were compared, STEF of both hands. The STEF declined significantly by the group over 24 months of morbidity period ($p<0.05$). [Discussion] The upper limb function of the RA patient didn't undergo influence of disease activity. Bone destruction of the hand progressed so that the morbidity period came long, and the upper limb function of RA patients declined.

P3-106

Association between medical evaluation and physical evaluation of function in patients with rheumatoid arthritis before the introduction of biologic therapy

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Conflict of interest: None

Objective: To examine the association between medical evaluation and physical evaluation of function in patients with rheumatoid arthritis (RA). **Methods**: We assessed medical evaluation (DAS28-ESR and mHAQ) and physical evaluation of function (10 meters gait test, Functional reach test, Timed up and go test, Disability of arm, shoulder and hand and Functional independence measure) in 30 RA patients at the start of biologic therapy. The mean age of all patients was 69.8 ± 8.1 years and the mean duration of disease was 14.2 ± 10.5 years. Their disease staging was described below: Stage I; 5 cases, Stage II; 6 cases, Stage III; 6 cases and Stage IV; 13 cases. We analyzed the correlation of various evaluations statistically. **Results**: There was no correlation between DAS28-ESR and each physical evaluation. On the other hand, there was correlation between mHAQ and each physical evaluation. **Conclusion**: There is not a little disaggregation between medical evaluation and physical evaluation of function in patients with long disease duration and with progressed joint destruction. When we evaluate functional capacity of these patients clinically, we need to use the specialized evaluation in individual cases.

P3-107

Evaluation of swallowing function in patients with rheumatoid arthritis (RA) complicated with cervical disease

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Conflict of interest: None

【Purpose】In RA patients complicated with cervical disease who "have a sense of residual throat", the ability to swallow was examined in comparison with other patients with dysphagia, cervical spine disease.【Method】Group A, 12 RA patients complicated with cervical disease, and group B, 51 patients with cerebrovascular disorders such as dysphagia were evaluated in videofluorography, comparing characteristics of the ability to swallow.【Result】In group A, there were cases of sore throat and bolus malformation during swallowing, and narrowing of the pharyngeal cavity and large amounts of residue into epiglottic vallecula. In group B, we found various stages of failure.【Discussion】Characteristics of group A, #1 External pressure on the posterior pharyngeal wall by cervical disease, and a bolus failure to pass caused large amount of residue into epiglottic vallecula. #2 Alternate swallowing and swallow repetition made it possible to eliminate residue because they could perceive residue into epiglottic vallecula normally by pharyngeal sensation.【Conclusion】In RA patients complicated with cervical disease, oral intake of a normal diet was considered to be possible because it was possible to eliminate residue into epiglottic vallecula.

P3-108

Light therapy has a potential as an adjunctive therapy for rheumatoid arthritis.

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Conflict of interest: Yes

Objective: The purpose of this study was to clarify whether or not light therapy with laser irradiation has a therapeutic potential as an adjunctive therapy against RA synovitis. **Patients and methods:** We had recruited 15 patients with RA (mean age: 64.9 years old). The devise of laser therapy (MEDILASER SOFT PULSE 10, Panasonic Healthcare CO., LTD.) was used. The laser was applied at one point over the swollen or tender joint for 5 minutes at each point, over a period of 4 weeks, once a week for a total of 5 sessions. Outcome measures included arthralgia, patients' global assessment, physician's global assessment and disability. Also, in addition to laboratory blood tests, serum concentrations of proinflammatory cytokines were measured. **Results:** Total 26 joints were treated. After the third or 4th treatments with laser irradiation, there were tendencies to decrease the number of swollen and tender joints. After the 4th treatments, the ADL and VAS scores trended to decrease significantly. Serum concentrations of MMP-3 and IL-6 were significantly decreased after the 5th treatments of laser irradiation. **Conclusion:** We would like to conclude that treatment with laser irradiation may have a therapeutic potential as an adjunctive therapy against RA synovitis.

P3-109

Quantification of Metacarpophalangeal joint subluxation caused by rheumatoid arthritis

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Conflict of interest: None

Metacarpophalangeal joint (MPJ) subluxation is often caused in patients with rheumatoid arthritis (RA). Usually early MPJ subluxation is reducible, but it often becomes irreducible while the patient is not conscious. Therefore, the quantitative evaluation method of MPJ subluxation doesn't exist now though it is necessary to diagnose the early stage of subluxation. The evaluation of MPJ subluxation is useful to select the drug therapy, the hand therapy, and the surgical therapy according to the progress of the disability. [Purpose] It aimed to develop the equipment to evaluate MPJ subluxation quantitatively. [Objects and Methods] RA patients who had reducible Nalebuff Type I in the right thumb was selected. The equipment that we designed pressurize MPJ subluxation from the palmar side with the low-pressure type air actuator. [Results] All cases need pressurizing 1.5MPa or less. [Conclusion] The air pressure for the reposition of the MPJ subluxation was measured by our device with an actuator of 2cm diameter. It was thought that the quantification of the MPJ subluxation in RA patients became possible by the use of our design of the device.

P3-110

The role of rehabilitation for individual patients with rheumatic diseases

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Conflict of interest: None

[Objectives] In this study, we investigate the role of rhabilitation for rheumatoid artritis patients on an individual basis. [Methods] We carry out a questionnaire to rheumatic patient and 117 valid responses were obtained. [Results] More than 50% of the patients do not exercise for symptom relief and prevention of deterioration, due to the reason of "not know what to do". In Approximately 80% of the patients have no experiences in rehabilitation. They answer the reason of this situation as no recommendation from their physician. More than 80% of the patients wish to recieve rehabilitation programs on an individual basis. We suggested that although many patients needs to receive the rehabilitation service, many patients cannot receive he rehabilitation service.

P3-111

A case report: pseudogout with repeatedly attacks in short period

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Conflict of interest: None

[Objectives] We report the case of a 76-year-old male with a chief complaint of pain, swelling and erythema in his left wrist since the past three months. [Cases] The symptoms subsequently relapsed. His left wrist was febrile with pain, swelling. Blood tests revealed CRP 8.4 mg/dl, leukocyte count: 10,500, rheumatoid factor (-), anti-CCP (-), and MMT-3: 43.4 ng/ml. Because there was no evident fluid retention in the wrist joint, a diagnosis of cellulitis was suspected. Cefazolin was administered and CRP decreased. But this effect was temporary, and the condition subsequently relapsed. CEZ was replaced by clindamycin, the effects of which were once again temporary. The patient's clinical course did not indicate the presence of an infection. Eventually, a diagnosis of pseudogout was made after plain X-ray images revealed calcifications in the wrist join, and then prednisolone 5 mg per day was initiated. His symptoms improved with no episodes of recurrence. There are some rare cases of repeated attacks occurring within a short period of time. In this situation, treatment comprises the administration of NSAIDs, colchicine, and methotrexate, although there is no data regarding appropriate oral dosage or duration of administration. This patient has not suffered any relapse for the past.

P3-112

Anti-renin effect of alphacalcidol in systemic lupus erythematosus

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Conflict of interest: None

[Objectives] It is reported that vitamin D_3 negatively regulate renin-angiotensin system (Li YC et al., *J Clin Invest*, 2002). Vitamin D_3 analogues are often used for glucocorticoid-induced osteoporosis in systemic lupus erythematosus (SLE). Hypertension is also seen in clinical courses of SLE treated with glucocorticoid. We investigate anti-renin effect of vitamin D_3 in SLE. [Methods] Seventy patients with SLE in Niigata University Medical and Dental Hospital were recruited. They were divided into two groups, alphacalcidol group (n=29) and non-alphacalcidol group (n=41). We analyzed their proteinuria, estimated glomerular filtration rate, systolic blood pressure, and diastolic blood pressure with Student's t-test retrospectively. [Results] No significant differences were observed in proteinuria in each group. The variation of estimated glomerular filtration rate in the alphacalcidol group was -6.6±14 ml/min/1.73 m^2 and those in the non-alphacalcidol group was -8.2±13 ml/min/1.73 m^2 (p=0.68). The variation of diastolic blood pressure were -5.4±12 mmHg and 6.8±13 mmHg respectively (p=0.09). However, the variation of systolic blood pressure in the two groups were -10.3±19.3 and 10.9±11.3 mmHg respectively (p=0.02). [Conclusion] Alphacalcidol can decrease systolic blood pressure in SLE.

P3-113

Efficacy of Adding low dose Tacrolimus in patients with Systemic Lupus Erythematosus using prednisone maintenance therapies.

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Conflict of interest: None

[Objectives] we retrospectively evaluate the efficacy of low dose tacrolimus (TAC) as add-on therapy in patients with Systemic Lupus Erythematosus using prednisone maintenance therapies, when C3c decreased or urine protein, insreased or clinical manifestation is observed. [Methods] This study was performed on 35 patients with SLE (female 27, male 8), mean age 44 years from2009

through 2011. They used only prednisone therapy or used combination prednisone with other immunosuppressive therapies. When they relapsed we added on TAC start with 1mg to 5mg monitoring trough level. [Results] 1) We can decrease steroid dose11.8±8.5mg/dayto 9.9±8.7mg/day(P<0.005) 2) We can increase C3 67.8±32.6 to 72.5±35.8 (P<0.05). 3) Anti-dsDNA have no remarkable change. 4) 35 patients have urine protein. Among them 23 patient have no change,9 patients improved, 3 patients worsened. [Conclusion] Adding low dose TAC in patients with Systemic Lupus Erythematosus using prednisone maintenance therapies is effective both those who have lupus nephritis and who don't have lupusnephritis.

P3-114

The clinical experience and the assessment of the safety of high dose tacrolimus for SLE

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Conflict of interest: None

Objective: To assess the backgrounds, clinical courses and the safety of high dose Tac in SLE retrospectively. **Patients and Methods:** 24 patients were treated with PSL and Tac, but not with other immunosuppressants. 10 patients were treated with high dose Tac (3.5-5mg/day, Group A), 14 patients with usual dose Tac (0.5-3 mg/day, Group B). **Results:** The disease activity in Group A was higher than that in Group B. The platelet count and the serum C3 level in Group A were lower (A vs B: 166,000 vs 255,000, P=0.06, 15.4mg/dl vs 25.6mg/dl, P=0.04), and the titer of anti-dsDNA-Ab was higher (261.2IU/ml vs 197.7IU/ml, P=0.12). After 6 months of Tac initiation, the platelet count, the C3 level and the titer of anti-dsDNA-Ab were improved in both groups (294,000 vs 277,000, 90.9mg/dl vs 91.5mg/dl, and 6.6 IU/ml vs 12.6 IU/ml). The dose of PSL in Group A was higher than that in Group B (17.6mg/day vs 11.7mg/day). There was no significant difference in the adverse events. In Group A, the increased level of creatinine was found in 1 case, and infections in 2 cases, In Group B, glucose intolerance was found in 1 case. **Conclusions:** Although patients treated with higher dose of Tac had higher disease activities, the occurrence of adverse events was not increased in these patients.

P3-115

A case of thrombotic microangiopathy induced by tacrolimus in Systemic Lupus Erythematosus.

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Conflict of interest: None

[Case] A 42y.o. woman with SLE, Sjögren syndrome and myasthenia gravis, was treated by tacrolimus 3mg/d for hypocomplementemia and elevated level of anti-DNA antibody. In 8 months acute renal dysfunction with proteinuria developed accompanied by anemia and thrombocytopenia. Because recurrence of SLE or tacrolimus-induced renal failure was suspended, the dose of prednisolone was increased (15mg/d) and tacrolimus was given up. Although proteinuria and hematuria were detected, the change of complements level and anti-DNA antibody titer was not seen. She was diagnosed as thrombotic microangiopathy (TMA) due to elevated level of LDH and t-bilirubin with decrease of haptoglobin, and detection of schistocytes, in spite of absence of fever or disturbance of consciousness. After stopping tacrolimus, the serologic findings were improved without plasma-exchange. Renal biopsy was performed since anemia and thrombocytopenia recovered. The result of renal biopsy was compatible with acute renal failure and TMA caused by calcineurin inhibitors. [Discussion] The effectiveness of tacrolimus-treatment for autoimmune diseases is clear, however, sometimes are reported clinical cases of nephropathy or TMA complicated by the agent.

P3-116

Therapeutic drug monitoring of cyclosporine microemulsion in systemic lupus erythematosus

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Conflict of interest: None

Combination therapy of steroids and cyclosporine-A(CSA) is effective for steroid-resistant renal involvement and hematological disorders with systemic lupus erythematosus(SLE). The area under the blood concentration-time curve(AUC) of CSA is the best index of the optimal therapeutic drug monitoring of CSA, But this is not so suitable for use in daily management. In this study, we calculated AUC0-6 with C0, C2, C4 and C6 of CSA in patients with SLE, and analyzed its correlation with CSA levels at blood sampling time points to investigate the optimum monitoring and dosing regimen. Fifteen SLE patients were enrolled into the study. The blood concentration at 2h(C2) after CSA administration correlated best with AUC0-6 (R^2=0.903). The trough level(C0) was not correlated with AUC0-6 (R^2=0.218). C2 was significantly higher (p=0.02), when CSA was administered once daily before breakfast than twice daily after meal. But there were no difference in C0 between both. In conclusion, our data suggested that C2 was the best therapeutic drug monitoring for clinical effects of CSA, and once daily administration of CSA before meal is beneficial in SLE patients.

P3-117

Successful management of systemic lupus erythematosus by immunoadsorption therapy (IAPP) and low-dosage oral prednisolone with the hope of pregnancy

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Conflict of interest: None

[Backgrounds, Objectives] IAPP is available for refractory SLE with insurance coverage in Japan, and is effective for CNS lupus and lupus nephritis. IAPP is also available for some patients in whom immunosuppressive drugs cannot be used, for example, pregnant women. The IAPP technique is simpler and easier than simple plasma exchange and double filtration plasma exchange, and albumin solution and/or fresh frozen plasma is unnecessary as sustained liquid. We report the successful management of SLE in a pregnant woman using IAPP in substitution for immunosuppressive drugs. [Case] A 39-year-old female SLE patient was diagnosed at 18 years old. She was administered mPSL pulse and simple plasma exchange with fresh frozen plasma, and approximately 15mg of PSL was used. The activity was worsened twice with an increasing the anti ds-DNA antibody level, but controlled using mPSL pulse therapy. At the third recurrence, an immunosuppressive drug was recommended, but she refused because of the hope of pregnancy. As an alternative therapy, IAPP was added to steroid

therapy. About 150 sessions of IAPP were performed for her as an outpatient, and no side effect occurred. Since the start of IAPP, her disease condition has been stable in combination with prednisolone.

P3-118

An effective treatment for refractory skin ulcer by negative pressure wound therapy in a patient with systemic lupus erythematosus and antiphospholipid antibody syndrome

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Conflict of interest: None

Negative pressure wound therapy (NPWT) is a treatment to promote wound healing using a controlled negative pressure. The use of NPWT in the management of refractory ulceration in patients with connective tissue diseases has seldom been reported. Case report; A 29-year-old woman was diagnosed with systemic lupus erythematosus (SLE) and antiphospholipid antibody syndrome (APS) at the age of 11. She has been treated by steroid, cyclosporine and warfarin because of the history of deep vein thrombosis and ulceration on her left lower extremity. She was refered to our hospital because of an ulceration with pain on her left ankle joint, and the ulcer gradually worsened and increased to the size of 6 cm wide, 5.2 cm long and 1 cm deep. She was then admitted to our hospital and treated with anticoagulants, antibiotics and surgical debridement. Although the local blood flow was maintained, the formation of granulation tissue was poor. Shortly after the application of NPWT (VAC ATS® system), the volume of healthy granulation increased and skin graft was performed for wound closure. Conclusion; NPWT may be an option for refractory ulcer in a patient with SLE and APS, when primary diseases activity, local infection and pain are under control.

P3-119

A Case of Systemic lupus erythematosus which steroidal osteonecrosis of the femoral head was reversed.

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Conflict of interest: None

[Objectives/Background] Steroidal osteonecrosis of the femoral head (ONF) associated with systemic lupus erythematosus (SLE) is a disease which pathogenesis is not clear yet and also its subsequence is variable. We report a case of SLE which we could reverse ONF within the preclinical stage. [Case] We report a case of 52-years-old female patient who developed SLE in September 2003. In this time she started to take plednisolone 40mg/day. She started to take etidronate from 6 months after onset. She exchanged etidronate to alendronate and started to take activated vitamin D_3 and vitamin K for the prevention from ONF in June 2004. Afterward she exchanged alendronate to risedronate with concomitant vitamins. She discontinued bisphosphonate(BP) in April 2007 from the aspect of long term safety. But she was experienced pain around the left femoral head in March 2008. Then she restarted to take BP since ONF(IIB) and arthritis was diagnosed. Finally in June 2011 she was freed from pain and also ONF had been reversed on the diagnostic image.

P3-120

A case report of multiple brainstem vasculitis associated with systemic lupus erythematosus

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Conflict of interest: None

A 38-year-old woman was diagnosed as anti-phospholipid syndrome (APS) from LAC and embolism in 1999. She was treated by aspirin. In December 2010, she was diagnosed as systemic lupus erythematosus (SLE) from positive anti-nuclear antibody, positive anti-dsDNA antibody, photosensitivity, proteinuria, and arthralgia. In January 2011, she was admitted to another hospital because of stomachache, diarrhea and vomiting. She had edema of gastrointestinal canal and ascites in enhanced CT. Then, she was diagnosed lupus enterocystitis and treated with PSL 40mg/day. But, four days after, she was admitted to our hospital because of suddenly disturbance of consciousness and convulsive seizure. T2-weighted and FLAIR MR images showed an elevated sedimentation rate in both temporal lobes. There were stenosis in both middle cerebral arteries by MRA, she was diagnosed as brainstem vasculitis. She was treated mPSL 80mg/ day following pulse therapy. IL-6 of CSF was high at 7600 and IgG index was high at 1.1. Therefore she was diagnosed NPSLE. After treatment, her symptoms and clinical findings were improved. We report the case of brainstem vasculitis associated with SLE, and the literature review.

P3-121

Rapid progressive cerebral atrophy in systemic lupus erythematosus

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Conflict of interest: None

Cerebral atrophy (i.e. cortical atrophy and ventricular dilation) determined by magnetic resonance imaging (MRI) was prevalent in 18% of newly diagnosed systemic lupus erythematosus (SLE) patients and the most frequent abnormal findings by MRI. A 30-year-old woman with a 5-year history of SLE had a flare-up with fever and disturbed consciousness. The initial MRI with fluid-attenuated inversion-recovery revealed multiple high intensity areas in the deep white matter. Stroke and infection were excluded following investigation. Accordingly, we diagnosed her with an acute confusional state (delirium) caused by SLE. Despite aggressive treatment, including steroid pulse therapy and pulsed intravenous cyclophosphamide, her consciousness rapidly deteriorated into coma. Four months later, we noted significant cerebral atrophy, characterized by a loss of brain volume, along with multiple continuous high intensity areas. She never recovered from coma and was transferred to another hospital. Although mild brain atrophy is a common abnormal brain MRI finding in neuropsychiatric SLE (NPSLE), rapidly progressing moderate to severe brain atrophy, as in this patient, has seldom been reported. Her MRI findings reflect the severe clinical outcome.

P3-122

BAFF levels in the cerebrospinal fluid of patients with neuropsychiatric lupus

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Conflict of interest: None

Purpose: It has recently been demonstrated that Belimumab, a humanized monoclonal antibody against B cell activation factor (BAFF), is an effective therapeutic agent of SLE. However, the role of BAFF in patients with neuropsychiatric lupus (NP SLE) remains unknown. The purpose of this study is to determine whether the measurement of BAFF in the cerebrospinal fluid (CSF) is useful for the diagnosis of NP SLE. Methods: We measured BAFF levels in the CSF of NP SLE patients (n = 6) and non-NP SLE patients (n = 6) by ELISA. Results: BAFF levels in the CSF of NP SLE patients tended to be higher than those of non-NP SLE patients (NP SLE 569 ± 412 pg/ml vs. non-NP SLE 51 ± 79 pg/ml). Conclusion: The measurement of BAFF levels in the CSF seems to be useful for the diagnosis of NP SLE.

P3-123

A Case of neuropsychiatric lupus successfully treated with intravenous cyclophosphamide therapy for refractory cognitive dysfunction and cerebral hemorrhage

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Conflict of interest: None

A 41-year-old female, who was diagnosed with systemic lupus erythematosus and was treated with 150mg of cyclosporine and 8mg of prednisone (PSL) daily, was admitted to oure hospital because of fever and consciousness disturbance in June 2011. She had disorientation to date, brain MRI abnormality, and elevation of IL-6 concentration in cerebrospinal fluid. She was diagnosed as neuropsychiatric lupus and the dose of PSL was increased to 50mg per day. However her cognitive dysfunction (CD) such as left hemispatial neglect, acalculia, construction apraxia, and memory disorder was worsened. Therefore intravenous cyclophosphamide therapy (IVCY) (700mg/day) was started. But she did not get improvement of CD and a new cerebral hemorrhage (CH) at right frontal lobe was detected by follow-up brain CT. Since cerebral aneurysms, vascular abnormalities, tumors, and infections were excluded, neuropsychiatric lupus was thought to be a possible cause of CH. Despite steroid pulse therapy and IVCY (700mg/day), her CD and CH did not improve. Therefore the dosage of IVCY was increased to 1000mg/day and it was resulted in improvement of her neurological symptoms and CH. This is a suggestive case of neuropsychiatric lupus successfully treated with IVCY for refractory CD and CH.

P3-124

Successful treatment of refractory lupus transverse myelitis with mycophenolate mofitil and intravenous dexamethasone; a case report

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Conflict of interest: None

[Objectives] Longitudinal or transverse myelitis is a rare condition reported in 1-2% of SLE patients and may lead to a serious sequela. Use of glucocorticosteroids and cyclophosphamide is the standard therapy, but in severe cases some authors additionally use intravenous immunoglobulins, and there are also single reports on the efficacy of rituximab, bone marrow transplantation and intrathecal therapy with dexamethadone and methotrexate. However, there is a scarce description on the use of mycophenolate mofitil on myelitis although there are several positive reports in patients with lupus nephritis, NP lupus and multiple sclerosis. [Case] We report a case of a 38-year-old female with SLE who developed transverse myelitis in the course. Hiccup, bilateral motor disorder and sensory disturbance appeared abruptly and her MRI showed enhanced lesion in Th1 - Th5. Despite repetitive high dose methylprednisolone and intravenous cyclophosphamide therapy, the conditions persisted and she had severe allergic reaction to subsequent therapy of rituximab infusion. Alterenatively, she was given intravenous dexamethasone and oral mycophenolate mofitil. This resulted in significant improvement of the sensory and motor nervous symptoms and disappearance of the MRI enhancement.

P3-125

Successful treatment of multiple therapy for CNS Lupus

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Conflict of interest: None

A-33-year-old female had fever, butterfly rush, lymph node swelling, and proteinuria in 1991. She was diagnosed as SLE with lupus nephritis(WHO II). Treatment with prednisolone after methylprednisolone pulse therapy resulted in improvement. She had not visited hospital from July 2010. In April 2011, she had leg edema and proteinuria again. She was treated with methylprednisolone pulse therapy and increased prednisolone as an outpatient, but high fever and butterfly rush made her hospitalization necessary. Laboratory data was Cr:1.4mg/dl, ferritin:37710μg/l, CH50:14U/ml, anti-dsDNA antibody:26IU/ml, uric protein:8.7g/gCre. Methylprednisolone pulse therapy resulted in defervescence and laboratory data ameliorated. However bilateral ascending palsy occurred and conscious level deteriorated and became GCS E2V1M6 in a week. Cerebrospinal fluid examination showed high concentration of IL-6 and anti- neuronal antibodies. So she was diagnosed as CNS lupus. Although the symptoms of CNS lupus did not well respond prednisolone, plasma exchange(PE), IVCY, and IVIG, neurological disorder slowly improved after rituximab infusion. We conclude that multiple therapy such as steroid, PE, IVCY, IVIG, and rituximab for refractory CNS lupus was effective for ameriolation of neurological symptoms.

P3-126

A male SLE who developped peripheral polyneuropathy and lupus nephritis

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Conflict of interest: None

P3-127

Characteristics of patients with systemic sclerosis complicated with other autoimmune diseases

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Conflict of interest: None

[Objectives] To investigate characteristics of the cases with SSc complicated with other autoimmune diseases. [Methods] All the patients treated as SSc on April 1, 2011 were extracted from patient database. Clinical information was obtained from their medical records. [Results] Of 113 patients with Sc, 38 were complicated with any autoimmune disease; systemic autoimmune diseases in 28 (Sjogren's syndrome in 19, RA in 5, polymyositis in 4, dermatomyositis in 2, SLE in 2 and temporal arteritis in 1), and organ-specific diseases in 17 (PBC in 5, Hashimoto thyroiditis in 4, autoimmune hepatitis in 4, ITP in 3 and MG in 1). Age of SSc onset, SSc duration and rate of complicating pulmonary artery hypertension were similar in the group with and without other autoimmune diseases. Significantly more cases had interstitial pneumonia in group with other autoimmune diseases. Larger rate of coexisting other autoimmune diseases was observed in female, limited cutaneous (lc) SSc than male, diffuse cutaneous (dc) SSc, respectively, but without statistically significance. Organ-specific autoimmune diseases were complicated significantly more in lcSSc than in dcSSc. Antitopoisomerase-I antibody positivity was significantly associated with complicating no other autoimmune diseases.

P3-128

Systemic scleroderma with senile systemic transthyretin cardiac amyloidosis: A case report

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Conflict of interest: None

A 80-year-old man with systemic sclerosis(SSc) was admitted to our hospital because of progressive heart failure. At first we suspected ischemic heart disease or myocardial damage caused by SSc and we performed echocardiography. The echocardiographic examinatiom showed diffuse thickening of wall and increased echogenicity. Since our finding suggested that cardiac amyloidosis, cardiac catheterization and myocardial biopsy were performed. The result of congo red staining of myocardial tissue was diagnosed with cardiac amyloidosis. At first, we suspected from the incidence of AL amyloidosis. But Bence Jones protein was not detected and possibility of multiple myeloma was negative on clinical examination. We therefore conducted a further differentiation of amyloidosis. Immunostaining and genetic test were diagnosed with senile systemic transthyretin cardiac amyloidosis. After treatment of heart failure, symptoms were stable. Though the merger of cardiac amyloidosis is rare, it's important to suspect the possibility of cardiac amyloydosis when we find unexplained heart failure patiants with SSc. And is important to differemtiate the AL and ATTR amyloidosis because the treatment and prognosis quite differ between them.

P3-129

A case of systemic sclerosis complicated by severe digital ulcers successfully treated with ambrisentan

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Conflict of interest: None

A 49-year-old woman was diagnosed as systemic sclerosis in 2005. Exacerbation of interstitial pneumonitis was treated with immunosuppressive therapy in 2008. Afterwards, she felt bilateral digital pain and digital ulcers (DU) developed. She was treated with combination therapy with bosentan, sildenafil and beraprost, and the symptoms ameliorated. However, DU relapsed in July, 2011. She was treated with alprostadil intravenously for 2 weeks and bosentan was switched to ambrisentan with concomitant use of sildenafil and beraprost. After introduction of this therapy, the DU improved and were completely healed in August. In the present case, DU were resistant to combination therapy with bosentan, sildenafil and beraprost. It was reported that bosentan prevented to develop DU, whereas it could not heal the established DU. On the other hand, if both bosentan and sildenafil are administered, the serum levels of bonsentan are increased and those of sildenafil are decreased through drug-drug interaction. Furthermore, selective endothelin A receptor blocker ambrisentan may be more beneficial for DU healing than dual endothelin receptor antagonist bosentan. Our case suggested that switching from bosentan to ambrisentan may be potent alternative therapy for severe intractable DU.

P3-130

A case of intractable skin ulcer occurring in conjunction with systemic sclerosis and for which use of ambrisentan and tadalafil was effective

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Conflict of interest: None

[Objective] We report a case of intractable cutaneous ulcer occurring in conjunction with systemic sclerosis and for which ambrisentan and tadalafil was administered **[Case]** A 64-year-old woman **[History of Present Disease]**In 2,000, the patient experienced Raynaud phenomenon and cutaneous sclerosis in digits and toes of both sides. The diagnosis was diffuse systemic sclerosis. Cutaneous ulcer was also present when the diagnosis was made. The treatment started with oral use of beraprost sodium, etc and intravenous lipoPGE1 but the disease was treatment-resistant. Cutaneous sclerosis slightly improved with additional oral bosentan. In August, 2007, complications occurred such as renal crisis and secondary pulmonary hypertension. In May, 2011, skin ulcer of the 3rd and 5th toes of the right lower limb aggravated and necrosis occurred, so sarpogrelate and bosentan were changed to ambrisentan and tadalafil. **[Outcome]**In the 4th week subsequent to the change of medication, the blood flow in the ulcer was improved and its size decreased. In our case of cutaneous ulcer in the 3rd and 5th toes of the right lower limb, complete cure was achieved in the 20th week of ambrisentan and tadalafil administration.

P3-131

Successful treatment with Ambrisentan for pulmonary hypertension (PH) and digital ulcer (DU) of Systemic Sclerosis (SSc) with low left ventricular function

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Conflict of interest: None

A 63 years old woman, diagnosed as SSc in 2001, was performed emergency percutaneous coronary intervention for acute myocardial infarction in August 2010. After the intervention, her dyspnea worsened. She was introduced to our hospital, the symptom was thought to be associated with SSc. She had anti-Scl-70-antibody, interstitial lung disease, DU, and also seemed to have PH because ultrasound cardiography revealed estimated right ventricular pressure (eRVSP) was 44mmHg. Left ventricular ejection fraction (LVEF) was 27%, PH was likely to be secondary to low left ventricular function than PAH. Although cardiac resynchronization therapy improved LVEF to 35%, eRVSP was deteriorated to 55mmHg. So she was diagnosed as PAH. Moreover DU was exacerbated, her distal phalanges were exposed. Then, Ambrisentan was started. After a month, eRVSP was 32mmHg, and WHO class was improved from III to II. At 6 month, DU was getting better without significant adverse effects. There are few reports Ambrisentan remedies DU like this case in Japan.

P3-132

Efficacy of Bosentan on Raynaud's phenomenon in patients with connective tissue diseases

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Conflict of interest: None

[Objective] To analyze the efficacy and safety of bosentan on Raynaud's phenomenon in patients with connective tissue diseases. [Patients] Two males and 14 females, with a mean age of 61.4 years were studied. Mean disease duration was 19.4 years. SSc (limited; 9, diffuse; 2); 11 cases, mixed connective tissue disease; 3, SLE; 1, overlap syndrome (SSc and polymyositis); 1. [Methods] Effects of bosentan on Raynaud's phenomenon were assessed by diary cards. Evaluation points in the card included number of occurrence, duration of Raynaud's phenomenon during a day and patient's visual analog scale of its accompanying symptoms (cold sensation, numbness and pain). The improvement (≧ 20%) more than 2 out of 3 points was judged as "effective". Thermography of hands and feet was additionally performed. [Results] 1) Number and duration during a day of Raynaud's phenomenon were significantly improved after the administration of bosentan ($P < 0.01$). 2) Cold sensation and numbness as accompanying symptoms 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.

P3-133

Characteristics of Systemic Sclerosis without Interstitial Pneumonia and Pulmonary Hypertension

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Conflict of interest: None

[Objectives] To assess clinical characteristics of Systemic Sclerosis (SSc) patients without Interstitial Pneumonia (IP) and Pulmonary Hypertension (PH). [Methods] This study comprised a total of 26 SSc patients without IP and PH. We assessed pulmonary function tests (PFT). We analyzed the comparison of clinical findings between group A (%VC/%DLco>1.7) and B (%VC/%DLco<1.7). [Results] Eight patients was diffuse cutaneous type. PFT showed that %VC was normal (105.3±13.7%) and %DLco was decreased (57.9±17.2%). There were no significant differences of the percentage of SSc-specific autoantibody, Hb, and serum KL-6 between Group A and B. Group A showed that the increased percentages of diffuse cutaneous type, digital ulcer, and teleangiectasis, and the increased level of BNP (A vs B: 32.6 pg/ml vs 16.35 pg/ml, $p=0.02$). [Conclusion] SSc patients with decreased %DLco have high risk factors for PH

P3-134

Intramuscular Benzathine Penicilline in Systemic Sclerosis (Two Successful Experience)

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Conflict of interest: None

[Objectives] Systemic sclerosis (SSc) is a connective tissue disease characterized by overproduction of collagen fibers by abnormal fibroblasts and microvascular and endothelial abnormalities. Anti-inflammatory penicillin derivatives were discovered by Thompson, Kevan. Penicillamine is a metabolite of penicillin which was used routinely in SSc. It prevents collagen cross-linking. After accidental successful experience with intramuscular penicillin and after getting written consents from the patients, intramuscular benzathine penicillin was prescribed for them. [Methods] 22 year old Zoroastrian girl and A 42 years old man with history of SSc for years with progressive skin stiffness, polyarthralgia and Raynaud's phenomenon, diagnosed with SSc on the basis of typical clinico - serological manifestations. D-penicillamine and pentoxyfylline orally and illoprost intravenously had unfavorable response. They received monthly penicillin injections for three months. [Results] clinical indeces of Raynaud's phenomenon and skin stiffness improved significantly based on patient's and physician's global assesment 4-6 weeks after initiation of treatment.

P3-135

Scleritis, Hypopigmentation, Dermatitis and Multiple Sclerosis-Like Neurologic Feature (Manaviat-Owlia syndrome)

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Conflict of interest: None

[Objectives] Aggregation of some sign and symptoms from different organ system are important issues in medicine. Scleritis, vitiligo, poliosis, dermatitis and multiple sclerosis-like neurologic feature are features with common immunologic base. Herein we describe a 23 years-old man with probable new association of scleritis, hypopigmentation, dermatitis and multiple sclerosis-like neurologic manifestations. [Methods] a 23-years-old male with history of whitish hair discoloration, hypopigmentation and dermatitis, severe burning sensation all over the body and painful red eye. In physical examination, scleritis, vitiligo, poliosis and signs of upper motor neuron disease were evident. [Results] This could be the first report of constellation of scleritis, vitiligo, poliosis and MS-like presentation in a patient. So, if other observations proved similar presentation, it could be considered as a new and independent entity. (Manaviat-Owlia syndrome)

P3-136

Successful treatment with tacrolimus of interstitial pneumonia associated with systemic sclerosis

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Conflict of interest: None

A 85-year-old woman was admitted to our hospital because of few years history of dyspnea and cough. Physical examination showed shin thickness from her fingers to trunk. An arterial blood gas analysis revealed PaO_2 of 44.2 Torr, and $PaCO_2$ of 35.6 Torr. The serum level of KL-6 was elevated with a value of 789 U/ml. Computed tomography of the chest demonstrated ground-glass opacities and traction bronchiectasis in the bilateral lower lungs. She was diagnosed as having systemic sclerosis associated with interstitial pneumonia with acute aggravation. She was treated with prednisolone (25 mg/day), followed by tacrolimus (2 mg/day) with favorable response. There were no adverse events of tacrolimus 6 months after the treatment. Tacrolimus may be the worthy trying treatment for interstitial pneumonia in systemic sclerosis.

P3-137

A case of systemic sclerosis combined with bullous pemphigoid in whom reversible posterior leukoencephalopathy syndrome developed induced by cyclosporine A

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Conflict of interest: None

A 59 year-old woman visited us because of Raynaud's phenomenon and bullous lesion of her skin. She was diagnosed as systemic sclerosis (SSc) combined with bullous pemphigoid (BP) based on the histological findings and positive anti-BP180 antibody. PSL of 30mg/day was administrated for BP. Because decrease in the dose of PSL induced exacerbation of BP several times, dermatologists thought that her BP is difficult to control, and 100mg/day of cyclosporine A (CyA) was added in July 2011 with 20mg/day of PSL. She visited our hospital because of headache, dysconsciousness developed in August 2011. Communicative ability was completely abolished. Meningitis was denied based on the findings of cerebrospinal fluid, EEG, and physical examinations. High density signal recognized on brain MRI T2WI and flair images combined with dysconsciousness of acute onset made us reach the diagnosis of reversible posterior leukoencephalopathy syndrome (RPLS). CyA was discontinued and anti-hypertensive drug was administrated by drip-infusion. Consciousness improved gradually after CyA was discontinued and finding of brain MRI also improved, which made us convince that it was RPLS induced by CyA. In conclusion, PRLS developed in the course of SSc is rare and we report this case hire.

P3-138

A case of systemic sclerosis with syncope by complete atrioventricular block

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Conflict of interest: None

A patient was diagnosed as systemic sclerosis based on Raynaud phenomenon at 1987. Raynaud phenomenon was relieved by treatment and systemic sclerosis was well controlled. At 2011, she visited to our hospital because of syncope. At first, electrocardiogram showed normal sinus rhythm. But she fainted again, and we found at intravascular conduction defect on ECG. We placed a temporary pacemaker and could not find a myocardial ischemia on cardiac catheter. At last, a permanent pacemaker was implanted. In systemic sclerosis, atrioventricular block was a famous but rare complication. We report the case with some speculations.

P3-139

Clinical findings of systemic sclerosis with cardiac dysfunction

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Conflict of interest: None

We analyzed the clinical features of 47 patients with systemic sclerosis (SSc) and 13 (28%) had cardiac dysfunction (cardiac failure, LVEF<60%, ventricular arrhythmia or block, cardiac effusion). Age, sex and the incidence of interstitial lung diseases did not show any difference between SSc patients with or without cardiac dysfunction. Diffuse type SSc (62%), positive cases for Scl-70 antibody (46%), pulmonary hypertension (62%), and renal dysfunction (39%) were more prevalent in patients with cardiac dysfunction. The mean %VC was low (69%) and mean cardio-thoracic ratio of chest X-P was high (58%) in these cases. In addition, hypertension and diabetes were observed more frequently.

P3-140

Novel therapy of bone marrow exposure with occlusive dressing for rheumatic gangrene

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Conflict of interest: None

[Background] Gangrene in rheumatic disease such as systemic

sclerosis, is mostly intractable. Patients suffering from painful ulcers eventually undergo major amputation such as below-knee level. Consequently, there is a strong need to decrease the number of such major amputation, as well as to develop simple, reasonable treatment procedure. Bone marrow cells contain multipotent stem cells that can differentiate into macrophages, endothelial cells, fibroblast, which play important role in tissue repair process. Therefore, aggressive debridement of sequestrum, and exposure of fresh bone marrow cells into wound site could be appropriate treatment for gangrene. [Case] 74-year –old man who has been suffering from foot gangrene accompanied with systemic sclerosis, was referred to us, complaining that he was diagnosed as indication for below-knee amputation. X-ray showed bone lysis in his first toe, and osteomyelitis was also found in MRI. Debridement with metatarsal bone level could rescue his lower limb, and the patient was discharged on his own foot. [Conclusion] Bone marrow exposure with occlusive dressing therapy is considerably novel, simple, and effective procedure, which can prevent major amputation and keep better patients' quality of life.

P3-141

A case report. Progressive finger and wrist contractures responsible for the linear scleroderma.

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Conflict of interest: None

Linear scleroderma is an unusual disorder characterized by linear streaks of fibrotic skin involvement which can lead to sever limb deformities and contractures. The author reports a 57-year-old male, farmer, with progressive bilateral finger and wrist contractures. Linear streaks of fibrotic skin involvement and skin biopsy revealed that the contractures were responsible for the linear scleroderma. In general, medications and surgical procedures are usually of little benefit in ameliorating the symptoms and contractures. However, corticosteroid injections and hand therapy stopped the progression of the contractures in this case. Therefore, early detection and treatment might improve the prognosis for the finger and wrist contractures, which are due to linear scleroderma.

P3-142

Sarcoidosis in a woman with limited cutaneous systemic sclerosis

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Conflict of interest: None

A 67-year-old woman had developed purple erythema on the fingers and bilateral dorsum pedis in 2010. In January 2011, she presented Raynaud's phenomenon, and was referred to our hospital. Physical examination revealed skin sclerosis restricted to the hands, nailfold capillary changes, and purple erythema on the fingers and bilateral dorsum pedis. Histologic study of the incisional biopsy obtained from erythema on the left hand disclosed epithelioid granuloma without necrosis around the vessels in the subcutaneous tissues. Laboratory date included positive anticentromere antibody and elevated serum angiotensin converting enzyme. The chest high-resolution CT showed multiple nodular lesions in both lung fields. Those findings suggested coexistence of limited cutaneous systemic sclerosis and sarcoidosis. Although some cases with autoimmune diseases were reported to be complicated with sarcoidosis recently, it has been increased that the case reports of with sarcoidosis, coexistence of systemic sclerosis and sarcoidosis has seldom been indicated.

P3-143

Analysis of T cell receptor diversity in patients with systemic sclerosis who received autologous hematopoietic stem cell transplantation

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Conflict of interest: None

[Objectives] Clinical trials have indicated that autologous hematopoietic stem cell transplantation (HSCT) can persistently suppress disease activity in patients with severe systemic sclerosis (SSc), but the mechanism of the effectiveness has remained unclear. We studied the mechanism of immune reconstitution by analyzing T cell receptor (TCR) diversity. [Methods] The patients who received HSCT were enrolled. RNA was extracted from the frozen peripheral blood mononuclear cells and was reverse-transcribed into complementary DNA (cDNA). TCR Vβ rearrangements were amplified from cDNA using Vβ family-specific oligonucleotide primers, and then we analyzed the frequency of Vβ repertoire usage and complementary determining region 3 (CDR3) size distributions by using DNA sequencer. [Results] Before HSCT, the increases of specific TCR Vβ repertoires and the skewed patterns (oligoclonal, monoclonal and missing peak) of CDR3 size distributions were often observed. TCR diversity evaluated over time after HSCT had a tendency to improve the skewed pattern even 3-6 months after HSCT, but in some cases the abnormality of TCR diversity was persisting for a long time. [Conclusion] Abnormality of TCR diversity may improve after HSCT in patients with SSc.

P3-144

A case of systemic sclerosis associated with severe thrombocytopenia and renal dysfunction which was successfully treated with thrombopoietin receptor agonist and intravenous cyclophosphamide

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Conflict of interest: None

We report a case of systemic sclerosis (SSc) associated with severe thrombocytopenia and renal dysfunction which was successfully treated with thrombopoietin receptor agonist and intravenous cyclophosphamide. The patient is 47-year-old woman who had a history of SSc for 11 years and treated with predonisolone. She was admitted to our hospital because of thrombocytopenia, hypertension and renal dysfunction. Renal biopsy revealed scleroderma renal crisis, but she had no sign of hemolytic anemia. ADAMTS13 activity level was normal. These data suggested the diagnosis of renal crisis with autoimmune thrombocytopenia. She was treated with ACEI, thrombopoietin receptor agonist and intravenous cyclophosphamide, which improved renal dysfunction and thrombocytopenia.

P3-145

A case of polymyositis complicated with psoriatic arthritis

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Conflict of interest: None

A-54- year-old woman was consulted clinic because of myalgia and arthralgia of bilateral finger joints appeared in 2009. Her laboratory and X-ray findings were revealed CRP, RF and anti CCP antibody were negative, there were bone destruction at DIP joints. It was diagnosed as arthritis of unknown origin, at of oral prednisolone (PSL) 5mg/day was started. Erythema of finger and hand was appeared in 2011. She consulted our hospital because of "mechanic's hand" and hyperkeratotic erupution of the hand and the elevation of creatinine kinase (CK). Laboratory findings were showed CK was 6147 IU/ml, aldorase and myoglobin were high, anti Jo-1 antibody was positive. Hand X-ray finding showed bone erosion of DIP joint as typical psoriatic arthritis "pencil in cup". Muscle MRI finding showed elevated abnormal signal. Muscle biopsy was revealed there were necrosis and fibrosis with inflammatory cell infiltration of muscle fiber. And there was hyperkeratotic eruption which showed pathological findings of psoriasis at elbow joint and finger. So we diagnosed polymyositis complicated with psoriatic arthritis and 1mg/kg of oral PSL were given. Polymyositis/Dermatomyositis complicated with psoriatic arthritis is rare, so, it is interesting with clinical characteristic including skin liesion

P3-146

Utility of IVIg Therapy for Refractory Myositis in 4 cases

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Conflict of interest: None

[Case 1] In 200W,44 years old woman diagnosed as PM. She was referred to our hospital because of poor reaction nevertheless PSL/CyA/MTX. She had increased PSL dosage and prescribed IVIg [Case 2] A 34 years old woman diagnosed as PM in 200X. She was received IVIg for repeats of aggravation in spite of multiple immunosupression therapy. [Case 3] 71 years old woman have had general fatigue and developed erythema of fingers in 200Y, and diagnosed as DM/IP.PSL therapy didn't show clinical improvement. As CyA or TAC couldn't continue because of adverse reactions, IVIg was prescribed. [Case 4] 49 years old man, diagnosed as PM/IP in 200Z. He have received PSL and IVCY/CyA therapy with good response. In 200Z, he got IVIg because of high level of CK while reducing the PSL dosage. [Course] Of the four cases with IVIg, Cases 1 and 2 showed good response with repeated therapy. In Case 3, decrease of PSL dosage was possible by IVIg. IVIg was not effective in Case 4. [Conclusion] Four cases of refractory myositis were treated with IVIg. Dalakas et al. recommend that IVIg therapy for PM/DM patients who was not obtained clinical improvement with the initial therapy. We will report and discuss a favorable or unfavorable cases of IVIg therapy based on a review of the literature.

P3-147

Case Reports: 2 Patients of Dermatomyositis with Interstitial Pneumonia (IP) treated by Intravenous Immunoglobulin (IVIG)

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Conflict of interest: None

Case1 : 58y woman complained heliotrope rash, loss of strength, ulcer of skin and pharynx, and IP, Jan. 2010. Diagnosis of DM was given. Since recurrent diseases, she was treated by 3 course of IVIG since Nov. 2010, at monthly interval. Muscular strength was improved and skin lesions were vanished. The titer of KL-6 was decreased from1902 to1031. Case2 : 35y woman. Onset of DM was on 2000 at her 24y old with myositis (CK 2282, Aldolase 68.3), skin lesion and IP. End of 2010, short of breath appeared as a result of the deterioration of IP, consistent with worsening of myositis. IVIG therapy was chosen added on 19mg of PSL presently taken, because she had had MAC infection of skin. The first course of IVIG was given on May 17th, 2011. The titer of KL-6, CRP and aldolase was declined with improvement of her symptoms. However, her illness was worsened with fever, elevated titer of KL-6 and aldolase on Jun. 17th. The second course of IVIG and higher dose of PSL(30mg) were given. The third course of IVIG was performed on Aug. 2011. As a result of persistent therapy, her illness turned in better condition with decreased titer of KL-6 and aldolase from 1300, 14.6 to 832, 4.6 respectively. IVIG is thought to be effective for DM complicated with IP, as well as, for muscular weakness.

P3-148

A case of malignancy-associated dermatomyositis successfully treated with intravenous immunoglobulin.

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Conflict of interest: None

A 68-year-old female presented with skin rash, muscle weakness and dysphagia. She was diagnosed with dermatomyositis, as a result of a muscle and skin biopsy. Furthermore, left breast cancer was detected through screening for cancer. Despite the high dose corticosteroid administration over 3 months and a radical resection of the breast cancer, her muscle involvement did not improve, obligated to be fed via gastrostomy and to be bedridden. Therefore, monthly infusions of immunoglobulin were initiated. Shortly after the first infusion, her swallowing ability ameliorated, followed by other physical functions. After the treatment with five courses of intravenous immunoglobulin, she became able to take all of the meal orally, and to walk with auxiliary tools.

P3-149

A case of polymyositis positive for the serum anti-SRP antibody that was successfully treated with intravenous immunoglobulin therapy.

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Conflict of interest: None

The idiopathic inflammatory myopathies are systemic autoimmune diseases characterized by chronic inflammation, leading to progressive weakness of the proximal muscles. Myositis-specific or associated autoantibodies are often found in the serum of polymyositis (PM) and dermatomyositis patients. Anti-SRP (signal rec-

ognition particle) antibody is thought to be associated with severe forms of the disease, particularly those with heart and lung involvement and resistant to adrenocorticosteroids. We present a 66-year-old female polymyositis patient with serious muscle weakness and high CPK level (21550 IU/L). Although initial high-dose steroid therapy methylprednisolone (1g/day x 3 days, i.v.) followed by predonisolon (1mg/kg/day, p.o.) plus cyclosporine A (150 mg/day), muscle weakness was not improved and CPK level did not decrease to less than 3000 IU/L. After the patient was treated with intravenous immunoglobulin (IVIG), muscle strength was improved gradually and CPK level decreased to less than 700 IU/L. To our knowledge this is the first reported case of PM positive for serum anti-SRP antibody treated with IVIG. IVIG therapy might be therapeutic agent of choice for the anti-SRP antibody sever positive PM patients.

P3-150

Mass gamma-globulin therapy for combined hemolytic anemia and CADM/IP

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Conflict of interest: None

In May 20XX, a 59-year-old man noticed an edema in the upper eyelid. An erythema was observed adjacent to the lateral elbow. In August, he presented at the dermatology department with fever, muscle and finger-joint pain and Gottron's papules. At consultation, he tested negative for Jo-1 antibodies, and CPK (127 IU/L) was administered to alleviate the symptoms. Clinically amyopathic DM (CADM) was diagnosed. Ga scintigraphy revealed rapid progression of pulmonary disorder throughout the lung. Steroid pulse therapy with CyA and PSL 60 mg was started. Because of slightly decreased oxygenation, IVCY pulse therapy was started on Day 10th. No improvement was noted, and interstitial pneumonia (IP) progressed. IVIG was administered from Day 49th. Subsequently, IP progression subsided, but erythrocyte deformation was observed from 13th October. On Day 67th, the Hb level decreased to 6.9 g/dL. Haptoglobin level decreased, direct Coombs test was positive, and urinary myoglobin was detected. He was diagnosed with hemolytic anemia. Erythrocyte deformation was observed until Day 72th October, after which anemia improved and PSL was progressively reduced, resulting in stable respiration. Our findings suggest that CADM/IP can be treated with IVIG, but hemolytic anemia may rarely develop.

P3-151

A case of amyopathic dermatomyositis with refractory pulmonary disease successfully treated with intravenous-immunoglobulin therapy

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Conflict of interest: None

[Case report] A 64-year-old woman was admitted to our hospital because of severe malaise and liver dysfunction. She had sufferd erythema on both eyelids for a few years. On admission, other skin rashes were seen on her neck and upper arms. Although her blood sample showed normal CPK level, her muscle biopsy revealed perifasticular atrophy consistent with dermatomyositis. Chest X-ray and CT showed BOOP-like lesions. She was diagnosed as amyopathic dermatomyositis, with pulmonary disease. Her treatment with prednisolone 40mg daily, cyclosporine 200mg daily and intravenous cyclophosphamide (500mg per every 2 weeks) was started. Her malaise and skin rashes were disappeared, but pulmonary disease was aggravated 10 weeks after and she became to fell difficulty in breathing. Methylprednisolone pulse and intravenous-immunoglobulin therapy were added to her treatment. She recovered well in breathing and pulmonary lesions were disappeared after second course of intravenous-immunoglobulin therapy. [Conclusion] intravenous-immunoglobulin therapy seems to be very effective for amyopathic dermatomyositis with refractory pulmonary disease.

P3-152

Intravenous immunoglobulin (IVIG) improves clinical manifestations and muscle inflammation detected by MRI in inflammatory myopathy.

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Conflict of interest: None

【Purpose】: To clarify effects of intravenous immunoglobulin (IVIG) therapy on clinical manifestations, laboratory findings and muscle inflammation detected by MRI in inflammatory myopathy. 【Methods】 We reviewed medical records of 7 patients with refractory myositis to intensiveimmunosuppressive therapy including corticosteroid and immunosuppressants (CsA, FK506, MTX and IVCY) which decreased CK levels partially, but failed to improve symptoms. The patients include 4 of DM (amyopathic DM 2), 2 of PM and 1 of IBM. 【Results】IVIG improved subjective symptoms in all patients, enhanced muscle power in all patients except 1 IBM and decrease in serum CK levels in all patients with CK elevation. Sequential MRI examination was performed on 4 patients. Before IVIG, T2 hi lesions in muscles were found in all these 4 patients whose CK levels were decreased partially by intensive immunosuppressive therapy. IVIG rapidly improved the T2 hi lesions in all patients. 【Conclusion】 IVIG is effective on refractory inflammatory myopathy except IBM. Improvement of MRI-detectable muscle inflammation by IVIG in refractory patients suggests that mechanism of resolution of myositis by IVIG might be different from that by immunosuppression.

P3-153

Efficacy of Rituximab in Refractory Polymyositis

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Conflict of interest: None

We describe the effectiveness of rituximab, an anti-B lymphocyte monoclonal antibody, in a case of refractory polymyositis with immunosuppressive agents resistance. A 52-year-old man is myositis of the onset for 2007. He ran over recurrent myositis, and we added immunosuppressive therapy, but there was not an effect. So he was given 4 weekly intravenous infusions of rituximab at 500 mg/body, while maintaining PSL at 15 mg/day and MTX at 6mg/week. Prior to rituximab, he had significant muscle weakness with creatine phosphokinase (CPK) elevation(4000IU/L). Two courses later, his CPK was decrease(4400IU/L→2200IU/L) and muscle strength was improved. ^{18}F-fluorodeoxyglucose positron emission tomography-computed tomography (^{18}F-FDG PET-CT) showed decrease in accumulation of ^{18}F-FDG. Serum immunoglobulin levels were not significantly decreased by rituximab, and significant morbidity such as fulminant chronic hepatitis B reacti-

vation or progressive multifocal leukoencephalopathy have been noted to date. Rituximab was well tolerated, and its efficacy in inflammatory myositis should be evaluated in further controlled studies.

P3-154

Efficacy and safety of physical therapy in active polymyositis/dermatomyositis patients.

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Conflict of interest: None

[Background] Physical therapy (PT) including a controlled muscle training and exercise program in patients with inflammatory myopathies is considered beneficial to the well-being and recover of muscle strength. For fresh and active polymyositis/dermatomyositis (PM/DM) patients, however, whether the early induction of PT is effective and safe, is controversial. [Methods] We retrospectively examined newly diagnosed PM/DM patients who received PT during admission between 2005 and 2011. Six patients (group A) were introduced PT within 1 weeks from starting corticosteroid and another 6 (group B) were not introduced PT until 4 weeks. We evaluated efficacy and safety of early PT by checking manual muscle strength test (MMT) and disease activity (CK and CRP) at day 0 and day 28 from corticosteroid therapy. [Results] In terms of characteristics, the two groups were almost matched at day 0. Average MMT of group A significantly improved from 3.4 to 4.0, on the other side, that of group B decreased (4.5 to 3.7). Percent CK at day 28 compared to CK at day 0 were not different between two group. [Conclusions] Compared with late PT introduction, early PT introduction provided better muscle recover in active PM/DM patients. Moreover, early PT introduction did not affect on disease activity.

P3-155

A combined therapy of corticosteroid and intravenous continuous administration of cyclosporin A in dermatomyositis patients with severe interstitial pneumonia

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Conflict of interest: None

[Objectives] Interstitial pneumonia (IP) is one of serious complications in patients with dermatomyositis (DM), especially clinically amyopathic DM. In the present study we retrospectively investigated clinical outcomes after a combined therapy of corticosteroid and intravenous continuous administration of cyclosporin A (CYA) in DM patients with severe IP. [Methods] Intravenous continuous administration of CYA was performed only when oral intake of CYA was impossible because of critical care for respiratory failure. CYA was started at 0.17 mg /kg / hr and the administration speed of CYA was controlled in order to keep the blood concentration of CYA at 250 - 350 ng / ml. [Results] Intravenous continuous administration of CYA was performed in 6 DM patients. The duration of the intravenous continuous administration of CYA was 7 to 15 days, and the interval between admission to our hospital and commencement of this treatment was 0 to 44 days. Two patients completely recovered from IP, and these 2 patients underwent the intravenous continuous administration of CYA right after admission to our hospital. [Conclusion] Intravenous continuous administration of CYA from early phase of illness might be a therapeutic option for DM patients with severe IP.

P3-156

A case of acute onset myopathy with swelling of right upper arm

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Conflict of interest: None

A 40 year-old male otherwise healthy saw a primary medical doctor(PMD) due to sore throat and right arm swelling. Blood examination showed elevated creatine kinase(CK) as high as 6,000 IU/L and he was introduced to our hospital. He claimed dull, painful and weak thighs, with swollen right arm. On physical examination, he was febrile, had facial rash, and proximal muscle weakness. Serum CK level was elevated to 20,000 IU/L and he was hospitalized emergently for further investigation and treatment. He had neither recent medical history, no vaccination, nor family history of neuromuscular diseases. He had no electorate, nor thyroid disorder. Upper arm CT denied abscess and thrombus, as possible causes of swollen arm. Muscle MRI showed symmetrical inflammation of the proximal muscles and EMG showed a slight myogenic pattern. Muscle biopsy revealed degenerated and necrotized muscles with infiltration of inflammatory cells. At first he was suspected to have an acute onset polymyositis. However, his muscle symptom as well as right arm swelling improved rapidly without any medication and his clinical course suggested that he had transient myopathy associated with viral infection. We here report this suggestive case when considering the differential diagnosis of inflammatory myopathy.

P3-157

Predictive factors of developing systemic lupus erythematosus in patients with primary antiphospholipid syndrome

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Conflict of interest: None

Background: Genetic background and clinical manifestations in primary antiphospholipid syndrome (PAPS) are similar to those in systemic lupus erythematosus (SLE). Objective: To clarify the predictive factor for developing SLE in PAPS patients. Method: In this retrospective study, 57 (female 50, mean age 41.3±16.1) PAPS patients, fulfilling the Sydney revised Sapporo criteria for definite APS, were recruited from 1990 to 2010. SLE was diagnosed by ACR revised criteria for classification in 1997. We analyzed the predictive factor of PAPS developing SLE. Result: The mean follow-up period was 5.9±4.1 years. Cerebral infarction was found in 33 patients, deep vein thrombosis in 6, pulmonary embolism in 3, and central retinal vein occlusion in 1. Among 50 women, 22 had obstetric complications. Among the aPL-related manifestations, thrombocytopenia was in 10, non-stroke neurological manifestations in 9, and cutaneous manifestations in 3. Ten PAPS patients developed SLE. The median period developed SLE was 1.5 years (3 month-14 years). Patients with non-stroke neurological manifestation developed to SLE more frequently than those without (50.0% vs 8.5%, OR 10.75; 95% C.I, 2.15-53.68). Conclusion: Non-stroke neurological manifestation was a predictive factor for developing SLE in PAPS patients.

P3-158

β2-Glycoprotein I 379 T/- polymorphism in patients with Antiphospholipid syndrome in Japanese populations.

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Conflict of interest: None

[Objectives] β2GPI is the principal target of autoantibodies in the APS. β2GPI 379T/- was identified in β2GPI deficient families (β2GPI Sapporo). Recently, β2GPI was found to inhibit complement activation. APS patients are known to have decreased complement levels in their serum. In this study, we investigated the possible contribution of β2GPI Sapporo in patients with APS. [Methods] Genomic DNA samples were obtained from 135 patients with APS, 296 patients with systemic lupus erythematosus (SLE) and 428 healthy controls. Genotyping was performed using TaqMan pre-designed SNP Genotyping Assay. Odds ration and 95%Cl were used compared the genotype and allele frequencies. The relativity of genotyping, serum levels of C3 and C4 and CH50 were analyzed by Man-Whitney's U test. [Results] Homozygous β2GPI was not found in our cohort. Heterozygous β2GPI deficiency was significantly more frequent in patients with APS. APS with positive aPL harbored heterozygous β2GPI deficiency more frequently than APS with negative aPL. Serum complement levels of C3, C4 and CH50 in APS patients with heterozygous β2GPI deficiency were lower than those homozygous for normal β2GPI genotype. [Conclusion] β2GPI hetero-deficiency is related with aPL antibody as well as APS itself, and with complement activation.

P3-159

A case of SLE and antiphospholipid syndrome with Moyamoya-like vascular changes

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Conflict of interest: None

A 28-year-old woman with SLE was admitted to our hospital due to bilateral pleural effusion and elevated anti-double strand DNA antibody. She has been also suspected to have mental disorder and sometimes had amaurosis fugax for two years. On admission, MRI of the head revealed old cerebral infarction of right basal ganglia and right cerebral white matter. Subsequent angiography showed stenosis of the right internal carotid artery and occlusion of the proximal portion of the bilateral anterior cerebral arteries with moyamoya-like vessels. Laboratory investigations revealed raised levels of lupus anticoagulant, anti-β(2) glycoprotein I antibody IgG, anticardiolipin IgG, and phosphatidylserine-dependent antiprothrombin antibody IgG. Hence the patient was diagnosed SLE and antiphospholipid syndrome (APS) with Moyamoya-like vascular changes. There are only few reports regarding SLE and APS with Moyamoya-like vascular changes. However, the clinicians should investigate the co-existence of APS early when a patient with SLE has neuropsychiatric symptoms.

P3-160

A case of antiphospholipid symdrome with acute lymphocytic leukemia

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Conflict of interest: None

The patient was forty years old man. He had seizure from 25 years old. He took medicines for epilepsy. Seizure disappeared in recent year. His brain MRI appeared atrophy and multiple cerebral small infarctions. At August 2008, He was hospitalized, because he had seizure attack again. The cause of seizure was rechecked. Biological false positive reaction, anti cardiolipin IgG antibody(50U/ml) and anti cardiolipin β2GP1 antibody(89U/ml) were positive. APS were diagnosed by multiple cerebral small infarctions and positive antiphospholipid antibody. He started taking warfarin and vasodilator. Then, the blast cell was appeared at routine blood test. Acute lymphocytic leukemia was diagnosed by bone marrow puncture. After the chemotherapy, seizure was disappeared. Because of no report of case of APS with leukemia, we present this case.

P3-161

Transient pulmonary edema following acute adrenal infarction due to anti-phospholipid syndrome

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Conflict of interest: None

【Case presentation】A 17-year-old woman was diagnosed as having primary anti-phospholipid syndrome (APS), and started to take warfarin and clopidogrel. At age 20 she developed sudden-onset left chest pain, and 3 days later she was admitted to our hospital. The pain seemed to increase with deep breathing. Chest-abdominal computed tomography (CT) demonstrated multiple ground-glass opacities (GGO) with no pleural effusion in bilateral lungs and obvious swelling in the left adrenal gland. After admission her chest pain quickly improved in parallel with disappearance of GGO in the lung on CT. Diffusion-weighted magnetic resonance imaging of abdomen showed an abnormal high signal in the left adrenal grand suggestive of acute infarction. She received anti-coagulant therapy, and was discharged from our hospital without sequelae 11 days after admission.【Discussion】In the present patient adrenal infarction secondary to APS might have caused pulmonary edema via the transient excess of serum catecholamine. Adrenal infarction needs to be considered as a cause of sudden-onset chest pain with pulmonary edema in patients with APS.

P3-162

Rapidly destructive coxarthropathy induced by antiphospholipid antibody syndrome: A case report

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Conflict of interest: None

【Objective】We experienced the rapidly destructive coxarthropathy induced by antiphospholipid antibody syndrome. We report the clinical course of this case.【Patient】The patient is 68 y.o. female who had left coxalgia. She consulted our institution because of rapidly destructive coxarthropathy. In laboratory data examined for preoperative examination of total hip arthroplasty (THA), we found prolonged APTT, positive RPR and negative TP-Ab. As the

results of additional examination of self-antibody, antiphospholipid antibody syndrome (APS) with SLE was diagnosed. The left THA was performed and clinical course after the operation was stable. 【Discussion】 It was reported that avascular necrosis can be detected in 20% of patients with primary APS. This case indicated that APS can be one of risk factor of rapidly destructive coxarthropathy.

P3-163

MMP-3 and anti-CCP antibodies titers are associated with changes in disease activity ?

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Conflict of interest: Yes

[Objectives] The aim of the present study was to investigate the effect of DMARDs treatment in patients with rheumatoid arthritis, and determine whether baseline MMP-3 and anti-CCP antibodies titers are associated with changes in acute phase reactants. [Patients and methods] 114 patients with refractory RA were treated with DMARDs included anti-TNFα and methotrexate therapy for refractory rheumatoid arthritis. Serum samples were tested for MMP-3, and for anti-CCP antibodies by an ELISA, were tested at baseline and after mean 1.2 years. Percentage change in C reactive protein (CRP), MMP-3 titers and anti-CCP antibodies titers were calculated. [Results] Anti-cyclic citrullinated peptide (CCP) antibodies were found in 82.5% of patients before therapy; anti-CCP antibody titre decreased in 54patients and increased in 60 patients. At baseline and 1.2 years RF titres and anti-CCP antibodies were unchanged. At the time of good response of the DAS28(n=22) significantly improved SDAI, MMP-3 and CRP value. ($p<0.001$) However, the antiCCP antibody and RF titers did not change. Anti-CCP antibodies correlated inversely with changes in CRP and MMP-3 during treatment. [Conclusions] MMP-3 relates to disease activity, but the anti-CCP antibody titers did not relate.

P3-164

Multicenter survey on the relationship between maternal anti-SSA antibodies and neonatal lupus erythematosus (The 3rd report)

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Conflict of interest: Yes

[Objectives] To determine the relation between clinical status of the pregnant women with anti SS-A/Ro and the outcome of their children. [Methods] Medical records of pregnant women with anti SS-A/Ro who were treated from 2000 to 2009 at 5 hospitals to which researchers belong and other 60 hospitals in Japan were provided. Using those, clinical features, treatments, and laboratory data were analyzed. Anti SS-A/Ro antibodies were detected by DID and/or ELISA. [Results] Seven hundred thirty records including 67 patients with neonatal lupus erythematosus (NLE) were provided. There were 50 cases of cardiac NLE among them. We are analyzing these data now. We will report the results in this meeting.

P3-165

Autoantibodies to peroxiredoxin in patients with systemic autoimmune diseases

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Conflict of interest: None

[Objectives] In systemic autoimmune diseases (SAD), autoantibodies to anti-oxidative enzymes have been reported so far. We investigated whether autoantibodies to Peroxiredoxin (Prx), a redox enzyme, exist in patients with SAD. [Methods] We evaluated titers of antibodies to recombinant Prx1, Prx2 and Prx4 by ELISA and WB using serum samples from 92 patients with SAD. [Results] Anti-Prx1 antibodies were detected in 33% of the patients with SAD, in particular 57% of the patients with SLE. Anti-Prx 4 antibodies were detected in 17% of the same patients, in particular 32% of the patients with Behcet disease. Anti-Prx2 antibodies were detected in 30% of the patients with SAD, however, were detected in 60% of the patients with primary vasculitis syndrome, in particular 88% of the patients with Takayasu arteritis. Clinically, anti-Prx1 autoantibody titer was correlated with lower serum levels of CH50, C3, and C4 and higher serum levels of IgG. Titers of D-dimer and TAT were found significantly higher in the anti-Prx2 positive patients with vasculitis than the negative ones. Furthermore anti-Prx2 titers tended to change in parallel with activity of the vasculitis. Anti-Prx antibodies may affect the pathophysiology of SAD through enhancement of cell damage by oxidative stress.

P3-166

Constrictive vasculopathy (digital necrosis, pulmonary hypertension and scleroderma renal crisis)-associated autoantibodies to ACE2: the 3rd report

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Conflict of interest: None

[Background] We have reported inhibitory autoantibodies to angiotensin converting enzyme 2 (ACE2) in patients with rheumatic disease and pulmonary artery hypertension (PAH) or digital necrosis. The anti-ACE Ab are also detected in patients with active SLE without vasculopathy, and those antibodies do not inhibit in vitro ACE2 activities. In this study we estimated the prevalence of positive anti-ACE2 Ab in more patients with constictive vasculopathies. [Patients and Methods] ELISA for serum anti-ACE2 Ab was performed in 8 PAH with collagen diseases, 10 digital necrosis, 1 SSc renal crisis, 3 idiopathic PH, 2 thrombotic PH and 1 ASO. [Results] Anti-ACE2 Ab was positive in 11 of 15 (73%) PAH patients, and was negative in all patients with idiopathic pulmonary hypertension, thrombotic PH, or ASO. Two patients with SSc renal crisis had positive serum anti-ACE2 Ab: 79-year-old female on hemodialysis having a history of renal crisis (9 years ago), and s76-year-old female with a history of renal crisis (4 years ago). [Conclusion] Anti-ACE2 antibody may be associated digital necrosis, PAH with collagen disease and scleroderma renal crisis.

P3-167

Common autoantibody markers for SLE and vascular diseases

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Conflict of interest: None

The mortality rate of myocardiac and cerebral infarction is high in systemic lupus erythematosus (SLE). The recent studies reported that specific autoantibodies appear in not only collagen diseases but also arteriosclerosis. [Objective] The purpose of present study is to investigate common autoantibody markers for SLE and vascular diseases. [Methods] By using protein microarrays we examined six sera from SLE and healthy subjects to identify autoantibody patterns and associated antigens. Twenty-eight immunoreactive antigens showed the higher prevalence in SLE samples. Furthermore we compared patient's sera (SLE: 80samples, myocardiac infarction: 95samples, cerebral infarction: 47samples) with 95 healthy donor sera by using AlphaLISA. [Conclusion] Level of 19 antibodies in SLE sera was higher than those of control sera. Two of 19 SLE specific antibody makers were more high level in myocardiac infarction sera. We would predict the onset of myocardiac infarction in SLE by these two makers.

P3-168

Successful treatment with weekly adalimumab on entero-Behcet's disease with fluctuated symptoms by biweekly administration

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Conflict of interest: None

A 46 year-old Japanese female visited a hospital because of arthralgia and treated with 30mg of predonisolone(PSL) under diagnosis of arthritis unkonwn origin. At 41 year old, she developed diverticulitis perforation, colostomy was performed at our hospital. When PSL was tapered to 17mg/day, somatitis, genital ulcers and mucosal ulcers at the site of colostomy were frequently developed. Under diagnosis of possible Behcet's disease, she was treated with additional colchicines that improved her symptoms slightly. When PSL was tapered to 15.5mg/day, somatitis and genital ulcers were worsened and folliculitis and intestinal ulcers near the site of the colostomy were newly developed. She was diagnosed as enter-Behcet's disease and treated bi-weekly adalimumab (80mg/2w) in addition to 20mg/day of PSL which improved her symptoms dramatically. However, her conditions fluctuated during the interval of injections. Before injection of adalimumab, her symptoms were returned to the wosened conditions. Instead of biweekly administration, adalimab was given weekly(40mg/w) which stabled her condition well. This case indicates weekly adalimmab is an optional therapy for patients with fluctuated symptoms during interval of the injections.

P3-169

Treatment with anti-TNF antibodies, not with etanercept, improved entero-Behcet's disease.

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Conflict of interest: None

A 42 year-old Japanese woman visited our hospital because of recurrent oral ulcers. She developed pharyngeal ulcers, folliculitis, and arthritis, was diagnosed as having Behcet`s disease and was treated with corticosteroid and cyclosporine. In spite of the treatment, her oral ulcers were worsened and she frequently developed diarrhea. Colonoscopic examination showed no abnormalities. Additional infliximab treatment was started which improved her conditions dramatically. Effects of infliximab were gradually lost and anti-TNF therapy was switched from infliximab to etanercept. After the switching, she developed melena by intestinal ulcers in addition to exacerbations of muco-cutaneous symptoms. Adalimumab was given instead of etanercept which dramatically improved her condition including intestinal ulcers. This case indicates that Treatment with anti-TNF antibodies, not with etanercept, was effective on entero-Behcet's disease.

P3-170

A case of entero-Behçet's disease associated with myelodysplastic syndrome with trisomy 8

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Conflict of interest: None

[Objectives] We report the effectiveness of infliximab for entero-Behçet's disease with myelodysplastic syndrome with trisomy 8. [Methods] case report [Results] A 33-year-old woman with myelodysplastic syndrome with trisomy 8 presented high-grade fever, and right lower quadrant abdominal pain. After temporal relief by intravenous antibiotics, she abruptly developed intestinal perforation and emergency operation was performed. She was diagnosed as entero-Behçet's disease by pathological examination on the resected intestine. Cyclosporin was not effective. She was successfully treated by infliximab. We review the effectiveness of infliximab for entero-Behçet's disease with myelodysplastic syndrome with trisomy 8.

P3-171

Two cases of intestinal Behçet's disease that have been successfully treated with TNF inhibitors

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Conflict of interest: None

Case 1: A 50-year-old woman was presented with arthritis, erythema nodosum, anemia and oral aphtha. The endoscopic examinations revealed multiple ulcerations in the stomach, the duodenum, the ileum and the colon. She was diagnosed as gastrointestinal Behçet's disease. She was treated with prednisolone (PSL) 40mg, colchicine, azathioprine (AZA), sulfasalazine (SSZ), mesalazine and tacrolimus (TAC). Because the enteric lesions were difficult to control with the standard regimens, we initiated infliximab (IFX) 5mg/kg. The intestinal ulcers healed completely and PSL was tapered and stopped successfully. Case 2: A 43-year-old woman presenting with fever, abdominal pain, oral aphtha, genital ulcer and arthritis, was given a diagnosis of Behçet's disease. IFX 5mg/kg was started since the enteric lesions were refractory to PSL40mg, mesalazine, AZA and methotrexate (MTX). However, despite the initial improvement of the stomach ulcers with IFX, the enteric le-

sions recurred with tapering doses of PSL. So we switched IFX to Adalimumab (ADA) 40mg biweekly. The patient is now on PSL, AZA, ADA and mesalazine. Discussion: TNF inhibitors were effective in 2 cases that were refractory to glucocorticoid and immunosuppressant. ADA might be an alternative choice for patients that have problems with IFX.

P3-172

A clinical study of Behçet's disease in Nagoya City University Hospital

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Conflict of interest: Yes

[Objectives] We clarify the clinical features about the Behçet's disease (BD) patients who visited in Nagoya City University Hospital. [Methods] We examined the type, the symptom and the treatment of the Behcet's disease patient who visited our hospital more than six months from January 2001 to September 2011. [Results] Eighty three BD patients are included. Mucous membrane manifestations were oral aphthosis seen in 100%, and genital aphthosis in 64% of patients. Skin manifestations were seen in 88%. Ocular manifestations were seen in 27%. Joint manifestations were seen in 50.5% (arthralgia, monoarthritis, oligo/polyarthritis, ankylosing spondylitis). Neurological manifestations were seen in 9.6% of patients. Gastrointestinal manifestations were seen in 16.9% of patients. Vascular involvement was seen in 4.8% of patients. HLA-B51 in 45% of patients.

P3-173

Excessive CD4+ T cells co-expressing IL-17 and IFNγ in patients with Behcet's disease

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Conflict of interest: None

[Objectives] We have presented evidences that support excessive Th1 cell activity in BD. This investigation was designed to study the pathogenic role of Th17 cells in Behcet's disease (BD). [Methods] We studied Th17-related gene expressions in BD peripheral blood mononuclear cells with 25 primer pairs, comparing with those in normal controls. Gene expression profiling demonstrated that TGFβ/Smad signaling pathway was significantly enhanced in BD ($P<0.05$). We conducted Th17-related cytokines stimulation analysis on naïve CD4+ T cell obtained from peripheral blood. We observed that mRNA expressions of IL-17, RORC and IL-23 receptor were significantly elevated in the presence of IL-23 in BD ($P<0.05$). Intracellular cytokine staining analysis of IFNγ and IL-17 on memory CD4+ T cells revealed that IFNγ+ IL-17+ CD4+ T cell frequencies were significantly increased in BD peripheral blood ($P<0.01$). [Results] These results suggest that IL-17+ IFNγ+ CD4+ T cells play a role in the pathogenesis of BD and the cells are overproduced though IL-23 stimulation in autocrine/paracrine manner, and though skewed TGFβ/Smad signaling pathway.

P3-174

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

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Conflict of interest: None

[Objective] Th1-skewed immune responses, conducted by T cells and monocytes/macrophages, play a pivotal role in the pathophysiology of Behcet's disease (BD). To elucidate the pathophysiology of BD, we comprehensively analyzed protein profiles of peripheral blood mononuclear cells (PBMCs). [Methods] Proteins, extracted from PBMCs from 3 BD patients and 3 healthy control subjects (HC) were separated by 2-dimensional gel electrophoresis. Then the protein spots of interest were analyzed by mass spectrometry. [Results] In all the 586 protein spots detected, intensity of 94 spots was altered in BD ($\geq|1.5|$ folds: BD>HC, 32 spots; HC>BD, 62 spots; $p<0.05$). The 19 protein spots ($\geq|2.0|$ folds), identified by mass spectrometry, included an inhibitor of neutrophil function, an anti-oxidant enzyme, a heat shock protein, a coagulation factor precursor, and cytoskeletal proteins. [Conclusion] The proteomic analysis of PBMCs was useful for detection of proteins, expression of which was significantly altered in between BD and HC. The alteration of those protein expression may be associated with the pathophysiology of BD.

P3-175

Gastrointestinal manifestations of Behçet's disease in Japan: a study of 43 patients

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Conflict of interest: None

[Objectives] We analyzed the clinical gastrointestinal (GI) characteristics of Behçet's disease (BD) patients in Japan. **[Methods]** We retrospectively reviewed the clinical charts of 412 patients who fulfilled the 1987 Japanese criteria for BD. **[Results]** Forty-three patients (10.4%) had BD related GI lesions which were shown by imaging examinations. Mean age at BD diagnosis and onset of GI episodes were 34.2 and 36.2 years, respectively. The patients suffered from abdominal pain (70%) and GI bleeding (42%), while they had lower frequency of eye involvement and higher incidence of arthritis and vascular involvement than BD patients without GI lesions. The lesions were prevalent in the ileum (74%) followed by cecum (49%) and esophagus (21%). The patients were treated with mesalazine and sulfasalazine (96%), corticosteroids (74%), immunosuppressants (30%), and infliximab for 7 patients having refractory lesions (16%), while 10 patients had surgical operation (23%). Two patients died due to non-GI events during the observation. **[Conclusions]** The diagnosis of BD was often difficult because of lack of eye involvement. Surgery is required for some patients in spite of intensive immunosuppressive therapies. Appropriate use of anti-TNF agents may be promising for the GI involvement.

P3-176

Entero-Behcet's disease with extensive ulceration of colon

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Conflict of interest: None

We report the clinical course of two patients with entero-Behcet's disease (eBD) with extensive ulceration of colon. Case 1 40-years-old male was presented with diarrhea, melena, oral aphtha, genital ulcer, folliculitis and arthritis in February, 2011. Then she was suspected to have Behcet's disease, and admitted to our hospital. Colonoscopy revealed deep ulcers from ascending to sigmoid colon. So he was diagnosed with eBD and was treated with prednisolone and mesalazine. This treatment successfully improved his symptom and colon ulceration. Case 2 33-years-old female was presented with fever, folliculitis and arthritis in February, 2011. Then she was admitted to our hospital. Physical examination showed erythema nodosum, oral aphtha, genital ulcer, arthritis and melena. Colonoscopy revealed erosive mucosa and longitudinal ulcers in whole colon. So he was diagnosed with eBD and was treated with prednisolone and mesalazine. This treatment improved his symptom and colon ulceration. eBD is characterized clinically by the presence of ileocecal ulceration. Some cases were reported eBD with extensive ulceration that was needed to distinguish from inflammatory bowel disease. In severe case intestinal perforation was reported. So we think colonoscopy should be performed immediately.

P3-177

A Case of HLA-B27(+)B51(-) Intestinal Behçet's Disease distinguished from Inflummatory Bowel Disease or Spondyloarthropathy

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Conflict of interest: None

[Objectives] Behçet's disease (BD) has relationship with HLA-B51, and the colitis is similar to inflammatory bowel disease (IBD). HLA-B27 is related to spondyloarthropathy (SpA), moreover extra-intestinal manifestations of IBD is included in SpA. We would like to present a HLA-B27(+) intestinal BD male patients. [Case report] Before the age of 30, his oral aphthous ulcers (OAU) recurred, stomach and duodenum ulcers were revealed in his 30s. Since 40-year-old, high-grade-fever with arthritis and genital ulcers had recurred, respectively. At the age of 48, colon polyp was resected. At the age of 49, his bloody stool with high-grade-fever was occurred. Thus, he was suspected having anal abscess due to IBD, thereafter he was introduced and drainage was performed; however, his inflammatory was not improved with using antibiotic and 20mg PSL. Colonoscopy was revealed multiple ulcers in sigmoid colon, and the pathological findings was similar to ulcerative colitis. Steroid pulse therapy was ineffective, therefor total colectomy was performed. The intestinal manifestation of present BD case were improved; however, OAU, acuneiform eruption, and erythema nodosum were recurred mildly. [Conclusion] We experienced a case of HLA-B27(+)B51(-) intestinal BD distinguished from IBD or SpA.

P3-178

Three cases of Bechet's disease with intestinal and vascular involvements

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Conflict of interest: None

[Objectives] We investigate about aspects of Bechet's disease with intestinal and vascular involvements. [Methods] Case 1 is a 67-year-old woman who showed erythema nodosum and thrombophlebitis. She was suffering from ileocecal ulcer and thrombosis of portal vein, inferior vena cava and bilateral iliac veins about 10 months ago. Inspite of the treatments of prednisolone and azathioprine, intestinal ulcer was not recovered. She was administerd infliximab. Case 2 is a 62-year-old man who showed erythema nodosum and anal gangrene, thrombosis of bilateral pulmonary artery, and hemorrhagic shock last year. He was suffering from fever, erythema nodosum and tarry stool about 15 days ago and he was transferred to our hospital due to hemorrhagic shock again. Gastrointestinal endoscopy did not reveal the focus of bleeding. Anticoagulation therapy and immunosuppression therapy was not done because vascular involvement was not active with positron emission tomography. Case 3 is a 47-year-old-woman with abdominal aortic aneurysm and intestinal stenosis. She had melena three times last year. She fell into hemorrhagic shock and died because of massive hematemesis and hematochezia. [Results] Bechet's desease with both intestinal and vascular involvements may have life-threatening lesions.

P3-179

Revised Guidelines of Intestinal Behçet's disease (Draft): Consensus Statement

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Conflict of interest: None

[Objectives] To establish clinical guideline from the diagnosis to the therapy in Intestinal Behcet's disease (BD). [Methods] We revised consensus statements for the diagnosis and management of intestinal BD using a modified Delphi approach in 2007. The individual statements were re-evaluated in expert meeting members based on the literatures and a national survey of infliximab (IFX) therapy for intestinal BD. [Results] The statements consist of diagnosis, assessment of clinical activity, treatment, supplementary comments, and attached figures. The diagnosis of intestinal BD is made based on round or oval shaped deep ulcers in the ileocecal region in addition to meeting the 1987 Japan BD classification Criteria. Clinical activity is comprehensively determined by systemic and local findings including endoscopic findings and laboratory data. Recommended pharmacological therapies include corticosteroids, mesalasine, sulfasalazine surazosulfapyridine, and immunosuppressants such as azathioprine. IFX is listed as an option especially in patients having refractory intestinal lesions to conventional therapies. Surgical operation is considered when massive bleeding, perforation, and stenosis occurred and when pharmacological therapies were insufficient.

P3-180

A case of mixed connective tissue disease with rapidly progressive interstitial pneumonia

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Conflict of interest: None

A 36-year-old woman had suffered from Raynaud phenomenon since October 2010. Serological data showed positive results of antinuclear antibody and anti-RNP antibody without other symptoms. She admitted to our hospital in January 2011 because of progressive dyspnea. Physical examination on admission showed erythema on the dorsal surface of the hands and muscle weakness. Chest high-resolution computed tomography (HRCT) scan revealed diffuse ground glass opacities and liner opacities in bilateral lower lobes. She was diagnosed as having mixed connective tissue disease (MCTD) with interstitial pneumonia (IP), and treated with prednisolone and azathioprine with favorable response. However, the clinical manifestation and chest HRCT findings deteriorated rapidly in March. She was treated with intravenous cyclophosphamide (IVCY pulse therapy), prednisolone and cyclosporine (CyA). Her clinical conditions and chest HRCT findings improved. We report a rare case of MCTD with rapidly progressive IP successfully treated with IVCY and CyA.

P3-181

Mixed connective tissue disease complicated by autoimmune-associated hemophagocytic syndrome

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Conflict of interest: None

[Case Report] A 34-year-old woman presented with Raynaud's phenomenon, arthralgia, myalgia and general fatigue lasting over nine months. Hematological result showed a positive titer of anti-U1-RNP antibody and the elevation of the KL-6 level. A chest X-ray and a chest computed tomography revealed interstitial pneumonia, and a cardiac ultrasonographic study showed mild pulmonary hypertension. Infection, malignancy and other collagen diseases were excluded, and mixed connective tissue disease (MCTD) was diagnosed. Initially, she was treated with 25 mg prednisolone (PSL) daily. However, on day 7 after PSL initiation, she complained with a high fever and a hematological test showed abnormalities; decreases of Hb and platelet count, and elevation of AST, ALT, LDH, TG, CRP, and serum ferritin level (7260 ng/mL). Infection was excluded again (including EB virus). Bone marrow biopsy showed hemophagocytosis. Therefore, steroid pulse therapy was started and 50 mg PSL daily was subsequently continued. Afterward, her clinical course improved despite the tapering of PSL to 7.5 mg daily without flare of MCTD and HPS. [Discussion] Autoimmune-associated HPS commonly occur in the setting of systemic lupus erythematosus and Adult-onset Still's disease, whereas MCTD with HPS is extremely rare.

P3-182

Mixed connective tissue disease overlapped by Wegener's granulomatosis

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Conflict of interest: None

A 47-year-old woman with mixed connective tissue disease (MCTD) was admitted to our hospital due to developing nasal obstruction, epistaxis, and anosmia. She was diagnosed as MCTD 7years ago, based on Raynaud's phenomenon, a high titer of anti-RNP antibody, polyarthralgia, and scleodactylia. She was taking oral prednisolone and MTX, and had used some biologics for arthralgia. She also suffered from relapsing and refractory ulcerations of fingers, painful purpuric maculae in her legs and ankles, followed by livedo reticularis An otorhinological consultation revealed granulomatous bloody masses of the both nasal cavity complicated with the perforation of the septum. Histology of the livedo reticularis showed the filtration of inflammatory cells in the small vessel walls. She was diagnosed as MCTD overlapped by Wegener's granulomatosis. Because she was taking some immunosuppressant, she had no lung and renal disease and was PR3 ANCA-negative. Therapy with 1 mg/kg prednisolone and intravenous cyclophosphamide resulted in dramatic improvement of nasal symptoms and dissolution of the cutaneous lesion. Overlapping WG is rare in MCTD, but this disease should be considered as a possible diagnosis for more appropriate treatment in case of presenting skin lesions with vasculitis.

P3-183

A case report of nodular regenerative hyperplasia (NRH) of the liver associated with mixed connective tissue disease (MCTD)

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Conflict of interest: None

An autopsy case of 66-years-old woman. She was diagnosed as SLE and interstitial pneumonia 17 years ago, and as MCTD 7 years ago. She had been administered prednisolone and azathioprine. She was admitted because of edema, pleural effusion and ascites. In the hospital, she died of hemorrhagic SHOCK due to rupture of esophageal varix. Autopsy revealed NRH of the liver as the cause of esophageal varix. NRH is characterized by diffuse benign transformation of the hepatic parenchyma into small regenerative nodules with minimal or no fibrosis. Some cases of NRH of the liver associated with collagen vascular disease such as SLE or CREST syndrome had been reported, so we should pay attention to those condition.

P3-184

Evans syndrome associated with Mixed connective tissue disease

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Conflict of interest: None

A 22-year-old female was admitted to the hospital for severe anemia, jaundice, and fever. She was aware of finger pain and Raynaud's phenomenon, and diagnosed as mixed connective tissue disease (MCTD) 6 months ago. Laboratory findings showed normocytic anemia (RBC : $281\times10^4/\mu l$, Hb : 7.8 g/dl, Ht : 23.0 %). A diagnosis of autoimmune hemolytic anemia (AIHA) was made by elevated lactate dehydrogenase (LDH), positive Coomb's test, and remarkable reduction of haptoglobin. She responded insufficiently

to the treatment of methylpredonisolone pulse therapy, and thrombocytopenia was occurred. Because thrombotic thrombocytopenic purpura (TTP) was suspected, she was treated by plasma exchange. Clinical and laboratory findings were improved. Her phychologic state and creatinine level are normal, in addision to a lack of red cell fragmentation in peripheral blood, a disintegrin-like and metalloproteinase with thrombospondin type 1 motifs 13 (ADAMTS13) activity was not decreased. As a result, she was diagnosed as Evans syndrome. We report a rare case of Evans syndrome associated with MCTD with references.

P3-185

Successful treatment of thrombotic thrombocytopenic purpura with plasma exchange in a patient with mixed connective tissue disease

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Conflict of interest: None

Thrombotic thrombocytopenic purpura (TTP) occurring in a patient with mixed connective tissue disease (MCTD) is very rare and has been described in only more than ten cases. We report a female case of TTP with MCTD. A 21-year-old female who had been diagnosed as having MCTD in 2010, was admitted to our hospital due to general fatigue and high fever in March, 2011. Her laboratory findings revealed thrombocytopenia, microangiopathic hemolytic anemia and disturbance of renal function. The activity of disintegrin and metalloproteinase with thrombospondin type 1 motifs 13 (ADAMTS13) was severely decreased. She was diagnosed as TTP, and plasma exchange with 30 unit fresh frozen plasma was started immediately. Her clinical and laboratory findings improved rapidly only by plasma exchange without other additional therapies such as corticosteroids and immune-suppressive agents. The findings in this case suggested immediate treatment intervention in the early stage is necessary to provide a good prognosis.

P3-186

A case of pulmonary arterial hypertension (PAH) associated with MCTD, corticosteroid therapy was effective for worsening of PAH after the bacterial infection.

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Conflict of interest: None

A 68-year old woman was admitted to our hospital complaining of gradually worsening dyspnea for about two years. She was diagnosed as mixed connective tissue disease(MCTD) because of anti-RNP anitibody ≧500U/L, interstitial pneumonia(IP), pulmonary arterial hypertension(PAH). Vasodilators and warfarin were started for PAH and her symptoms improved. We didn't use corticosteroid or immunosuppressants at first. A month later, her IP and PAH became worse with the bacterial infection. Then she was treated with methylpredonisolone pulse therapy and her symptoms improved dramatically. Immunosuppressive therapy is effective for PAH associated with SLE, better than MCTD, systemic sclerosis. It is reported that immunosuppressants for MCTD-PAH is effective temporary, but they lose effect in the end. Moreover, acute onset PAH is more effective than chronic. In our case, her PAH took chronic course, and immunosuppressive therapy was not expected to be effective at first. But when the disease became worse, corticosteroid therapy was very effective for PAH. In conclusion, MCTD-PAH may be responded to immunosuppressants, even in the chronic case, especially when the disease become worsening.

P3-187

JAK-STAT pathways are involved in the production of IL-6 by BAFF stimulated human monocytes.

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Conflict of interest: None

[Objectives] BAFF plays an important role in the pathogenesis of Sjögren's syndrome (SS). We have demonstrated that BAFF induces robust production of IL-6 by SS monocytes. In our previous study, we found that the induction of IL-6 production by BAFF in IFN-gamma-primed THP-1 (Human acute monocytic leukemia cell line) was strongly suppressed by a JAK3 inhibitor. In the present study, we have further investigated a regulatory mechanism of the production of IL-6 by BAFF stimulated THP-1. [Methods] IFN-gamma-primed THP-1 cells were stimulated with soluble BAFF (sBAFF) in the presence or absence of a JAK3 inhibitor. The expression levels of IL-6 and STAT protein families were analyzed by ELISA and/or quantitative RT-PCR. [Results] We demonstrated that stimulation of IFN-gamma-primed THP-1 with BAFF enhanced the expression level of JAK3. Similarly, the expression level of STAT4 in the cells was increased upon stimulation with BAFF, while the expression of STAT3, STAT5 and STAT6 did not change under the same conditions. A JAK3 inhibitor suppressed the elevated expression of STAT4. These data suggest that a JAK3-STAT4 pathway may be involved in the production of IL-6 by THP-1 induced by sBAFF.

P3-188

IL-6 is involved in osteoporosis induced by arthritis

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Conflict of interest: None

Backgroud The incidence of osteoporosis is increased in patients with RA to 2 to 4 times that in the general population. Tocilizumab, anti-IL-6R antibody therapy shows an excellent therapeutic effect in RA patients. However, it is not fully understood whether tocilizumab improves osteoporosis in patients with RA. **Objective** We examined whether IL-6 involves in bone loss in trabecular bone of distal femur using mouse arthritis model. **Methods** Arthritis is induced by the immunization of GPI. After sacrifice, femurs were excised and the trabecular bone volume (BV/TV) of distal femur was analyzed using μCT. **Results** Bone volume in arthritis mice was decreased more than 30% in day 7 (beginning of arthritis) and 60% in day 14 (peak of arthritis) compared with normal mice. Thereafter, bone volume was gradually increased and recovered to 60% of normal mice by day 35. To examine IL-6 involvement in bone loss, we injected anti-mouse IL-6R antibody (MR16-1) 5 days after immunization. MR16-1 suppressed the development

of arthritis and decrease of bone volume in MR16-1 treatment was less than in control mice. **Conclusions** We here demonstrated that IL-6 plays a crucial role in bone loss induced by inflammation. It is suggested that IL-6 blockade shows beneficial effect on osteoporosis in RA patients.

P3-189

The difference in response related to inflammation of fat between IL-6 and TNF-α

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Conflict of interest: None

[Objectives] In visceral fat, enlarged adipocytes induce macrophage accumulation, resulting in chronic inflammation. It is thought that adipocytes and infiltrated macrophages are involved in the exacerbation of inflammation via MCP-1 production. In this study, we examined the effect of IL-6 and TNF-α on MCP-1 production by using the co-culture system of adipocytes and macrophages. **[Methods]** 3T3-L1 adipocytes (3T3) and RAW264.7 macrophages (RAW) were cultured for 24 h in mono- and co-culture system by using transwells. After culture, MCP-1 production in supernatants and IL-6 and TNF-α expression in each cell were measured. Moreover, each cell was cultured with IL-6 or TNF-α for 24h, and MCP-1 production was measured. **[Results]** Under non-stimulated condition, large amount of MCP-1 was detected in co-culture, but MCP-1 production in mono-culture was marginal. MCP-1 production in co-culture was suppressed by anti-IL-6R antibody and TNF inhibitor. RAW strongly expressed TNF-α mRNA and 3T3 expressed IL-6 mRNA. Moreover, IL-6 induced MCP-1 production from RAW and TNF-α induced from 3T3. In conclusion, MCP-1 production might be induced by the effects on adipocytes of TNF-α from macrophages and on macrophages of IL-6 from adipocytes in the co-culture system of adipocytes and macrophages.

P3-190

The effect of IL-6 blockade and TNF blockade on the differentiation of mouse Th17 cells

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Conflict of interest: None

[Objectives] It has been reported that TNF blockade increase Th17 development in collagen-induced arthritis model. Here, we examined the effect of IL-6 blockade and TNF blockade on the development of Th17 using glucose 6-phosphate isomerase (GPI)-induced arthritis model. [Methods] 1) Anti-IL-6 receptor antibody (MR16-1) and TNF receptor-Fc (TNFR-Fc) were administered once a week and three times a week from the first day of immunization to autopsy. On 14 days after immunization, IL-17 production from splenic CD4+T cells was measured. 2) Naïve CD4+T cell and CD11b+cell from normal mouse spleen were co-cultured with anti-CD3 antibody, TGF-β and LPS, and then Th17 development was examined. [Results] 1) The onset of arthritis was reduced by both treatments. MR16-1 reduced IL-17 production from CD4+T cell, whereas TNFR-Fc increased it. 2) LPS increased IL-6 production and Th17. MR16-1 inhibited Th17 development by LPS, on the other hand TNFR-Fc and anti-TNF antibody further augmented Th17 development Moreover, TNFR-Fc and anti-TNF antibody increased IL-23 receptor mRNA expression. In this study, we demonstrated that IL-6 blockade suppressed Th17 development, whereas TNF blockade increased Th17 development via the induction of IL-23 receptor mRNA expression.

P3-191

Differential requirement for IL-2-signaling in clonal expansion of Th1 and Th17 cells in vivo

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Conflict of interest: None

[Objectives/methods] IL-2 plays an important role for clonal expansion of antigen-specific T cells. CyclosporineA and FK506, which block IL-2 transcription, are used for the treatment of rheumatoid arthritis (RA). However, it was recently reported that IL-2 suppressed the differentiation of Th17 cells, which are believed to play pathogenic role in RA. Because the role of IL-2 for *in vivo* clonal expansion of Th17 cells remains unclear, we analyzed the development of antigen-specific Th17 cells in IL-2Ra-deficient, ovalbumin (OVA)-specific T cell receptor transgenic mice. [Results] We found that *in vivo* expansion of OVA-specific Th17 cells was not augmented but slightly diminished by the absence of IL-2Ra, while the lack of IL-2-signaling severely decreased the number of OVA-specific Th1 cells. Consequently, Th17/Th1 ratio was increased in IL-2Ra-deficient T cells. *In vitro* neutralization of IL-2 during the induction of Th17 cells also resulted in an increased percentage of Th17 cells without affecting their numbers. Th17 cells expressed lower levels of IL-2Ra than Th1 cells, which might be due to low levels of IL-2 production. Thus, IL-2 does not inhibit but rather promotes clonal expansion of Th17 cells *in vivo*, which is consistent with the therapeutic effect of IL-2 blockers in RA.

P3-192

Stimulation with CCL18 enhanced production of IL-6, MCP-1 and MMP-3 by fibroblast-like synoviocytes from patients with rheumatoid arthritis

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Conflict of interest: None

[Objectives] CCL18 is a chemokine expressed by dendritic cells (DC) and monocytes/macrophages, and induces chemotactis for lymphocytes, monocytes and DC. It was reported that CCL18 was abundantly expressed in synovial fluid from rheumatoid arthritis (RA) compared to osteoarthritis (OA). The aim of this study is to explore novel functions of CCL18 on RA. [Methods] Expression of CCL18 and its receptor, PITPNM3, was examined by immunohistochemistry and Western blot. Cytokine production by fibroblast-like synoviocytes (FLS) was measured by ELISA. Phosphorylation of Akt and ERK1/2 was analyzed by Western blot. [Results] CCL18 and PITPNM3 were highly expressed in the RA synovial tissue compared to OA. CCL18 was expressed on macrophages, endothelial cells and FLS in the synovium, and PITPNM3 was expressed on macrophages, DC, B cells and FLS. Stimulation with

CCL18 increased production of IL-6, MCP-1 and MMP-3 from RA FLS *in vitro*, which was blocked by pertussis toxin, a Gi-coupled receptor inhibitor. Moreover, CCL18 induced phosphorylation of Akt and ERK1/2 of FLS. [Conclusion] CCL18 might play an important role on FLS stimulation in the RA synovium, probably via PITPNM3 with phosphorylation of Akt and ERK1/2. Interaction with CCL18 and PITPNM3 could be a new therapeutic target for RA.

P3-193

IL-32alpha develops inflammatory arthritis and endotoxin shock with TNFalpha induction via NFκB and ERK signaling pathways.

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Conflict of interest: None

[objective] To date, IL-32 has been shown to be inducer of TNFalpha, however, signaling pathways downstream of IL-32 have not been fully elucidated. We have investigated about the effect of IL-32alpha on development of endotoxin shock in mice and the potential signaling pathway of IL-32alpha-TNFalpha axis was analyzed in vitro. [Methods] IL-32alpha transgenic mice (Tg) was generated under a control of ubiquitous promoter. Endotoxin shock was induced with intraperitoneal injection of LPS and D-galactosamine. Etanercept, was simultaneously administered with LPS in some mice. Using Raw 264.7 cells, in vitro effect of exogenous IL-32alpha on TNFalpha production was assessed with or without inhibitors for NFkappaB or MAPKs. [Results] Tg mice exhibited severer lethality than wild type mice 48 hours after the LPS challenge, but blockade of TNFalpha by etanercept protected. Exogenously added IL-32alpha solely stimulated Raw264.7 cells to produce TNFalpha, which was inhibited by the inhibitors of NFkappaB and ERK1/2, not by those of p38 and JNK. [Conclusions] This study showed that IL-32alpha contributed to development of endotoxin lethality. IL-32alpha solely induced TNFalpha production in Raw264.7 cells via NFkappaB and ERK1/2 signaling pathways.

P3-194

Serum resistin level is associated with inflammation, but not atherosclerosis, in systemic autoimmune diseases

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Conflict of interest: None

[Objectives] We investigated the role of adipokines in patients with systemic autoimmune diseases receiving glucocorticoid therapy. [Methods] Fifty-two patients with systemic autoimmune diseases who had started glucocorticoid therapy and 140 healthy persons as controls were enrolled. Serum levels of 3 adipokines [resistin (RS), leptin (LP), and high molecular weight adiponectin (HMW-AD)] were measured with ELISA kits before and weekly for 4 weeks during glucocorticoid therapy. [Results] Serum RS levels at baseline were significantly higher in these patients than those in the controls, and RS levels decreased after glucocorticoid therapy. Consistent with these results, dexamethasone inhibited LPS-induced up-regulation of RS expression in mononuclear cells *in vitro*. There was a significant correlation between the serum RS levels and high sensitivity C-reactive protein, whereas no association between serum adipokines, and intima-media thickness and/or dyslipidemia was observed. Serum LP and HMW-AD levels were lower in the patients than in the controls at baseline, and both adipokines increased after glucocorticoid therapy. These findings suggest that RS may be associated with the inflammatory process, but not atherosclerosis, in patients with systemic autoimmune diseases.

P3-195

Treatment strategy of the adult onset Still's disease (AOSD) to approach from cytokine profile: IL-18 is useful marker to make a diagnosis and to evaluate disease activity.

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Conflict of interest: None

OBJECTIVES: To find the index marker for diagnosis and treatment of AOSD. METHODS: We measured the following serum cytokines in five patients with AOSD: interleukin(IL)-6, IL-18, tumor necrosis factor(TNF)-alpha, soluble TNF-receptor I, soluble TNF-receptor II, neopterin, and soluble IL-2 receptor. Finally we profiled these cytokine level on the cobweb chart. RESULTS: Almost all serum cytokine levels were elevated in patients with AOSD. Especially serum IL-18 level was significantly elevated, which was very characteristic pattern on the cobweb chart. Even though the symptom of the fever and the rash disappeared, and the laboratory data such as AST, ALT, CRP, and ferritin level was normalized, serum IL-18 level was still elevated. CONCLUSIONS: Cytokine profiling may be useful indicator to make a diagnosis in patients with AOSD. Among these cytokines, especially following the serum IL-18 level could be important to evaluate the disease activity in patients with AOSD.

P3-196

Comparative proteomic analysis of neutrophils from patients with microscopic polyangiitis and granulomatosis with polyangiitis.

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Conflict of interest: None

[Objective] Both microscopic polyangiitis (MPA) and granulomatosis with polyantiitis (GPA) belong to ANCA-associated vasculities, in which dysfunction of polymorphonuclear neutrophil (PMN) 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 PMN were analyzed using two-dimensional difference gel electrophoresis (2D-DIGE). [Methods] Proteins extracted from PMN obtained from 3 MPA patients, 3 GPA patients, and 3 healthy controls (HC) were separated by 2D-DIGE. Differentially expressed protein spots were identified by MALDI-TOF MS. [Results and Discussion] In all the 927 protein spots de-

tected, 50 spots were found to be significantly different ($p<0.05$) among the three groups by the ANOVA analysis. 23 spots out of the 50 spots were identified by mass spectrometry. The protein spots whose intensities were higher in GPA than in MPA or HC included proteins related to generation or detoxification of reactive oxygen species (ROS), such as malate dehydrogenase, glutathione synthetase, protein S100-A9. These results suggest the possibility that ROS generation was more activated in GPA than in MPA.

P3-197

ANCA-Associated Vasculitis in a Community-Based Hospital in Japan

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Conflict of interest: None

Objective: To investigate the diagnosis, treatment and prognosis of ANCA-associated vasculitis (AAV). **Methods:** A total of 34 patients (23 females and 11 males) with physician-diagnosed AAV who admitted to our department or department of nephrology from 2003 to 2009 were included. We reevaluated the clinical diagnosis of AAV by applying the European Medicines Agency (EMEA) algorithm (Ann Rheum Dis 2007;66:222). We examined whether there was a difference in clinical outcomes between corticosteroid alone and corticosteroid and cyclophosphamide in combination as induction therapy. **Results:** The Clinical diagnosis of 34 patients were Churg-Strauss syndrome (CSS) (n = 4), Granulomatosis with polyangitis (GPA) (n = 3), Microscopic polyangitis (MPA) (n = 27). Of 27 patients diagnosed with MPA, after applying the EMEA algorithm, 3 and 3 were reclassified into GPA, and unclassified vasculitis, respectively. 23 of 34 patients received corticosteroid (CS) alone, and 9 patients were treated with CS and cyclophosphamide in combination as induction therapy. The mean (±SD) follow-up was 30.1±24.2 months. Overall survival at 5 years after initial treatment was estimated to be 60.8% by using Kaplan-Meier method, and it was 41.6% in cases with five factor score (Medicine 1996;75:17) ≥ 2.

P3-198

A case of sudden onset of Takayasu's arteritis (TA) after normal delivery

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Conflict of interest: None

A 37-year-old woman without any complication had been hospitalized for her 2nd delivery. 2 days after her normal delivery, she suffered from high fever up, headache and hypertension with increased CRP and WBC levels. Her enhanced thoracic CT revealed not only severe stenosis between the right side common carotid artery and the internal/external carotid artery but also the vessel wall thickness between the aortic arch and the descending aorta. She fulfilled the diagnostic criteria for TA and her whole body arteries were evaluated using MRA and SPECT. The stenoses of other arteries including renal arteries were not detected, but SPECT indicated a decrease of cerebral blood flow. After she was given Prednisolone (60mg/day), all the symptoms were diminished immediately and two weeks later showed a patient in good clinical condition. Although TA is generally found out from a mass of chronic FUO, the delivery hinted at the possibility of triggering for TA, because she also had experienced spontaneous resolved high fever and continuous CRP elevation after her 1st delivery.

P3-199

Two cases of microscopic polyangitis complicated with thrombotic thrombocytopenic purpura

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Conflict of interest: None

Case1: A 69-year-old woman was diagnosed with microscopic polyangitis (MPA) because of alveolar hemorrhage, crescentic glomerulonephritis and high titer of MPO-ANCA. High-dose PSL therapy and IVCY was initiated. A year later, pneunocystis pneumonia(PCP) developed. After that her platelet count and hemoglobin were decreased severely and RBC fragmentation was observed in peripheral blood. A diagnosis of thrombotic thrombocytopenic purpura(TTP) was made, and plasma exchange(PE) was initiated. Although PE was repeatedly performed, she developed CMV infection leading to the death of MOF. Case2: A 69-year-old woman was diagnosed with MPA because of mononeuritis multiplex, alveolar hemorrhage, abnormality of urinalysis and high titer of MPO-ANCA. High-dose PSL therapy was initiated, but her platelet count, hemoglobin and haptoglobin level were gradually decreased. A diagnosis of TTP was made and PE was initiated. However aspiration pneumonia, CMV infection and PCP developed soon. PE was repeatedly performed, but she died of uncontrolled alveolar hemorrhage. TTP secondary to MPA is a rare and fatal disease. Although the relationship between both of the illness is unknown, positivity of MPO-ANCA may be play a important role in development of TTP resulting from vascular endothelial damage.

P3-200

An atypical case of microscopic polyangitis presenting with acute tubulointerstitial nephritis without glomerular change.

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Conflict of interest: None

Renal involvement in myeloperoxidase-antineutrophil cytoplasmic antibody (MPO-ANCA)-associated vasculitis is characterized by focal segmental crecentic and/or necrotizing glomerulonephritis. However, a few cases have been reported to have only tubulointerstitial nephritis without any apparent glomerular lesions. Here, we recently treated and report a similar case. A 74-year-old woman was admitted with a 2-week history of pitting edema and fever and anemia. She was admitted to a nearby hospital. She showed acute deterioration of renal function, but no abnormalities in her urine examination and sediment. Abnormal concentrations in bilateral kidneys were found by gallium scintigraphy. For these reasons, she was transferred to our hospital. Her MPO-ANCA titer was 92 EU. Skin and renal biopsies demonstrated fibrinoid vasculitis, necrotizing angitis and tubulointerstitial nephritis without glomerular change, respectively. Microscopic polyangitis was diagnosed based on clinical and pathological criteria. Clinical improvement occurred after intensive immunosuppressive therapy,

PSL 50mg/day and IVCY, was given. This case illustrates an unusual renal presentation of tubulointerstitial nephritis in microscopic polyangitis. The possible pathogenetic mechanism will be discussed.

P3-201

The clinical characteristics of patients with microscopic polyangiitis (MPA), and the usefulness of B-VAS for the indicator of response to initial therapy.

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Conflict of interest: None

[Object] To determine the clinical characteristics of patients with microscopic polyangiitis (MPA), we scored the disease activity of MPA patients. [Method] We analyzed retrospectively 20 cases of MPA newly diagnosed from 2007 to 2011 at our hospital. To evaluate the activity of vasculitis at the point of diagnosis and after 4 weeks initial therapy, we used Birmingham Vasculitis Activity Score (B-VAS), serum level of CRP. [Result] The mean age of the 20 patients was 72. 5 ± 3.1 year-old. Five patients died during the observation period (one due to acute kidney failure, two due to infection, and one due to malignancy). The patient who died of acute renal failure died within two months after starting treatment. The average B-VAS at the beginning of therapy was 15.6 ± 3.5, and the mean level of CRP at the start of treatment was 9.3 ± 2.5mg/dl. 12 patients were treated with IVCY, and 14 patients were treated with mPSL pulse for initial therapy. We re-evaluated the vasculitis activity after 4 weeks of initial therapy. The mean CRP was 0.23 ± 0.10mg/dl, and the average B-VAS was 3.4 ± 1.1. B-VAS at the onset of the disease has a positive correlation with CRP after the initial therapy ($p < 0.05$). [Discussion] B-VAS may be an useful indicator of response to initial therapy.

P3-202

Prognostic changes and factor in microscopic polyangiitis

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Conflict of interest: None

[Objectives] To evaluate prognostic changes and identify prognostic factor of microscopic polyangiitis(MPA). [Methods] From 1995 to 2000, we reviewed clinical data of 60 patients with MPA of our institute including prognostic changes and factor. [Results] 60 patients, diagnosed with MPA according to the Watts'algorithm (23 men and 37 women with a mean age of 71 years). Cerebral hemorrhage was present in 2 patients, gastrointestinal bleeding was seen in 2 patients. 10 patients had alveolar hemorrhage and 1 patient pancreatitis. In Kaplan-Meier survival analysis, the survival rates at 180 days was 79%. But from 2004 to 2010, the survival rates was 90%. In univariate analysis, BVAS and the rate of decrease of ANCA were significant risk factor. [Conclusion] This study showed an improved survival for MPA patients in the latest period.

P3-203

A case of Churg-Strauss syndrome (CSS) with 9 organ involvement

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Conflict of interest: None

[Objectives] CSS most usually involves such organs as peripheral nerves or skin. We treated a patient with multiple organ involvement with a marked eosinophilia. [Case Report] A 65-year-old male visited a dermatologist because of blisters and edema on legs, when eosinophile count was 14420/mL. He had had eosinophilia at the age of 32, and sinusitis and asthma in his 50's. On admission, wheeze, and 2X2 cm vesicles, and severe edema and spotty hemorrhagic macules on legs were observed. Manual muscle test showed 4/4 in toe extensor and flexor. Eosinophile count was 23200/microL, IgE 60 U/mL, CRP 1.75 mg/dL, LDH 699, ALT 104, Al-P 580, CK 428 IU/L, Trop T +, myosin-LC1 22 ng/mL, RF 141 IU/mL, MPO/PR3-ANCA -/-, ECP 515 μg/L. 75% of cells in sputum were eosinophiles. Nerve verbosity was decreased in bilateral medial nerves. Graphical signs include pericardial effusion, opacities in sinuses, GGOs in lungs, and MRI findings compatible with myositis/fasciitis. Biopsies revealed eosinophilic skin-vasculitis, bullous pemphigoid, and eosinophilic sinusitis. 0.8mg/kg/day of prednisolon cured all of the features. [Summary] This case was considered to develop clear involvement in as many as up to 9 organs simultaneously, with an eosinophilia of 20000</mL. Peripheral nerves were less disturbed.

P3-204

A case of high dose Intravenous Immunogloblin therapy was effective in the multiple mononeuritis of the MPA

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Conflict of interest: None

A 68-year-old female was admitted to our hospital with a high fever, numbness and purpura in the distal parts of the limbs, and muscle weakness. We accepted the fall of the sense motor nerves biography speed in an EMG. The urinarlysis showed occult blood and proteinuria. The serum levels of Cr, CRP, and, MPO-ANCA were 1.2 mg/dl, 15.5mg/dl, and 600EU, respectively. Based on the above findings, she was diagnosed having microscopic polyangiitis (MPA) complicated with multiple mononeuritis and 45 mg/day of prednisolone was initiated. Clinical and laboratory findings improved and PSL tapered to 35mg/day. However, her muscle weakness and scensory disorder of limbs remained and high dose Intravenous Immunogloblin therapy (20 g/ day for 5days) was performed with favorable response (MMTscore: 128→138, MBI: 80→81).

P3-205

A concomitant case of giant cell arteritis and microscopic polyangiitis with hemoperitoneum by rupture of the gastroepiploic artery

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Conflict of interest: None

[Introduction] Giant cell arteritis (GCA) mainly involves large-sized arteries, however, microscopic polyangiitis (mPA) mainly af-

fects small-sized vessels. [Case Report] An 80-year-old man was admitted with high fever and decreased appetite associated with weight loss. Furthermore, he had a new mild headache and jaw claudication. Infection and malignancy were excluded. Although he had a low titer of MPO-ANCA, GCA was suspected because of the presence of headache and jaw claudication. A biopsy specimen from the temporal artery was obtained, and GCA was diagnosed. There was no evidence suggesting a complication of polymyalgia rheumatica. Shortly afterward, an elevation of MPO-ANCA and progression of renal disturbance were detected, and chest CT revealed exacerbation of interstitial pneumonia. Therefore mPA was diagnosed. Steroid pulse therapy was started, and 60 mg prednisolone (PSL) daily was subsequently continued. However, sudden severe generalized abdominal pain appeared, and angiography revealed rupture of the gastroepiploic artery. Though angiographic embolization was performed, the patient died. [Discussion] This is a very rare concomitant case of GCA and mPA, rupture of the gastroepiploic artery may have been triggered by GCA and/or mPA.

P3-206

A case of pulmonary artery stenosis discovered by pulmonary embolism in a patient with elderly onset aortitis syndrome.

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Conflict of interest: None

A 83-year-old woman was diagnosed as aortitis syndrome. She has been pointed out angina since 10 years ago and received antiplatelet therapy. On August 2010, fever of around 38 degree and chest pain was observed. After admission, she was diagnosed elderly onset aortitis syndrome by computed tomography (CT) and PET-CT. She was started to treat with prednisolone (PSL) 30mg/day, and her symptoms improved. Around October of 2010, she had symptoms of exertional dyspnea and pedal edema. She was admitted to our hospital with exertional dyspnea, and diagnosed pulmonary embolism by contrast-enhanced CT. She was treated with anticoagulant therapy and the symptoms improved. After treatment, she was discovered pulmonary artery stenosis by contrast-enhanced CT and magnetic resonance imaging (MRI). It is a rare case of pulmonary artery stenosis discovered by pulmonary embolism in a patient with elderly onset aortitis syndrome. Thus, we report on this case adding consideration.

P3-207

Diagnosis of a 65-year-old female patient with Takayasu's arteritis by 18F-FDG PET/CT.

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Conflict of interest: None

[Objectives] Case Report [Methods] Case Report [Results] A 65-year-old female was admittede to our hospital becaouse of a 15-month history of a slight fever, fatigue, weight loss, proximal myalgia. On physical examination and laboratory findings, there was no evidence of infectious disease or malignacy. 18F-Fluorodeoxyglucose positron emission tomography/computed tomography(18F-FDG PET/CT) was performed which suggested Takayasu artheritis(TA). She was treated with oral predonisolone. After treatment, the inflammatory reactions of TA improved immediately and did not replase. 18F-FDG PET/CT might be an useful method of diagnosis in patient with TA. Thus, we report on this case adding cosideration.

P3-208

An infantile case of Takayasu Arteritis complicated with Sweet's Syndrome.

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Conflict of interest: None

Takayasu Arteritis(TA) is a chronic vasculitis affecting large vessel such as the aorta and its major branches. It usually occurs in young women, and a case of infantile onset TA is quite rare. On the other side, Sweet's syndrome (SS) is a skin disease, usually occurs in middle-aged women, characterized by fever, neutrophilia, and erhythema with neutrophilic infiltration. We present an infantile case of refractory TA complicated with SS. A case was a 21 month-old girl diagnosed as TA at 9 months old due to her inflammatory features and MRI/echocardiographic findings. She was initially treated with oral PSL, however, inflammatory findings repeatedly relapsed when the PSL dose was tapered. She was transferred to our hospital at age of 14 months. mPSL pulse and cyclophosphamide(IVCY) therapy were started to induce clinical remission, however, inflammatory findings relapsed again. At age of 19 months, 8mg/kg of tocilizumab was initiated after obtaining the ethical approval from the committee. Thereafter, erhythema rash appeared on her cervical lesion and the pathological findings of neutrophilic infiltration in the dermis were compatible with SS. Considering that previously reported 3 TA patients complicated with SS were all infantile onset, she was diagnosed as this rare disease.

P3-209

Two Case of AA Amyloidosis Secondary to Renal Cell Carcinoma

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Conflict of interest: None

AA amyloidosis has generally caused by chronic inflammation with progressive rheumatoid arthritis, but it was occurred by renal cell carcinoma in some previously reported. Case 1: 71 year-old man was diagnosed as having renal cell carcinoma (clear cell carcinoma) and received right neprhectomy in 2002. Two years after, he was pointed out lung metastasis, but he rejected the chemotherapy. In September 2010, he suffered from abdominal pain and diarrhea. A rectum mucosal specimen showed amyloid A deposition. Considering secondary AA amyloidosis from metastatic lung tumor, resection was performed. Her abdominal symptoms improved by the administration of tocilizumab after surgery. Case 2: 69 year-old woman, she was diagnosed as having renal cell carcinoma (clear cell carcinoma), and received the left nephrectomy. Metastasis was pointed out both the right kidney and the lung in 2009. The histopathological specimen of lung showed the clear cell carcinoma. Despite of during chemotherapy, her symptoms of ileus appeared in July 2011. She was diagnosed as having AA amyloidosis from the rectal-mucous-membrane biopsy. Without tumor resec-

tion, abdominal symptoms were improved by the treatment of tocilizumab. We confirmed the serum CRP, SAA and IL-6 of these two patients were elevated.

P3-210

Serum amyloid A (SAA) induces pentraxin 3 (PTX3) production in rheumatoid synoviocytes

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Conflict of interest: None

Objective:PTX3 is acute phase reactive protein participating in immunity and an inflammatory reaction. In the present study, we evaluated the relationship between PTX3 and SAA, another acute phase reactant, in rheumatoid synoviocytes.**Methods:** We stimulated RA synoviocytes with SAA, various cytokine and PTX3 mRNA expression was examined by RT-PCR and PTX3 protein was measured by ELISA. The inhibition of FPRL-1 which was a receptor of SAA used siRNA.**Results:**SAA induced expression of PTX3 mRNA and production of PTX3 in dose-dependency in RA synoviocytes. The production of PTX3 induced by SAA was approximately equal to PTX3 induced by cytokine (IL-1β, TNF-α) of high density. SAA induced PTX3 expression was attenuated when rheumatoid synoviocytes were nucleofected with FPRL-1 specific siRNA, suggesting the involvement of FPRL-1. Furthermore, SAA induced PTX3 expression was inhibited by NF-kB or MAPK specific inhibitors.**Conclusion**:Our data suggests that SAA plays a role in proinflammatory and immune responses in rheumatoid synovium by inducing PTX3. We provide the first evidence that SAA, which is produced systemically by hepatocytes, perpetuates the rheumatoid inflammatory processes by inducing another pro-inflammatory molecule, PTX3, locally in rheumatoid synovial tissues.

P3-211

Successful toclizumab treatment in 3 cases with AA (secondary) amyloidosis due to rheumatoid arthritis

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Conflict of interest: None

AA (secondary) amyloidosis is one of the most severe complications of rheumatoid arthritis (RA). We report successful tocilizumab (TCZ) use in three RA patients with AA amyloidosis. Case 1: A 65-year-old woman, diagnosed with RA in 1985, had been receiving treatment with disease-modifying anti-rheumatic drug and corticosteroids. In 2009, serum creatinine level increased, and renal and colon biopsy revealed amyloid deposition. She was treated with TCZ, which led to improved renal function. Case 2: A 77-year-old woman was diagnosed with RA in 1961 and nephritic syndrome in 2010. Renal and duodenum biopsy revealed amyloid deposition. Renal function improved after treatment with TCZ. Case 3: A 55-year-old woman, diagnosed with RA in 1987, stated treatment with methotrexate(10 mg/ wk) in 2000. In 2007, marked proteinuria, chronic diarrhea and the diagnosis of renal amyloidosis confirmed by renal biopsy initiated treatment with etanercept. A year later, C-reactive-protein increased and renal disorder progressed. TCZ was started, followed by a resolution of renal disorder and chronic diarrhea. TCZ may be a promising agent for the treatment of secondary AA amyloidosis.

P3-212

Acase of adult on set Familial Mediterranean fever.

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Conflict of interest: None

Acase of adult on set Familial Mediterranean fever. Familial Mediterranean fever (FMF) is a hereditary disorder characterised by recurrent attacks of fever with serotitis such as pleuritis or peritonitis, arthritis,. It is known, FMF caused by mutations in the MEFV gene that encodes pyrin/marenostrin. We report one case of adult on set FMF.A 55-year-old man was admitted to our hospital in April 2009 with symptoms of fever and skin rash. In this time, diagnosis of Sjogren syndrome and Reactive arthritis were confirmed. Although, he was treated with oral prednisone but he getting worse, and presenting with complaints of pleuritis, peritonitis and epididymitis. Autoinflammatory disease, such as FMF were suspected and DNA analysis demonstrated a heterozygous mutation in the MEFV gene, leading to a diagnosis of FMF.

P3-213

A case of Familial Mediterranean fever (FMF) associated with M694I/P715L mutation in MEFV gene

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Conflict of interest: None

Familial Mediterranean Fever (FMF) is a hereditary autoinflammatory disorder characterized by fever, serosal inflammation and arthritis. It most commonly affects people of Amenican, Turkish, Jewish and Arab origin and it has been considered to be a rare disease in Japan. In the current report, a novel mutation of the MEFV gene (P715L) in a Japanese woman presenting with periodic fever, recurrent attack of abdominal pain and arthritis is presented. The patient was a 23-year-old woman. She recurred attacks of fever, abdominal pain and joint pain several times a year. These symptoms usually improved 3-to-10 days later. The frequency of the attack became once a month from 22 years old. She visited our hospital in May 23, 2011. Her complaint was fever, abdominal pain and arthralgia. Laboratory studies revealed WBC of 9400/μl and CRP of 5.7mg/dl. No abnormal findings were found on either CT scans, or endoscopic examinations of the gastrointestinal tract. We suspected FMF and performed MEFV gene analysis. We detected a M694I/P715L mutation in exon 10. She responded dramatically to colchicine treatment and has remained in full remission. In Japanese FMF patients, a diagnostic delay is an issue to be resolved and appropriate diagnosis and early therapeutic intervention should be needed.

P3-215

A case of 2 years-old girl with TNF receptor-associated periodic syndrome (TRAPS) with a T50M mutation in TNFRSF1A gene.

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Conflict of interest: None

A girl of 2 years old 7 months was transferred to our hospital because of continuing fever that was resistant to antibiotics. She had similar 5 episodes of unidentified fever from six months after the birth and also episodes of periorbital oedema. Similar episodes were also observed in her father and her grandfather of father's family line during their childhood, and her father had been diagnosed as systemic juvenile idiopathic arthritis (sJIA). Her general condition was well and she had no other symptoms other than fever, although her laboratory tests indicated a remarkable increase in WBC count(32,330/μl) and in CRP(18.8mg/dl). As the spiking fever continued, ibuprofen was started on the day 22 of illness. The fever disappeared at day 25 of the disease. Genetic analysis revealed a heterozygous T50M mutation in TNFRSF1A, and she was diagnosed as TRAPS. TRAPS often develops in the childhood. To make diagnosis is difficult in early stage because the most of the cases reported in Japan were sporadic. They might be diagnosed as other inflammatory diseases such as sJIA as her father was diagnosed. We present a girl with TRAPS diagnosed at 2 years of age, the most youngest patient ever diagnosed in Japan, in order to deepen the recognition for this inflammatory disease in children.

P3-216

A novel mutation (V125M) in the gene encoding TNF receptor superfamily 1A (*TNFRSF1A*) in a Japanese pedigree with TNF receptor-associated periodic syndrome (TRAPS)

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Conflict of interest: None

A 21-yr-old Japanese female patient was suffered from high fever with unknown origin from childhood. We performed DNA sequencing of the *TNFRSF1A* gene. A novel mutation, a heterozygous G to A transition in exon 4 which substitutes a methionine for a valine at position 125 (V125M) was detected in the *TNFRSF1A* gene derived from the genomic DNA of this patient. This gene analysis and her clinical symptoms led to a diagnosis of TRAPS. Her mother, two sisters, and uncle, all with a similar clinical phenotype, also possessed the same *TNFRSF1A* mutation, suggesting that the penetrance of this mutation is very high. This is the first report of a TRAPS patient and her family with a novel *TNFRSF1A* mutation (V125M).

P3-217

Globally-distributed proteasome disability syndromes caused by *PSMB8* mutations: a new category of autoinflammatory syndrome with lipodystrophy

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Conflict of interest: None

Ubiquitin-proteasome system is the multifactorial system in which polyubiquitinated proteins are degraded by the proteasome complex. Activity of the immunoproteasome (IP), in which the catalytic beta subunits are exchanged to the inducible ones, is reportedly increased at autoimmune diseases. Last year we reported that a homozygous mutation of *PSMB8*, which encodes the beta5i subunit, impaired assembly and function of the IP to accumulate ubiquitinated proteins and caused Nakajo-Nishimura syndrome, a distinct inherited disease which onsets in infancy with a pernio-like rash and gradually develops into lipodystrophy in the upper part of body and long clubbed fingers with contractures, accompanied with periodic fever and nodular erythema-like eruptions, and has been considered to be unique in Japan. In JMP and CANDLE syndromes, which have been reported in 2010 from the American and the Spanish groups, respectively, and are considered the associating disorders characterized by inflammation and wastings, *PSMB8* mutations have also been identified. Actually, it has been shown that different mutations have been discovered in different ethnics. These mutations have been registered in INFEVERS as a new category of autoinflammatory syndromes with proteasome disability.

P3-218

Long term follow-up cases with childhood onset unclassified auto-inflammatory diseases

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Conflict of interest: None

The spectrum of periodic fever syndrome(PFS)/auto-inflammatory disease is expanding. Some of PFS including FMF, TRAPS share a similar future of sJIA. We summarized long term observation of 3 cases with unclassified childhood onset PFS. [Case profiles] 18, 18, 20 y Male. Onset age 1y, 7y, 8y. [Characteristics] Duration of fever: 1-2wk. Interval: 3-6M /y decreased along with glowing. Suspected provocation factor: season, fatigue, overwork, but not with infection. [Other symptoms] Malaise, myalgia headache, abdominal pain, mild arthralgia but no findings of arthritis. [Auto Ab] positive ANA for 2. [Treatment] Well responce to PSL treatment [Genetic analysis] On going. [Pathological findings] will be shown. Recruitment and follow-up of pediatric PFS/auto-inflammatory diseases cases analogous with sJIA · AOSD could provide us an opportunity to identify genetic or inflammatory markers. Unknown factors might affect the immune- system in the process of growing.

P3-219

IL-1β production in PBMCs from a case with Familial Cold Autoinflammatory Syndrome

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Conflict of interest: None

Background: Familial cold autoinflammatory syndrome (FCAS) which is characterized by urticaria and fever at cold is one of autoinflammatory syndromes. FCAS is caused by mutations in NLRP3 gene which encodes cryopyrin participating release IL-1β. But not all patients have a detectable genetic mutation. **Objectives:**

We report a potential to release of IL-1β, by cold stimulation, from PBMCs of a Japanese patient with FCAS who have no carrying of NLRP3. **Methods:** We centrifuged venous blood from this patient or healthy volunteers and separated PBMCs on Ficoll-Hypaque, and then incubated in FCS-free RPMI1640 at 32°C or 37°C. The concentration of IL-1β and TNF-α in supernatant were determined by ELISA kit purchased from R&D Systems respectively. **Result:** The release of IL-1β in PBMCs from patient was enhanced significantly at 32°C but not at 37°C. As for that of TNF-α, there was no significant difference between patient and HC. Interestingly, the patient PBMCs incubated at 32°C without LPS stimulation also increased IL-1β production. **Conclusion:** It is suggested that the excessive release of IL-1β may be caused in FCAS patient without or with mutations of NLRP3. Additionally, the cold stimulation might play an important role for the excessive release of IL-1β in FCAS patient.

P3-220

A case of PAPA syndrome that had long been diagnosed as JIA and Crohn's disease.

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Conflict of interest: None

We report a case of PAPA syndrome that had long been diagnosed as juvenile idiopathic arthritis (JIA) and Crohn's disease. The patient was a 21-year-old man. He had been noticed to have continuously elevated levels of CRP since 9 month-old. Since age of 6, he had developed recurrent pyogenic sterile arthritis, been given 5-30mg/day of prednisolone under diagnosis of RF-negative polyarticular JIA without sustained remission. He developed acne and pyoderma gangrenosum from the age of 15, and in addition, he was suspected to be associated with Crohn's disease because of recurrent abdominal pain, diarrhea, and colonoscopic findings. Proteinuria had been detected since age of 14. Recently, his pathognomonic clinical course and an E250K mutation in the PSTPIP1 gene led us to establish a diagnose of PAPA syndrome, though this was considered to be a sporadic case. Renal biopsy revealed advanced arteriosclerotic lesions, which was thought to be a cause of proteinuria. The intestinal lesions are also considered to be associated with his primary disease. He started with adalimumab, which decreased CRP, but the skin lesion and proteinuria have not been improved so far. PAPA syndrome has not yet been reported the in past literature from Japan, but some patients may remain undiagnosed.

P3-221

A case of PAPA syndrome with mutation G258A on PSTPIP1 gene.

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Conflict of interest: None

A case is 16 year-old woman, and sometimes had aphthous ulcers from infants. She sometimes has presented a low-grade fever, acne, headache, edema of limbs and face, cervical lymphadenopathy since 13 year-old and these symptoms were relieved without any therapies. She came to be aware of Raynaud's phenomenon at about 15 year-old. A Low grade fever lasted from about 16 year-old and sometimes accepted edema of limbs, both elbow joints and both knees arthralgia, cervical lymphadenopathy, lassitude of the back and limbs and face. As for these symptoms, antibiotic was not effective and were relieved naturally and repeat it. Antinuclear antibody, rheumatoid factor, MPO-ANCA and PR3-ANCA were negative. Soluble IL-2R was within the normal range. She did not accept an abnormal finding other than other sideropenic anemia. She had SNP in G258A of the PSTPIP1 gene. PAPA syndrome (Pyogenic Arthritis, Pyoderma gangrenosum, and Acne) is an autosomal dominant, hereditary auto-inflammatory disease arising from mutations in the *PSTPIP1*/*CD2BP1* gene on chromosome 15q. These mutations produce a hyper-phosphorylated PSTPIP1 protein and alter its participation in activation of the "inflammasome" involved in interleukin-1 production.

P3-222

Aseptic abscesses syndrome with multiple splenic abscesses at disease onset in a Japanese woman

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Conflict of interest: None

Aseptic abscesses syndrome (AA) is a new clinicopathologic entity proposed by Andre et al. in 2007. They surveyed 30 European patients with aseptic visceral abscesses that improved quickly with systemic corticosteroids. AA has common clinical features with autoinflammatory syndromes. We describe a 28-year old Japanese woman who had suffered recurrent fever and abdominal pain for 4 years. Computed tomography revealed multiple splenic abscesses. Repeated blood cultures produced no evidence of pathogenic microorganisms, and trial therapy with antibiotics was ineffective. Although oral aphthae, erythema nodosum, and ileocolitis were present, the diagnostic criteria for Crohn's disease, Behcet's disease, or any autoimmune diseases were not met. The patient's condition improved markedly after administration of oral prednisolone (PSL), but PSL withdrawal led to flare-up with pyoderma gangrenosum, seronegative arthritis, and consolidation in the right lung. After splenectomy, pathological and microbiological examinations demonstrated aseptic abscesses of the spleen. This case showed characteristics compatible with AA, and similar cases have been reported in Japan. Therefore we consider that AA is recognizable in the Japanese population.

P3-223

The diagnosis and treatment for remitting seronegative symmetrical synovitis with pitting edema (RS3PE) syndrome.

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Conflict of interest: None

[Objectives] To clarify the characterization of remitting seronegative symmetrical synovitis with pitting edema (RS3PE) syndrome. [Patients and Methods] Thirty-two patients, 10 male and 22 female, with RS3PE syndrome were checked of the type of onset, complication rate of carpal tunnel syndrome (CTS), the initial usage of doses of prednisolone (PSL), the tendency of recurrence, and the laboratory examination including CRP, rheumatoid factor (RF), anti-CCP antibody titers. [Results] The ratio of acute onset was 78.1% (25/32) and complication rate of CTS was 28.1%

(9/32). Five patients diagnosed as RA by former doctors were included, and other 5 patients had been suffered from DM. The average serum concentration of CRP was 6.2mg/dl (0.7-15.6). Titers of RF and anti-CCP antibody titers were elevated 6 cases. The initial use of doses of PSL was 11.9mg (10-20). The cases diagnosed within 3 months and started administration with PSL had been off within 24 months. The recurrence rate was 37.5% (12/32). [Conclusions] The patients with RS3PE syndrome should be diagnosed precisely and the treatment with PSL were started as soon as possible to obtain good results.

P3-224

A case of IgG4-related disease with an orbital tumor and systemic multiple intravenous tumors

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Conflict of interest: None

A 47-year-old male was suffered from swelling of left lower limb and ultrasonography of left femoral vein suggested deep venous thrombosis and received IVC filter placement and warfarinization at 2004. In May 2010, he experienced right conjunctiva hyperemia and exophthalmos. CT scan revealed right orbital tumor and biopsy was performed. He was diagnosed to MALT lymphoma of stage IE. He was treated with 30Gy of irradiation, but tumor was not reduced. PET/CT revealed that there were multiple intravenous tumors with high ^{18}F-FDG uptake, including SVC, azygous vein, left femoral vein, and orbital tumor. The pathological analysis of intravascular tumor revealed to have massive infiltration of IgG4 positive plasma cells. Serum IgG4 was significantly elevated to 1150 mg/dl, and in addition, pathological reanalysis of orbital tumor showed more than 50% of CD138 positive cells plasma cells were IgG4 positive. He was finally diagnosed to IgG4-related lymphoproliferative disorder (LPD). He was started 40mg of prednisolone daily. The symptom was immediately improved in a week. A month later, enhanced CT scan revealed that the sizes of orbital and intravenous tumors were dramatically reduced. It is the first report of IgG4-related disease with a systemic multiple intravascular LPD.

P3-225

A comorbid case of IgG4-related disease and Sjögren's syndrome (SS)

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Conflict of interest: None

A 63-year-old man, who had complained of dry mouth and bilateral swelling of the submandibular gland, was admitted to our hospital for further examination. Anti SS-A/Ro antibody was positive. The serum level of IgG4 was high to 1010mg/dl. Magnetic resonance imaging showed enlargement of the bilateral submandibular gland and sublingual gland. Immunohistochemically, IgG4-positive plasma cells in specimen from the submandibular gland were observed, and IgG4/IgG ratio was 61%. Lip biopsy showed over 50 lymphocytic infiltration into the salivary glands. In addition, the level of β2-MG in urine was high. The contrast-enhanced computed tomography showed heterogenous enhancement in the parenchyma of kidney. The significant accumulation of gallium scintigraphy was detected in the kidney and prostate, but not in the pancreas, the peripheral artery or retroperitoneum. We diagnosed as a comorbid case of IgG4-related disease and SS due to the result of these examinations. Radiological and serological findings improved soon after the initiation of oral corticosteroid therapy(35mg/day). The serum level of IgG4 was decreased to 213mg/dl. And the dysuria was improved.

P3-226

Study on clinical course of patients with IgG4-related disorders in our hospital

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Conflict of interest: None

[Objectives] IgG4-related disease (IgG4-RD) is a new disease concept which includes various disease spectrum. We report clinical analyses of patients (pts.) with IgG4-RD in our hospital. [Methods] Analyses of clinical and pathological findings, therapeutic responsiveness and prognosis were performed in 10 pts. with IgG4-RD. [Results] Male 4, female 6. Age 51.4±13.4 years. 3 pts. with Mikulicz's disease(MD), 4 with IgG4-related multiorgan lymphoproliferative syndrome and 3 with retroperitoneal fibrosis were diagnosed. One MD patient (pt.) complicated with autoimmune pancreatitis and effectively treated with 30mg of prednisolone (PSL). Serum IgG4 was improved from 380mg/dl to normal range. Another MD pt. effectively treated with 30mg of PSL. One more MD pt. had IgG4-related mammary nodule and treated together with cyclosporine because of ineffectiveness only with glucocorticoids (GC). A pt. with tumors in the ophthalmologic lesion was treated with 30mg of PSL effectively and serum IgG4 (2950mg/dl) was decreased. One pt. with upper lip tumor was treated with surgery. In a pt. with systemic lymphadenopathy, her lymphoadenopathy and serum IgG4 were significantly decreased (IgG4;1270 to 242mg/dl) without any treatment. [Conclusions] Almost pts. were favorably responded to GC treatment.

P3-227

A case of renal cell carcinoma with features of orbital masses, periaortitis and retroperitoneal fibrosis mimicking IgG4-related disese

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Conflict of interest: None

A 65-year-old Japanese man presented to a department of ophthalmology with a chief complaints of bilateral exophthalmos lasting 6 months. MRI examination showed orbital masses that were suspected to be malignant lymphomas and a biopsy was performed. Histopathological examination of orbital masses showed less than 40% of IgG4-positive plasma cells in fibrous tissue and no malignant cells. Although blood tests revealed normal IgG(1354mg/dl) and IgG4 levels(24mg/dl), IgG4-related disease was suspected. Contrast enhanced CT of chest and whole abdomen showed a 4cm-mass in the left kidney and soft-tissue-density lesions surrounding bilateral kidney and an aortic arch to femoral arteries which were consistent with retroperitoneal fibrosis and periaortitis respectively. The left renal biopsy finding was similar to what was seen in orbital masses except for the presence of clear

cell renal cell carcinoma. Soon after the nephrectomy, he presented fever, chest pain, double-vision and lacrimation for one month. Prednisolone 60mg/day was initiated and eye symptoms and fever were improved. MRI and CT performed one month after treatment revealed little improvement on orbital masses, periaortitis and retroperitoneal fibrosis, which was different features from those of IgG4-related disease.

P3-228

A case of IgG4-related pulmonary disease with rapid improvement.

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Conflict of interest: None

We report a 72-year-old man with respiratory involvement of IgG4 related disease, who developed dry cough and shortness of breath on effort for a year. Chest CT showed massive diffuse ground glass opacity, interlobular thickening and bronchial wall thickening. Infiltration of IgG4-positive plasma cells (IgG4+/IgG+ plasma cells: 76.5%) in transbronchial lung biopsy and high serum IgG4 concentrations (835mg/dl) were revealed. We made diagnosis as respiratory involvement of IgG4 related disease. The present case demonstrated solely respiratory involvement of IgG4-RD. He was treated with 0.6mg/kg prednisolone. Marked improvement of lung opacity was observed. The respiratory involvements are often complicated with IgG4-RD, but it is rare in IgG4-RD for no other lesions except a pulmonary lesion to be detected. We report an IgG4-RD case involving only the respiratory system who was treated successfully with oral corticosteroid.

P3-229

A case of IgG4-related Disease with ulcerative colitis-like colonic lesion and hypertrophic pachymeningitis

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Conflict of interest: None

A 56-year-old male who was diagnosed as having ulcerative colitis (UC) in 1998, and treated with low-dose prednisolone, leukoapheresis, mesalazine and salazosulfapyridine. He noticed that the inguinal mass had increased in size from January 2008. In 2009, excisional biopsy was performed for diagnosis. The inguinal mass biopsy specimens showed lymphoid follicles. He was admitted to our hospital on April 2011, because of recurrent submandibular glands swelling. The laboratory examination revealed that he had markedly elevated IgG levels (2178 mg/dL) with particularly high IgG4 levels (1090mg/dL). The submandibular gland biopsy disclosed prominent infiltrates of IgG4-positive plasma cells with fibrosis, consistent with IgG4-related disease. The endoscopic colonic biopsy and the previous biopsy specimens in the inguinal lymph node also revealed numerous IgG4-positive plasma cell infiltrations. He was diagnosed as IgG4-related disease with UC-like colonic lesion. Additionally, he presented with headache and tongue deviation in 2011. Brain MRI revealed hypertrophic pachymeningitis. His neurological symptoms were improved rapidly with oral prednisolone treatment (20 mg/day). We report here a rare case of IgG4-related disease with UC-like colonic lesion and hypertrophic pachymeningitis.

P3-230

Pancreatitis, interstitial nephritis and lymphadenopathy in a man with IgG4-related disease

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Conflict of interest: None

A 30-year-old man had developed acute pancreatitis on June 2011. Physical examination revealed lymphadenopathy of the nech, groins and axllae. Laboratory findings included elevated serum IgG4 level, elevated urine β2-microglobin and NAG and positive results for rheumatoid factor, ANA and anti-SS-A antibody. Lymph node biopsy revealed proliferation of IgG4-positive plasma cells. Gallium scintigraphic findings included the accumulation in the both kidneys. Renal histological findings showed marked infiltration of IgG4-positive plasma cells in the interstitial regions, suggested IgG4 related disease. Treatment with 35 mg/day prednisolone resulted in improvement of those manifestations.

P3-231

Pulmonary hypertension associated with IgG4-related syndrome: a case report

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Conflict of interest: None

A 22-year-old female was admitted to our hospital in April, 2011 because of general lymphadenopathy and hyper –γ - globulinemia. She developed symmetrical swelling of the lacrimal glands and the parotid glands. The laboratory data revealed WBC 9000/μl and CRP 0.09mg/dl. Immunological tests indicated elevated levels of serum IgG (7183mg/dl), serum IgE (1388IU/ml) and serum IgG4 (3230mg/dl), declined complement(CH50 <15U/ml), negative for anti-SS-A antibody. Chest CT demonstrated interstitial pattern, while cardiac US indicated pulmonary hypertension (Right cardiac catheterization proved PA average was 40mmHg), and upper GI scope showed abnormal thickness of gastric mucosa. The biopsy specimens of lip, lymphonode, gastrointestinal tract and bronchus showed infiltrations of IgG4 positive plasma cells. She was diagnosed with IgG4-related disease. Administration of daily 50mg PSL was started, the abnormalities of laboratory data and clinical symptoms improved immediately. This patient showed a lymphoproliferative disorder to multiple organs associated with PH. The possible causes of PH have been considered as myocardial injury or pulmonary angiitis due to plasma cell infiltration. This case may be interesting from the findings of variety of organs invasion with IgG4-plasma cells.

P3-232

Nasal and sinus mucosal biopsy for IgG4 related disease: report of two cases

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Conflict of interest: None

[Objectives] To propose the usefulness of the less invasive sinus and random nasal mucosa biopsy to diagnose IgG4 Related Disease (IgG4RD). [Methods] We describe two cases of IgG4RD who were diagnosed by sinus and random nasal mucosa biopsy. [Results] Case 1. A 78-year-olde female with a past medical history of chronic sinusitis and chronic pancreatitis presented with multiple lung nodules and elevated serum IgG4 level of 820 mg/dL. IgG4RD was suspected and invasive diagnostic biopsy of lung or pancreas was initially recommended, however, she refused these procedure. She underwent planned (less invasive) endoscopic sinus surgery for relief of her nasal symptom. The surgical specimen from nasal and sinus mucosa revealed IgG/IgG4 ratio of more than 90%, which confirmed the diagnosis of IgG4RD. Case 2. A 63-year-old female with a past medical history of chronic thyroiditis was found to have asymptomatic retroperitoneal fibrosis on annual physical check. Her blood test showed an elevated serum IgG4 level of 205 mg/dL. Although there was no obvious nasal symptom or sign, random biopsy from her nasal mucosa was performed which revealed marked infiltration of plasma cell with IgG4/IgG raio of 79.2%.

P3-233

IgG4-related systemic disease in our hospital: clinical survey of the patients newly diagnosed after April 2011

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Conflict of interest: Yes

[Objectives] To determine the frequency and clinical findings of IgG4-related systemic disease (IgG4-RSD) at general hospital. [Patients & Methods] Eleven patients had been diagnosed as having IgG4-RSD, based on the organ manifestations and IgG4+ plasma cell infiltrates by biopsy or serum IgG4 elevation, at our hospital since April, 2011 were surveyed. [Results] As previously described, the organ manifestations of our IgG4-RSD patients included involvement of the salivary glands, lymph nodes, thyroid glands, pancreas, aorta, retroperitoneal, bile ducts, and salivary glands. In about half of the patients, anti-nuclear antibody was positive and serum soluble IL-2 receptor and CRP were increased. Steroid therapy was needed in 6 patients due to the organ manifestations; 3 patients with severe manifestations, including the urinary obstruction caused by retroperitoneal fibrosis, the thoracic aortitis accompanied by constitutional symptoms, and the tracheal obstruction by progressive thyroid swelling, were treated with high-dose prednisolone and azathioprine. [Conclusion] Further recruitment of the newly diagnosed patients will be expected with extended follow-up being conducted.

P3-234

IgG4 related syndrome: Speculation on exacerbation factors

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Conflict of interest: None

[Objectives] To introduce interesting case of considering exacerbation factors of the IgG4 related syndrome [Case] A 75 year-old-male was been to our hospital because of exacerbation of dyspnea. He had past history of recurrent submandibular mass, and autoimmune pancreatitis, and nephrotic syndrome due to membranous nephropathy, which was well controlled by using low dose steroid and immunosuppressant drug, still in the process of decreasing doses of both drugs slowly. He was diagnosed to have bronchitis due to *B.catarrhlis,* but at the same time, NTM(*M.intracellulare*) was observred in his sputum, and slight after, it contained some fungus (*Aspergillus fumigatus*) After bronchitis, His IgG4 level increased to 1730 mg/gl (from 183 mg/gl), and complement level (C3) decreased. Pathophysiologically, exacerbation was seemed to be induced by bronchitis, or some microorganism (*M.intracellulare* or *Aspergillus fumigatus,*), which in some report was the culprit of this disease. But his data abnormality improved after increment of steroid doses. [Conclusion] We must consider multiple factors such as infections (especially granuloma forming ones), vasculitis, and dose of steroids when IgG4 related syndrome become worse.

P3-235

Clinical feautures of six cases with IgG4-related disease in our institute

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Conflict of interest: None

[Objectives] To clarify the clinical features of IgG4-related disease (IgG4RD) in our institute. [Methods] We retrospectively reviewed medical records of six patients with IgG4RD in our institute. [Results] Mean age was 69.7 years old (male 5, female 1). Four of 5 male patients were smokers. Patient numbers of each organ involvement were as follows; lacrimal gland 3, submandibular gland 6, paranasal sinus 2, bronchi 1, lung 5, pancreas 2, liver 1, gallbladder 2, retroperitoneum 4, coronary artery 1, and abdominal aorta 1. Serum IgG, IgG4 level were 4188 mg/dl and 1628 mg/dl respectively. All patients had high serum level of IgE and three had hypocomplementemia and immune complex. Diabetes mellitus including impaired glucose tolerance was seen in 4 cases and one had allergic rhinitis. [Conclusion] In our institute, submandibular, lung and retroperitoneum lesions were commonly involved in IgG4RD. Aged male smoker patients seemed to be a dominant population of IgG4RD. Elevation of serum IgE level in all patients suggests IgG4RD may co-exist with allergic diseases including allergic rhinitis or asthma.

P3-236

Sequential clinical and pathological evaluation of IgG4-related kidney disease patients

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Conflict of interest: None

[Objectives] To evaluate the clinicopathological features of IgG4-related kidney disease before and after glucocorticoid thera-

py. [Patients and Methods] We enrolled and followed-up 5 patients (3 males and 2 females) with IgG4-related kidney disease presenting to our hospital between April 2010 and March 2011. [Results] Four patients were tubulointerstitial nephritis (TIN) and one patient was membranous nephropathy. In 4 patients with TIN, light microscopy demonstrated dense cell infiltration predominantly composed of plasma cells and lymphocytes. Interstitial fibrosis surrounding nests of lymphocytes was characteristic. Mean initial prednisolone (PSL) dose was 0.57mg/kg/day. Laboratory findings ameliorated as follows; serum creatinine 1.66mg/dL to 1.15mg/dL, IgG4 4880mg/dL to 1164mg/dL, U-β2M 11826μg /L to 149μg /L. Repeated renal biopsy was performed 43 days after initial treatment. The stage of interstitial fibrosis seemed to progress. Serum levels of IgG4 elevated after reduction of the PSL dose in 3 cases. In the patient with membranous nephropathy, 40mg of PSL and 50 mg of CyA were prescribed and complete remission was achieved after 7 weeks. [Conclusion] The distinctive clinicopathological features can distinguish IgG4-related TIN from other causes of TIN.

P3-237

A case of long-term observation of kidney involvement of multicentiric Castleman's disease (Clinically mimics IgG4-related disease)

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Conflict of interest: None

We report a case of a 62-year-old woman with multicentric Castleman's disease (MCD) and progressive renal dysfunction due to membranoproliferative gloemrulonephritis (MPGN) with tubulointerstitial nephritis. At age 48, she was referred to our hospital due to hypergammaglobulinemia. Because of systemic lymph node swelling, she underwent right inguinal lymph node biopsy and MCD (plasma cell type) was diagnosed. During this period, microscopic hematuria and persistent proteinuria occurred and her renal function deteriorated. Microscopic examination showed MPGN, accompanied by mild lymphoplasmacytic tubulointerstitial nephritis. Treatment with oral prednisolone reduced her lymphadenopathy and improved the renal function. At age 62, however, her renal function deteriorated with urinary proteinuria and elevation of serum IgG4 and soluble interleukin-2 receptors. The second renal biopsy showed the inprovement of the glomerular lesion. However, threre was persistent tubulointerstitial nephritis without IgG4 positive cells. This case showed that multicentiric Castleman's disease had kidney involvement for long-term observation, and clinically mimics IgG4-related disease.

P3-238

Successful treatment with Cyclosporine in a case of inflammatory Myopathy with Abundant Macrophages (IMAM) with Interstitial pneumonia

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Conflict of interest: None

A 36-year-old woman who suffered from high fever, redness of neck, arm and muscle pain, was admitted to our hospital in Aug. 2005. The level of serum CPK was normal, but anti Jo-1 Ab was positive with elevated CRP. She was diagnosed with dermatomyositis and fasciitis because enhanced MRI images of her thigh showed high intensity signals at the site of fascia. Clinical symptoms and laboratory data were improved after initiation of therapy with prednisolone (PSL) 40mg/day, but relapsed according to reduction of PSL to 10mg/day. For reduction of PSL, Tacrolimus (TAC)3mg/day and etanercept(ETN) 50mg/w were added in Aug. 2006 and Jun. 2007, respectively. Since her myalgia of thigh was continued, muscle biopsy was done in Dec. 2006. The specimen showed a dominant infiltration of CD68-positive macrophages in the fascia, and she was diagnosed as IMAM. Dry cough since Jan. 2010, elevated KL-6 and chest CT findings led to complication with interstitial pneumonia(IP). After TAC and ETN were discontinued, steroid pulse therapy followed by PSL and oral cyclosporine 200mg/day were started in Mar. 2010. PSL was gradually reduced to 7mg/day with no exacerbation of IP and fasciitis was improved in Aug. 2011. The present case suggested that cyclosporine is useful for the treatment of IMAM with IP.

P3-239

This case is differentially diagnosed as CPK-linked Immunoglobulinemia from allergic granulomatous vasculitis or polymyositis.

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Conflict of interest: None

35-year-old woman was revealed a CPK level of 400~700 IU/l without any symptom, few years ago. She developed bronchial asthma and treated with inhaled-glucocorticoid in 2010. On August. 2011, her laboratory finding revealed a CPK level of 2770 IU/l and hypereosinophilia without muscle weakness. She was transferred to our hospital for examination of the high level of CPK. Upper legs of MRI was performed no evidence of muscle inflammation. CPK isozyme electrophoresis demonstrated an extra band that migrated between the CPK-MB and CPK-MM band. The extra band immunoglobulin represented a macro-CPK-complexed with IgA. Light chains were identified as κ. Although macroenzymes are generally non pathologic, this case may be associated with auto-immune disease. It is necessary to observe her in the future.

P3-240

The case of eosinophilic fasciitis complicated with pulmonary aspergillosis

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Conflict of interest: None

A 54-year-old Japanese man had pulmonary aspergillosis treated with itraconazole for 16 months. He suffered from polyarthritis and came to our hospital in February 20XX. We also recognized joints swelling, flexion contracture of his hands, and whole muscular atrophy. We thought it was result from the disuse syndrome. X-ray examination showed no bone erosion. Auto-antibodies were negative. We diagnosed unknown multiple joints disorder and treated him with salazosulfapyridine and bucillamine. In May

20XX, he developed pulmonary embolism and entered the other hospital. He was received muscle biopsy, and the specimen revealed myositis. After he transferred to our hospital, we found high intensity area along the fascia by T2WI MRI and inflammatory cell infiltration of the fascia by biopsy. We diagnosed eosinophilic fasciitis (EF) and treated with oral prednisolone and mizoribine. After the treatment, the clinical condition was improved, though the flexion contracture was left. Etiology of EF is unknown. However, several factors including trauma, Borrelia burgdorferi infection, and drugs have been reported as inducers. We report a case affected EF during treating the pulmonary aspergillosis with itraconazole.

P3-241

A patient of fasciitis panniculitis syndrome with rheumatoid arthritis

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Conflict of interest: None

The patient was 48 years-old-woman, her rheumatoid arthritis (RA) was 9 years history. Her RA (stage IV, class 2) had been treated with 1 mg/day of prednisoloen (PSL), 300 mg/day of bucillamine, and 50 mg/week of etanercept, and her RA maintained clinical remission. She developed bilateral leg edema and admitted to our hospital in April 2011. White blood cell count was 6480/μl (eos 11%), C-reactive protein was slightly elevated to 0.86 mg/dl, total antinuclear antibody was 80 titer (diffuse pattern), and ANCA was negative. Thyroid function was normal, echocardiogram was normal, and deep venous thrombosis was not detected by blood vessel echo. Hypertrophic edema and inflammatory chage in bilateral fascia and tela subcutanea was observed in enhanced magnetic resonance imaging system. Inflammatory cells infiltration of panniculus subcutanea and fascia, fibrotic chage of connective tissue, and hypertrophic change of fascia were observed in biopsy. She was diagnosed as fasciitis panniculitis syndrome (FPS). She treated with 20 mg/day of PSL, and her FPS improved.

P3-242

A case of Cytophagic histiocytic panniculitis

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Conflict of interest: None

74 year male was admitted to our hospital because of high fever and left sided chest pain and swelling. Laboratry examination showed leukocytosis, liver enzyme elevation, hyperfferitinemia and elevation of soluble IL-2 recptor. Gallium centigram showed intense and limited uptake in lt sided chest region. Biopsy was done and pathological diagnosis was Histiocytic Panniculitis. Neither Vasculitis nor Malignancy were found. Clinical diagnosis was Cytophagic histiocytic panniculitis.

P3-243

A case: Relapsing polychondritis with a variety of pulmonary opacities.

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Conflict of interest: None

[OBJECTIVE] We experience relapsing polychondritis with a variety of pulmonary opacitie, auricular chondritis and episcleritis were helped to reach the diagnosis. [METHODS] Case is 63 year old man, 8 months ago, he had fever with pulmonary infiltrates. He was treated at a nearby clinic as pneumonia for one week. 2 months ago, hilar nodular shadows with intermittent fever appeared and abated spontaneously in two weeks. On admission, Multiple pulmonary nodular shadow with persistent fever was appeared, and also abated spontaneously in two weeks. With Ga citrate scintigraphy, there were accumulation in hilar, groin and neck lymph nodes and which seemed to show 'lambda sign' and 'panda sign.' With liver biopsy, no granulomatous lesion was demonstrated. After that, Episcleritis, left auricular chondritis, bilateral sensorineural hearing loss appeared. We diagnosed relapsing polychondritis. [RESULTS] Relapsing polychondritis is an inflammatory disease of unknown cause that occurs rarely. Mainly ear, nose, and tracheobronchial and laryngeal cartilage are target organs. Sometimes, scleritis, polyarthritis, valvular heart disease, and glomerulonephritis are associated. It is an interesting case presented with a variety of lung opacities, so we report this case here.

P3-244

Central nervous system involvement in relapsing polychondritis

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Conflict of interest: None

Central nervous system (CNS) involvment is a rare complication in patients with relapsing polychondritis (RP). We report a case of CNS vasculitis associated with RP. In May 2011, a 42-year-old male developed headache and unilateral auricular flare without pain. He also had bilateral ocular inflammation including episcleritis, hemorrhage and leukoma in the eyeground. He visited our hospital on June 27, and biopsy of ear was done on the same day. On June 29, he further had unilateral weakness in extremities. Diffusion weighted MR imaging (DWI) showed a high intensity on right parietal lobe. He was diagnosed as hemiplegia due to CNS vasculitis associated with RP. He was admitted to our hospital, and was treated with 2 courses of steroid pulse therapy (1000 mg methylprednisolone for 3 days). By 5th hospital day, his clinical symptoms were improved. 20th hospital day, the high intensity on DWI shrank. A biopsy of the ear showed inflammation and chondrocyte degeneration, consistent with RP. He was further treated intravenous cycrophosphamide and oral corticosteroid. He was discharged on 70th hospital day after corticosteroid was tapered,

P3-245

Peripheral neuropathy complicated by Cogan's syndrome: a case report

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Conflict of interest: None

Case Presentation: a 47-year-old japanese man fastly noticed

malaise in February 2011. From April 2004, he also noticed ringing and deafness ear, then the ophthalmologist diagnosed with sudden hearing loss and treated. Late may 2011, His ocular was appearanced blurred vision, conjunctival hyperemia. He was diagnosed with interstitial keratitis. Based on his sensorineural hearing loss and interstitial keratitis. Diagnosis of typical Cogan's syndrome was made. After the on admission our hospital, he seemed hearing loss, paralysis of the toes on both feet and anterior tibial muscle weakness. In this case his blood tasting showed not positive antinuclear antibody, ANCA, Syphilis reactions. Nerve conduction study showed decrease in conduction velocities with peroneal nerve. Therefore we thouget Cogan's syndrome complicated with peripheral neuropathy. The administration of a oral steroidal combined immunosuppressive treatment resolved of improvement clinical symptoms. Discassion: Cogan's syndrome is a rare autoimmune-like disorder characterised by nonsyphilitic interstitial keratitis and audiovestibular function disorder. It is a few reports of complicated with peripheral neuropathy. We report this case of Cogan's syndorome complicated with peripheral neuropathy.

P3-246

A case with elderly onset steroid-responsive Cogan's Syndrome

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Conflict of interest: None

An 81-year-old man had general fatigue since January 2011. A month later, he was diagnosed as having exudative otitis media. In March, he had eye congestion. Forty milligram per day of prednisolone was started and tapered to ten milligram per day. He suddenly stopped the therapy in August. Since mid-August, he had appetite loss, fever, and a 10 kg decrease in his body weight. He was admitted to our hospital on September 9th. On admission, he had scleritis and sensory deafness. Laboratory data were CRP 18. 34 mg/dL, RF 65 IU/mL, ESR 113 mm/h. ANA, ANCA, and TPHA were negative. He was diagnosed as having Cogan's Syndrome because he had scleritis and sensory deafness, and he showed no synptoms of other disease. Fifty milligram per day of prednisolone was started. After treatment, his symptoms improved, and CRP turned negative. Cogan's Syndrome is a rare autoimmune-like disorder characterised by nonsyphilitic interstitial keratitis and audiovestibular function disorder. We report this case because it usually occurs in young adult, and a case with elderly onset seems to be rare.

P3-247

A report of Familial Mediterranean Fever patient with nephrosclerosis secondary to hypertension and chronic inflammation

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Conflict of interest: None

A 37-year-old Japanese man with periodic abdominal pain was referred to our hospital for the assessment of renal failure. 7 months ago, he suffered from periodic abdominal pain and fever. These symptoms persisted one week and subsided naturally. Computed tomography showed no evidence of abdominal mass, imflammation nor ileus and blood culture did not identify a pathogenic organism. Genetic testing of MEFV gene identified E148Q homozygote. He was diagnosed Familial Mediterranean Fever (FMF). His blood pressure rose to 170/110 mmHg and his serum creatinin gradually worsened and rose to 4.6 mg/dL. Needle kidney biopsy was performed. The histopathological diagnosis was nephrosclerosis with glomerulocapillary wrinkling and arteriole intimal thickening but no evidence of renal amylodosis. Renal amyloidosis is known for major complication of FMF, but there is few report about other renal diseases. Responding to colchicine, he never experienced abdominal pain and his serum creatinin was no further significant worsen. These findings suggest chronic inflammation and hypertension make nephrosclerosis and this is the first report of nephrosclerosis in FMF patient.

P3-248

Protein-losing gastroenteropathy probably associated with collagen disease: successful treatment with glucocorticoid

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Conflict of interest: None

·A 78-year-old man was admitted to our hospital for the investigation of his severe systemic edema. His laboratory data showed severe hypoproteinemia and his computed tomography revealed large quantities of pleural effusion and ascites. The abdominal scintigram images showed abnormal radioactivity in the intestine. He diagnosed as protein-losing gastroenteropathy, but the primary disease had remained undiagnosed for several years. But based on slight elevation of antinuclear antibody and hypocomplementemia, some sort of collagen diseases were suspected to be involved to this patient. Thus glucocorticoid treatment was started. His total serum protein and albumin levels was significantly increased, and systemic edema was reduced. We report a case with protein-losing gastroenteropathy probably associated with collagen disease, in whom glucocorticoid treatment was highly effective.

P3-249

microRNA-7 is down-regulated and mediates excess collagen expression in localized scleroderma

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Conflict of interest: None

[Objectives] Localized scleroderma (LSc), a connective tissue disorder restricted to the skin and subcutaneous tissue, is characterized by skin fibrosis due to an excessive deposition of types I collagen. In the present study, we investigated the mechanism of fibrosis seen in LSc, focusing on microRNA. [Methods] miRNA expression was determined by PCR array, real-time PCR, and in situ hybridization. The function of miRNA was evaluated using specific inhibitor. [Results] PCR array analysis using tissue microRNA demonstrated miR-7 level was significantly decreased in LSc skin compared to normal skin in vivo. The transfection of specific inhibitor for miR-7 into cultured normal dermal fibroblasts resulted in the up-regulation of collagen protein in vitro. Also, the serum levels of miR-7 were significantly decreased in LSc patients compared with healthy controls. Taken together, systemic or local down-regulation of miR-7 may contribute to the pathogenesis of LSc via the overexpression of collagen, and serum miR-7 may be useful as a disease marker. Investigation of the regulatory mechanisms of tissue fibrosis by microRNA may lead to new treatments by the transfection into the lesional skin of this disease.

P3-250

A study of prolonged viral infection

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Conflict of interest: None

We reported 5 cases of sever viral infection which shows high fever sustained more than a week, wasting and sometime need admission, we named it "prolonged viral infection" (PVI) in JCR 2002. Simultaneously we reported its clinical manifestation. This time we report courses of subsequent of cases in JCR 2002, and 5 cases we experienced recently. [patients] 1.10 cases in JCR 2002. 2. 5 cases in this year. [methods] 1. Telephone interviews 2. Clinical manifestation, labolatory findings and imaging. [results] 1. 10 cases of JCR 2002 have been healthy and had no admission history. 2. 2 cases of arthritis, 2 cases of dermatitis, 3/2 cases of leucopenia/thrombocytopenia,4 cases of liver injury, 4/5 cases of hepato/splenomegalia. One case had positive parvoB19 IgM, and another one had positive CMV IgM. [conclusion] Cause of PVI, presumably as a primary infection with virus. Splenomegaly is an indicator of PVI.

P3-251

SAPHO syndrome diagnosed with unknown fever and pain of knee, a case report

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Conflict of interest: None

SAPHO syndrome is a rare condition involving the skin, bone and joints. The underlying causes of SAPHO are poorly understood, and clinical states are valiable. Treatment for SAPHO is unestablished, and often directed towards the individual symptoms. We report a case of 22-year-old woman with fever of 39 degrees Celsius and bilateral pain of knee. Treatment was initiated with antibiotics and non-steroidal anti-inflammatory drugs (NSAIDs), but clinical improvement was poor. Fever and slightly elevated serum C-reactive protein remained, but blood culture and autoantibody were negative. Bone scintigraphy revealed uptake for bilateral knee and left elbow, but sterno-clavicular joint and sacroiliac joint were intact. MRI revealed bone-marrow edema at proximal tibia and distal femur, therefore, we performed bone biopsy of the left proximal tibia and distal femur to differentiate the cause of osteomyelitis. On histological evaluation, marked infiltration of neutrophils has noted, but cultures were negative. With these findings, we diagnosed Chronic Recurrent Multifocal Osteomyelitis, a type of SAPHO syndrome. Despite the treatment with NSAIDs, the pain of knee has not improved, thus the patient started adalimumab. The symptoms and MRI findings showed substantial improvement.

P3-252

Successful treatment of corticosteroid and calcineurin inhibitors resistant AIHA in a patient with SLE; IVIG subsequent rituximab therapy

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Conflict of interest: None

A 55-year-old woman was admitted to our hospital in August 2010, because of wine-red urine. Blood examination revealed WBC 3400 /μl, Hb 6.8 g/dl, Plt 8.7x10^4 /μl, LDH 1152 IU/l, Haptoglobin<10 mg/dl, direct and indirect Coombs test positive, ANA 1:320(Ho & Sp), anti-DNA antibody(RIA) 11 IU/ml, anti-phospholipid antibody positive. Urinalysis showed proteinuria and cylinduria. SLE was diagnosed and 50mg of prednisolone(PSL) daily was initiated. Subsequently tacrolims was added but thereafter the AIHA deteriorated. We started methylprednisolone pulse therapy (1g/day for 3 days) in November 2010, subsequently she was treated by cyclosporine with 40mg of PSL daily. The anemia persisted, the high-dose intravenous immunoglobulin was initiated, subsequently weekly treatment with rituximab (375mg/m^2, weekly for 4 weeks) was added in January 2011. In February to March, the anemia deteriorated by gastrointestinal bleeding. The gastrointestinal bleeding gradually improved following the intravenous ganciclovir and PSL tapering. She was eventually discharged in June 2011. Recently it has been reported that rituximab was effective for patients with refractory AIHA, but a rituximab use for AIHA is off-license. I hope that rituximab has been licensed in the treatment of AIHA.

P3-253

A case of refractory adult-onset Still's disease successfully treated by tocilizumab

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Conflict of interest: None

We report a case of refractory AOSD successfully controlled with tocilizumab. The patient was a 21-year old Japanese women with AOSD, and her inflammatory condition could not be controlled despite of high dose steroid therapy coupled with cyclosporine A (100-225mg/day), methotrexate (15mg/day), 1 course of intravenous cyclophosphamide pulse, and 10 courses of leukocytapheresis. The serum TNFα level was within normal limits, and the serum IL-6 level was mildly elevated. Therefore she was administered 560mg (8mg/kg) of tocilizumab every two weeks. Immediately after the first administration, the disease became worse. However, after additional high dose steroid therapy, the condition was improved dramatically and steroid dose was successfully reduced. Although AOSD cases, treated by tocilizumab, have been reported recently referencing to the evidences of recent systemic juvenile idiopathic arthritis cases, precise roles of IL-6 in its pathogenesis are still unknown. In the present case, we measured the serum cytokine profiles through the clinical course and report the involvement and kinetics of serum inflammatory cytokines in the pathogenesis of AOSD treated by tocilizumab.

P3-254

A case of severe goat attack with MEFV mutation successfully treated with Colchicine

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Conflict of interest: None

We report a case of severe goat attack with MEFV mutation. A 59 years old man had realized arthralgia and then high fever was complicated at the same time about once a month. Polyarthritis with 39°C fever up and synovial bursitis of left knee and right el-

bow appeared. Elevation of ESR and CRP was found. We punctured the about 5cm synovial bursa and found white viscous fluid. Only uric acid Na crystal was contained in the fluid, but serum uric acid value was normal. In addition, MEFV Exon2 E148Q mutation was demonstrated. Medication of Colchicine (0.5mg/day) improved immediately symptoms and inflammatory findings. There is no relapse until now.

P3-255

Therapeutic effects on hypertension and menopausal-like symptom in female patients with Rheumatoid Arthritis and other autoimmune diseases

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Conflict of interest: Yes

[Objectives] Rheumatoid arthritis (RA) is a chronic disease characterized by joint destruction. Persistent pain could lead to depression. While, some women suffer from menopausal-like symptom, resulted in poor QOL. Autoimmune diseases such as RA may have significantly impaired QOL. In both diseases, sympathetic overactivity has been suggested. An angiotensin-receptor blocker (ARB) cardesartan cilexetil will have a suppressing effect of the sympathetic nervous system on both diseases, and is expected to ameliorate these symptoms. We examined the therapeutic effect on hypertension and menopausal-like symptom in female patients with RA and other autoimmune diseases. [Methods] A total of 10 patients were enrolled in this study. The observation period was 3 months. We measured systolic blood pressure, diastolic blood pressure, SMI and CES-D Scale. [Results] Systolic blood pressure, diastolic blood pressure were both significantly decreased (SBP153 ± 7 → 133 ± 11mmHg, DBP94 ± 9 → 76 ± 11 mmHg, $p < 0.01$). SMI showed a decline (33.6 ± 19.2 to 27 ± 11). CES-D Scale was significantly decreased (15 ± 6 to 8 ± 21). Based on these results, further trials are ongoing that hiring other ARB and Ca antagonist.

P3-256

Nocturnal hypertension in rheumatic disease

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Conflict of interest: None

【background】There are not so many reports that examine the relation between rheumatic disease and nocturnal hypertension, though it is reported that the nocturnal hypertension is risk factor of the cardiovascular event.【method】Prevalence of nocturnal hypertension was investigated in 29 rheumatic disease patients with 24 hour ambulatory blood pressure monitoring. Moreover, Influence that the treatment of the rheumatic disease gave the nocturnal hypertension was examined in 11 patients.【result】21 in 29 rheumatic disease patients presented nocturnal hypertension. Moreover, four patients have improved it, though eight of 11 before it treats presented the nocturnal hypertension.【conclusion】It was suggested to present the nocturnal hypertension in the high rate in the rheumatic disease. Moreover, it was suggested the possibility that the nocturnal hypertension improves in controlling the disease activity.

P3-257

Changes in physical symptoms & medical care of rheumatoid arthritis (RA) patients after the Great East Japan Earthquake ~Results from our questionnaire survey~

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Conflict of interest: None

Objective: Survey theGreat East Japan Earthquake's impact on RA pts' physical symptoms & state of medical care. **Methods**: Questionnaire on 242 RA out-pts; house damage, before/just after/2 months post-earthquake (p-e) physical status VAS, & state of p-e medical care; 204 pts w/ hypertension also surveyed for comparison. **Results**: VAS of 242 RA pts worsened p-e w/ greater change for complete collapse, followed by half collapse & none. Half pts w/ complete collapse received treatment at nearby hospitals or evacuation sites. 80% of pts w/ half collapse or none continued our treatment. Biologicals could somehow be given to half pts w/ complete collapse, but not to 1/4 due to exhausted drug stock or tsunami. Just after earthquake & month 2, VAS increased in pts unable to receive biologicals & pts w/ extended dose interval. P-e physical status: psychological stress symptoms like insomnia, mental instability, abdominal pain, diarrhea, constipation were major in all groups. RA & hypertension pts had similar physical change p-e showing its stress may have affected their physical condition. Regular medication or none in pts on biologicals may have affected their physical state; drug stockpile or establishing medication system in vicinities are needed for future earthquake disaster measures.

P3-258

The evaluation of arthropaty of outpatients in an university hospital general medicine

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Conflict of interest: None

We evaluated the prevalence of joint symptoms and studied the relationship between joint symptoms and other factors among patients visiting the general medicine clinic of Tokyo medical university Hachioji medical center between March and July 2011. We surveyed the patients' symptoms and the depressive tendencies, using the interview sheets consisted with the symptom-check list and the Zung's SDS. 151 patients filled out the sheets completely. 89% were women, and the mean age (SD) was 44.7 (17.8) years old. 36 (25%) patients had joint symptoms by the check lists, but only 6 patients complained of joint symptoms to their physicians. The patients with joint symptoms had more depressive tendencies than those without joint symptoms. General physicians should give attention to joint symptoms, even if the patients do not complain of them.

P3-259

The estimation of destructivity on our patients with seronegative rheumatoid arthritis (RA)

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Conflict of interest: None

Background: Patients with arthritis but without both rheumatoid factor (RF) and anti-CCP antibody (ACPA) (= seronegative) are thought to be difficult to be classified as having definite RA by 2010 ACR/EULAR classification criteria for RA. We need to know

the actual proportion and the tendency of structural damage of those seronegative RA patients to discuss on the necessity for the revision of the current criteria or the establishment of another criteria specific to seronegative arthritis patients. Methods and Results: Among our 173 outpatients followed as RA and with available information on RF and ACPA, 26 patients (15.0%) were seronegative, among whom 20 patients did not satisfy the 2010 crtiria. Among those 26 patients, 8 patients showed the bone changes typical of RA by X-ray or MRI and one patient showed the pathological change typical of RA in the resected synovial tissue. At least those collective 9 patients (5.2% out of total RA patients) are considered to have definitive RA with destructive nature, among whom 6 subjects (3.5% out of total RA patients) did not meet the 2010 criteria. Conclusion: We reconfirmed that a considerable number of seronegative RA patients without satisfying the 2010 criteria have the characteristics of the erosive disease.

P3-260

Research of inpatients of crystal deposition disease in this hospital

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Conflict of interest: None

[Background] Basic calcium phosphate or calcium pyrophosphate dehydrate (CPPD) are known that deposit on joints, tendons and cartilages, and produce arthritis or enthesitis. We have researched the 11 cases of inpatients of crystal deposition disease. [Result] 8 patients were pseudogout, 2 were crowned dens syndrome (CDS), and 1 was both. 4 were admitted to hospital as fever of unknown origin. The chief complaints of group of pseudogout were fever and arthralgia in all cases, on the other hand, of CDS were fever and posterior cervical pain mainly, without clear arthritis. Patients were diagnosed as pseudogout by mainly existence of CPPD in synovial fluid or calcification of knee joint with roentgenograms. Except one case, CPPD crystals were shown in all cases of group of pseudogout. One case of CDS had diagnosed as rheumatoid arthritis (RA) at first, and the other had been admitted to hospital as polymyalgia rheumatica (PMR). Both cases were finally diagnosed as CDS with calcification of odontoid process. At all of 11 cases, NSAIDs or a little corticosteroid were effective. [Conclusion] Crystal deposition disease must be kept in mind in differential diagnosis of fever of unknown origin with cervical or joint pains, because it sometimes mimics RA, PMR or other diseases.

P3-261

A case of the dialysis patient who repeats infectious arthritis

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Conflict of interest: None

A 63-year-old male, who was in hemodialysis with diabetes mellitus, was admitted to our hospital complaining of polyarthralgia in 2009. FDG-PET/CT demonstrated the increased FDG activity in bilateral shoulder, wrist, hip, knee and ankle joint. Furthermore, the infectious endocarditis(IE) was diagnosed by echocardiography. Treatment with an antibiotic improved not only IE but also polyarthralgia. Therefore polyarthralgia was diagnosed of IE. In 2010, he was admitted to our hospital a second time, in order to treat infectious myositis of a left leg. He had polyaruthralgia also on that occasion. Gallium - 67 scintigraphy demonstrated the increased uptake of Gallium in bilateral wrist, shoulder, and knee joint. Polyarthralgia has also been improved when infectious myositis was treated with the antibiotic. Therefore, we diagnosed the polyarthralgia as infectious arthritis. In 2011, he was admitted to our hospital a third time, in order to treat abscess of a right leg. He had polyaruthralgia also on that occasion and newly observed the change in sacroilliac joint. Polyaruthralgia has been improved also this time when abscess of a right leg was treated with the antibiotic. We experienced the case of the dialysis patient who repeated infectious arthritis with other infections.

P3-262

The case of myopathy that is suspected inclusion body myositis

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Conflict of interest: None

Patient was aware of the weakness of the lower extremities, such as creeping to sit on the toilet and stand up befire five years ago. He coluld not open the lid of the cap before a few month. He received hospital at March 14, 2011. He showed an increase in CPK and proximal muscle weakness and advantage on both lower legs. And thereafter slowly worsening muscle weakness, doctor suspected myositis and introduced to our department on April 12. Symptoms long since emerged that showed muscle weakness and distal femur fingers, CPK and aldolase and myoglobin in the blood, changes in EMG myogenic and octopus, we thought inclusion body myositis muscle and we do muscle biopsy. The result of muscle biopsy was the Reduction myopathy bodies, rimmed vacuolor myopathy, myofibrillar myopathy. Clinical symptoms alone differentiate inclusion body myositis. And myopathy is difficult in patients with a long clinical course as the present case. It isimportant to do a muscle biopsy.

P3-263

A case of Castleman disease showing Sjögren, antiphospholipid antibody and RS3PE syndromes

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Conflict of interest: None

A 80-year-old woman complaining of edema on the lower legs and insteps, livedo reticularis on the lower legs, and pain in the shoulders, knee, ankles was admitted to our hospital. Blood tests showed elevated serum IgG, MMP-3, CRP, IL-6[35.4pg/mL], plasma fibrinogen, FDP and D-dimer levels. Positive for anti-SS-A and anti-CL · β2GP I antibodies were observed. CT scan showed bilaterally hilar, inguinal and external iliac lymphadenopathies. Contrast-emhanced MRI demonstrated synovitis in the MP joints of the toes. She had dry eyes, retinal hemorrhage caused by the retinal vein occlusion, and thrombi in the great saphenous vein confirmed by ultrasound. She was suggested as Sjögren, antiphospholipid antibody and RS3PE syndromes. A biopsy of inguinal lymph node showed polyclonality by immunostainings for IgG, κ and λ chains. She was also diagnosed as mixed type of multicentric Castleman disease which is morphologically in-between hyaline-vascular and plasma cells types. Castleman disease is known to express a variety of autoantibodies, which may have caused Sjögren and antiphospholipid antibody syndromes. RS3PE syndrome is one of the paraneoplastic syndromes. It is possible that Castleman disease

with high level of serum IL-6 was associated with the appearing of RS3PE syndrome.

P3-264

A case of Sarcoidosis diagnosed from hypercalcemia

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Conflict of interest: None

A 39-year-old man had admitted to our hospital because of disturbed consciousness, low grade fever, and limb muscle weakness with hypercalcemia. Corrected serum calcium level was 14.0mg/dl. Fluid therapy and diuretic administration made his conscious clear, but serum calcium level was not corrected to the normal range. There were no evidences of malignancy, tuberculosis and hyperparathyroidism. By taking his past history in detail, it became clear that he had been indicated bilateral hilar lymphadenopathy (BHL) 10 years ago and mediastinal lymphadenopathy had been detected by positron-emission tomography (PET) 4 years ago. Laboratory examination revealed hypercalcemia, hypercalcinuria, increased serum levels of angiotensin-converting enzyme(ACE). Tuberculin skin test was negative. He had annular erythema at his cheek and upper arm. Skin biopsy showed noncaseating epithelioid cell granuloma. The diagnosis of Sarcoidosis was made. He received oral prednisolone therapy(20mg/day), which resulted in a complete resolution of hypercalcemia. We report a rare case of Sarcoidosis diagnosed from hypercalcemia.

P3-265

The association of chronic kidney disease and cardiovascular disease in rheumatoid arthritis

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Conflict of interest: None

Patients with rheumatoid arthritis (RA) have been reported to have higher prevalence of cardiovascular disease (CVD). Chronic kidney disease (CKD) was shown to be associated with CKD. However, it has not been whether CKD is associated with CVD in patients with RA. We examined 591 patients (83% female) with RA and analyzed the association of CKD and CVD. Renal function was assessed by estimated glomerular filtration rate (GFR) using the Modification of Diet in Renal Disease equation. 136 patients (23.0%) had CKD.48 patinets (8.1%) had CVD. 50% of patients with CVD had CKD. In conclusion, the presence of CVD was associated with the presence of CKD in patients with RA. The intervention for CKD might be effective to prevent CVD in patients with RA.

P3-266

Investigation of the gastroesophageal reflux disease (GERD) in RA patients

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Conflict of interest: None

[Objectives] Recently, Frequency Scale for the Symptoms of GERD (FSSG) has been reported as a useful marker in diagnosis of Gastroesophageal Reflux Disease. We investigated the presence or absence of GERD by using FSSG in patients with Rheumatoid Arthritis. [Methods] We investigated 118 patients with RA visited to our hospital during January 2010 to October 2011. [Results] The mean value of FSSG in patients treated with PPI were higher in patients with H2-blocker. Furthermore we examined gastroscope in 75 RA patients, the prevalence of GERD was 13.3%. The mean value of FSSG in GERD positive groups were significantly higher in GERD negative groups. The proportion using PPI in GERD negative groups were significantly higher in GERD positive groups. [Coclision] We demonstrated that mesurement of FSSG might be useful to diagnosis GERD in RA.

P3-267

A case of rheumatoid arthritis complicated with mycobacterium infection

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Conflict of interest: None

A 67-year-old women who presented with polyarthralgia and swelling joints. She was refered from her GP as suffering from rheumatoid arthritis with high activity. Her MP, PIP and wrist joints were swelling and hurting symmetrically suggesting synovitis. Some DMARDs were administrated to her, but her symptoms showed no improvement. We tried to treat her using Infliximab, however, her synovitis worsened. To clarify the pathogenesis of her joint disease, her joints were punctured, and joint effusion was removed and analyzed. Finally *mycobacterium intracellulae* was detected. The treatment agents of rheumatoid arthritis have been getting stronger, while the effect is getting more reliable, but the frequency of infection is also getting higher, including that of tuberculosis. One of the characteristics of infection related to Infliximab is extra-respiratory tuberculosis, suggesting that some rheumatoid arthritis patients already have a tuberculosis infection in their extremities. The pathological findings show similarities between the granuloma of tuberculosis and a rheumatoid nodule, which appear among the high active RA patients. This case indicated the possibilitythat the cause of RA might be related to bacterial infection.

P3-268

3 cases of Multicentric Castleman's disease (MCD) complicated with renal dysfunction

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Conflict of interest: None

[Objectives][Methods] We present 3 cases of Multicentric Castleman's disease (MCD) complicated with renal dysfunction who had kidney biopsy performed. [Results] Case1: A 56 year-old male developed swollen lymph nodes, positive urine protein and hypergammaglobulinemia at age 45. The previous doctor diagnosed IgA nephropathy / interstitial nephritis. He was treated with PSL. Because anemia was aggravated by reducing PSL at age 48, he was treated by added MTX. Hematuria, serum IgG of 4721mg/dl and renal dysfunction was seen at age 55. The renal histology was interstitial nephritis. Case2: A 58 year-old female noted anemia at age 50. Cervical lymph nodes enlargement, proteinuria and hematuria, anemia and serum IgG of 5072mg/dl developed at age 58. We diagnosed plasma cell variant MCD. The renal histology was

interstitial nephritis. PSL was effective, but later, urinary findings worsened by reducing PSL. Case3: A 38 year-old male noted swollen cervical lymph nodes at age 31. Swollen lymph nodes, anemia, renal dysfunction and serum IgG of 6237mg/dl were pointed out at age 38. We diagnosed him with plasma cell variant MCD. The renal histology was IgA nephropathy with mesangial deposits of IgA. Because PSL was ineffective, tocilizumab was started. His symptoms and proteinuria improved.

P3-269

Idiocyncratic adverse drug reactions to sulfamethoxazole-trimethoprim in patients with connective tissue diseases.

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Conflict of interest: None

Aim: To examine the incidence of idiosyncratic adverse drug reactions (ADRs) to sulfamethoxazole-trimethoprim (SMX-TMP) in patients with connective tissue diseases (CTDs). Methods: Medical records of patients with CTDs who were treated with SMX-TMP at the Division of Rheumatology in Nagoya City University Hospital between 2004 and May 2011 were reviewed. Rate of discontinuation of SMX-TMP were analyzed by the disease phenotypes of CTDs and by the therapeutic (320 mg/day of trimethoprim equivalent or more) or prophylactic doses of SMX-TMP. Results: SMX-TMP was administered to 146 patients. There were 28 patients (19.2%) who discontinued the SMX-TMP treatment by ADRs of SMX-TMP. Idiosyncratic ADRs such as drug rash, cytopenia, fever, eosinophilia were observed in 18 patients (12.3%), and were relatively frequently observed in patients with scleroderma (37.5%), rheumatoid arthritis (35.0%), adult Still's disease (33.3%), and systemic lupus erythematosus (18.2%). While, there are few or no idiosyncratic ADRs in patients with systemic vasculitis (3.6%), polymyositis, and dermatomyositis (4.2%). Conclusions: The incidence of idiosyncratic ADRs to SMX-TMP may vary from disease to disease. When we administer SMX-TMP to patients with CTDs, it is necessary to consider the underlying CTDs.

P3-270

A case of drug fever associated symptom like Behçet's disease

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Conflict of interest: None

The case is a 37 years old man. Due to multiple cerebral infarction pointed out in head CT he was introduced to our Hospital. Rhabdomyolysis was occurred using sodium valproate, and drug was changed to zonisamide. Fever and high level inflammatory reaction rose after discharged, and multiple mouth sores appeared. Granulomatous uveitis was pointed out before so Behçet's disease was doubted and prescribed colchicine. And it was diagnosed oral candida by oral surgery and was prescribed miconazole, and symptom was improved. However, high fever appeared in December again, Colchicine and antibiotics ABPC/SBT did not defervesce. At this time, symptom was improved after we used antibiotics MINO as atypical pneumonia. But fever appeared again in few weeks, and the inflammation reaction was elevated. Systemic convulsions were occurred in next February and he was transported to our Hospital for admission. Zonisamide was suspected about the causes of the inflammatory reaction. The fever defervesced and the inflammation reaction disappeared after we stopped oral medication. After that he was good in progress without fever and inflammatory reaction. We diagnosed drug induced fever by zonisamide although we considered possibility of Behçet's disease because the patient had HLA-B51 in HLA genotype.

P3-271

Examination of MTX-associated lymphoproliferative disorder (MTX-LPD) associated with autoimmune disease

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Conflict of interest: None

We examined 6 patients presenting with MTX-LPD associated with auto immune disease from 2002 to 2010 in our hospital. Regarding the breakdown of autoimmune disease, 4 cases were RA, 1 case was SLE and 1 case was AOSD. Age : range from 36 to 74 years old. Gender : 1 case was male and 5 cases were female. Auto immune disease duration : from 4.3 to 55 years. The administration of MTX ranged from 2 years to 18 years. MTX dosage ranged from 4mg/week to 8mg/week. Histopathologically, 4 cases were diffuse large B-cell lymphoma, 1 case was Hodgkin lymphoma and 1 case was Peripheral T-cell lymphoma. Clinical outcome : 3 cases demonstrated remission after the cessation of MTX treatment, one of these 3 cases relapsed and thereafter underwent cancer chemotherapy, but eventually died. Another 3 cases underwent cancer chemotherapy and demonstrated remission. 3 cases were EBV positive, but 1 case of the spontaneous remission cases was EBV negative. The treatment of autoimmune disease after MTX withdrawal: 2 cases were TAC, 1 case was SASP and 3 cases were only PSL. Due to the fact that we hesitate to treat patients with MTX and biologics who have autoimmune disease that are associated with MTX-LPD, a careful examination of this therapeutic regimen therefore seems to be needed.

P3-272

A case of hemophagocytic syndrome associated with Epstein-Barr virus and tubercle bacillus reactivation during infliximab therapy.

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Conflict of interest: None

A 79-year-old woman with rheumatoid arthritis had been treated by MTX(8mg/W), PSL(5mg), and infliximab(4mg/kg/8 weeks). As her renal function went down, pancytopenia appeared. MTX and infliximab was stopped and the number of hemocyte was improved. She was admitted to our hospital because of high fever after a month. CT scan image and blood examinations can't detect any bacterial infection, tumor and autoimmune disease. Antibiotic therapy (MEPM 0.5g×3) was ineffective. Bone marrow aspiration we did for DIC progress revealed hemophagocytic syndrome (HPS). Epstein-Barr virus(EBV)-DNA(1.7×10^3copy/10^6cell) was detected in peripheral blood and tubercle bacillus was cultivated from bone marrow aspirate -when infliximab therapy started, she took isoniazid(INH) for 9 months because she had anamnesis of tuberculosis. HPS associated with EBV and tubercle bacillus is very severe, so we should pay more attention to the occurrence of EBV and tubercle bacillus reactivation during biologic agent thera-

py.

P3-273

Comparison of anxiety among patients using the biologics infliximab and tocilizumab

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Conflict of interest: None

[Objectives] To compare anxiety in patients using infliximab (IFZ) and tocilizumab (TCZ) [Methods] Patients using IFX (26 patients) and TCZ (25 patients). Doctors, nurses, and pharmacists described the effects, adverse effects, and methods of using biologics to patients. Surveys for psychological analysis were conducted before and after the description and after administration of biologics. The visual analog scale (VAS) was used to evaluate anxiety. [Results] Of all IFX-receiving patients, 81%, 57%, and 52% showed anxiety before description, after description, and after administration, respectively (VAS, 5.7 ± 2.7, 3.3 ± 2.5, and 3.2 ± 2.1, respectively). The corresponding values for TCZ-receiving patients were 72%, 56%, and 56% (VAS, 3.7 ± 3.0, 2.5 ± 2.7, and 1.5 ± 2.1). Anxiety after use of biologics was persistent, showed relapse, and occurred even after change of drug. [Conclusion] Providing knowledge prior to introduction of biologics reduces anxiety to some extent. Although the method of use and action mechanism of IFX and TCZ are different, both drugs cause anxiety, and anxiety persisted in a fixed percentage of patients. Good response tended to reduce anxiety, but some patients remained anxious. We think that continual guidance even after introduction will help reduce anxiety

P3-274

Assessment of recent activities of Japan college of rheumatology after biologics

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Conflict of interest: None

[Objective]:Several problems were pointed out by several fields about Japan college of rheumatology (JCR) after biologics were emerged on the market. By adopting the methods of ACR and EULAR, I assessed some problems about recent JCR, which might help some improvement of JCR. [Methods] 1: I collected information by attending ACR, EULAR, and lectures of biologics. 2: I administrated biologics to 200 RA patients or more. 3: I submitted three articles to modern rheumatology. I assessed JCR about these three problems. [Results] 1: PMS committee members advertised and analyzed biologics. This structure is very exceptional and indicates that they hardly give fair judgment including conflict of interest. 2: Dose and frequency (twice a week) setting of etanercept had problem, lacking of 10mg dose of etanercept. 3: All submitted articles were rejected. They were accepted by other journals (Average impact factor around 5). [Conclusion] 1: JCR management might be disturbed by PMS committee members with great influence. 2: For Japanese etanercept were recommended to start 25mg once a week. Clinical study must be investigated minutely. 3: The improvement of science and English ability are need to the reviewers of modern rheumatology. In view of those problems, I expect improvement of JCR.

P3-275

The influences on vital reaction and infusion reaction at Infliximab (IFX) administration

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Conflict of interest: None

[Objectives] We analyzed the vital response and infusion reaction in patients with RA who were administrated IFX for the object of improving the nursing practice. [Methods] Medical-service date and the nursing record of the 112 patients with RA who Were administrated IFX were investigated. The alternative formulas questionnaire method was enforced about patient characteristics. [Results] Concerning to the influence of IFX infusion on the vital sign, there was not so large difference in the results of blood pressure, pulse rate, body temperature and SpO2 at 1-hour or 2-hour after the infusion as compared with administration before. In the smoking-group, patients with less than 95% of SpO2 before the administration were 10% larger in number than the patients of non-smoking-groups. Concerning to the relation between DAS28-ESR and sysotolic blood pressure, a possibility that the disease activity had affected the BP was suggested. We also report the adverse events at IFX infusion. We reported the change of the vital reaction by IFX administration. It is important to sufficiently understand patient characteristics and to perform it carefully on IFX administration.

P3-276

Examination of usefulness of checking procedure and training after introduction of home self-infusion

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Conflict of interest: None

Objective: To figure out whether patients do self-infusion without problems and examine usefulness of training. **Methods**: We surveyed 25 RA outpatients who started home self-infusion treatment (etanercept; 14 cases, adalimumab; 11 cases) by questionnaire and checked the procedures of self-infusion, drug conservation and its disposal. We trained patients who failed the procedures, and rechecked after a few months of training. **Results**: 46% of patients made some sort of mistake, of which 58% was patients whose years of experience were less than two years. These mistakes were found at the step of preparation (40%), at the step of manner (16%) and at the step of clearance (20%). In the association with their physical function (Class, Stage and mHAQ), patients with advanced Class, with advanced Stage and with high mHAQ tended to make at least one mistake. In the recheck after training, most patients reformed their conventional false cognition. **Conclusion**: Most patients answered the questionnaire that they did self-infusion without problems, in fact a lot of mistakes were found. We need unify the training for patients and check regularly in order to continue safe home care. Especially we had better train early to patients who have little experience and have low functional capacity.

P3-277

The association between assessment of synovitis by ultrasonography and structural deterioration in Rheumatoid Arthritis Patients achieving remission

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Conflict of interest: None

[Object] the purpose of this study was to evaluate the association between assessment of synovitis by ultrasonography and structural deterioration in rheumatoid arthritis (RA) patients achieving remission. [Methods] We studied 13 RA patients receiving disease-modifying antirheumatic drug therapy who were judged to be in remission (DAS28-CRP<2.3). Imaging of hands using standardized scoring techniques (grade0-3) with Power Doppler ultrasonography (PD-US) was performed and assessment of radiography was performed after 12 months. [Result] Despite their being in clinical remission, 6 patients continued to evidence of active inflammation, as shown by PD-US. In symptomatic joint, PD-US showed that 71% had synovitis. Even in asymptomatic joint, PD-US showed that 2% had synovitis. The joints detected synovitis by PD-US were displayed deterioration in radiographic joint damage over the study period. [Conclusion] RA patients receiving disease-modifying antirheumatic drug therapy who satisfied the remission criteria had imaging-detected synovitis. The finding indicates that joint detected synovitis by PD-US progress radiographic damage in even those patients.

P3-278

Joint Diseases in Asia during the Medieval Ages

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Conflict of interest: None

The concept that medicine is exclusively the products of western minds remains unquestioned by most individuals. A review of any of the standard texts or encyclopedias regarding the history of medicine would support this view. Most texts give little or no mention of the advancements made by ancient Indian, Chinese or, particularly Asian medieval physicians. Asian physicians, during the Middle Ages, have played a considerable role in the field of medicine development in general and joint diseases in particular. Al-Razi is considered the first who described what is called now Baker's cyst, which is attributed to the English surgeon William Baker (1839-1896) who described it in 1877. Avicenna (ibn-Sina) is considered one of the most celebrated physicians during the Middle Ages. Al-Qanunn Fit-tib (or Code of Laws in Medicine) represents the most important work of Avicenna, and as William Osler described it, the most famous medical textbook ever written. Avicenna has talked in details about the predisposing factors, causes and treatment of gout and sciatica. The aim of this paper is to shed light on some joint diseases in Asian Medicine during the Medieval Ages, to reveal the accomplishment and contribution of Asian physicians in this field of medicine.

P3-279

Apoptosis of rheumatoid synovial cells by statins through blocking protein-geranylgeranylation

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Conflict of interest: None

Though improving result of RA treatment, it is sometime reported that re-active type B hepatitic virus under using immunosuppressant. We examined RA treatment complicating Type B or Type C hepatitis. The subjects were 3 cases (man 1 women 2), average age was 65.3, average morbidity period was 7.0 years. 2 patients were controled enoughly, but other one using nucleac analogue drug for HBs positive was not. It is necessary to consult hepatologist starting immunosuppressant for RA patients complicating hepatitis.

P3-280

The clinical analysis of the case that Seronegative RA in our department was diagnosed

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Conflict of interest: None

[objective] Seropositive and seronegative RA reveal a report that there is a difference for response for the biological DMARDS, and various clinical condition vary. Therefore we investigated seronegative RA about the case treated in our department. [subject] Seronegative RA was diagnosed in our department or other medicine and intended for 31 cases treated in our department. The sex was 13 men and 18 women. The average observations period was 24.3 months. At first examination average age was 63.6 years old. [methods] We investgated ACPA at the first, and evaluated disease activity in DAS28CRP. Also, we investigated the evaluation on the medical record at the first in retrospective and were based on 2010ACR - EULAR criteria and calculated points. [results] ACPA was all cases negative. Mean DAS28CRP was 4.61 at the first and 2.21 at the last, the disease activity decreased in the last in comparison with first. At the first points of 2010ACR - EULAR criteria was mean 5 points, and case of more than 6 points was 11 cases. [discussion] Response was good, and the disease activity decreased early, and control was almost good. But it was thought that we looked back with RA at the first, but course was different from RA, and the case that it was thought with overdiagnosis were present.

P3-281

The medical questionnaire of peripheral neuropathy in outpatients with ANCA-associated vasculitis (AAV)

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Conflict of interest: None

[Objective] In order to clarify the degree of peripheral neuropathy in patients with AAV, the activity of daily life (ADL) and the localization of peripheral neuropathywere examined. [Methods] Twelve outpatients with AAV were examined. Seven had microscopic polyangiitis (MPA), 3 had Churg-Strauss syndrome (CSS) and 2 had granulomatosis with polyangiitis (GPA: Wegener's granulomatosis). The average age of the AAV patients was 64.4 years old (53-83), 9 females and 3 males. Visual analog score (VAS), Modified Barthel Index (MBI) were analyzed by the medical questionnaire before consultation. [Results] The pain or numbness were shown in 10 patients (83%: 10/12), individually. The average MBI was 47.3 (46.4-49.3) and the lowest MBI was shown in patients with MPA. The average VAS was 39.6 (0~83), which had no significant differences between MPA, CSS and GPA. Ten patients had pains in both lower limbs, 2 had them in both upper limbs. Eight patients had the numbnesses of the lower limbs, 7 had them in upper limbs. The pain in the lower limbs was shown in all patients.

The pain of the upper limbs was not shown in MPA. Average number of numbness -location area in all patients was 2.3 and 4.3 in CSS. A lot of complaints about ADL were shown even in the patients with low MBI.

P3-282

Nontuberculous mycobacterial arthritis misdiagnosed as a reumatoid arithritis

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Conflict of interest: None

We experienced a case of nontuberculous mycobacterial arthritis which had been misdiagnosed as rheumatoid arthritis. The patient was a 80 year-old man. He complained of pain and swelling in the right wrist. After examination, reumatologist diagnosed as Serongative RA. After two years of treatment, the little finger swelling was observed, and we performed surgery. Surgical exploration of the lesion revealed rice bodies in the common flexor tendon synovial sheath. Mycobacteria culture was performed and detected of Mycobacterium intracellulare by PCR. Wrist swelling was still observed, and we perfomed surgery. Mycobacterium intracellulare was detected as well. All drugs for rheumatoid arthritis were stopped. Triple antibiotic therapy for nontuberculous mycobacterial infection was chosen. After treatment, he showed improvement of symptoms. We need to include nontuberculous mycobacterial infection in their differential diagnosis of reumatoid arthritis.

P3-283

Arthrodesis for rapidly destructive arthropathy of Lisfranc joint - A case report -

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Conflict of interest: None

We report a rare case of rapidly destructive arthropathy of Lisfranc joint. A 46-year man had right mid-foot pain two months before consulting our department. No abnormality of radiograph was detected and he was conservatively treated by other hospital, but it was ineffective. There were diabetes mellitus, renal cancer and chronic renal failure treated by hemodialysis in past history. Bone scintigram was done for followup of surgery of renal cancer in our hospital and there was the uptake of the right Lisfranc joint, therefore, he consulted our department. Radiograph showed the destruction of 1st tarsometatarsal joint and MRI revealed abnormal intensity at 1st, 2nd and 3rd tarsometatarsal joint. The specimen of the biopsy did not show inflammation and amyloid but fibrous tissue, therefore, diagnosis of amyloid arthropathy was excluded. Infection was excluded because of no growth of mico-organisms by culture. Charcot arthropathy was also excluded by the presence of joint pain. The etiology of this case was probably different from the common primary osteoarthritis of Lisfranc joint which has slow progress of joint destruction. Arthrodesis of Lisfranc joint underwent with bone autograft from ilium using Acutrak® screws and there was no pain five months after the surgery.

P3-284

Pathological fracture of the clavicle associated with palmoplantar pustulosis

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Conflict of interest: None

We report a case of pathological fracture of the clavicle associated with palmoplantar pustulosis. A 63-year-old man had palmoplantar pustulosis from the age of 45 years. He is initially treated with sulfasalazine and corticoid steroid, followed by methotrexate with only partial clinical response. The treatment was interrupted on numerous occasions. After he landed on his left hand and felt left shoulder pain, he was admitted to our hospital again. Left clavicular fracture was evident in addition to the hyperostosis and osteitis of the left clavicle. Although the fracture was conservatively treated with the external fixation, fracture healing was uneventful after three months. Because pathological fracture of the clavicle associated with palmoplantar pustulosis is difficult to treat, a tight control therapy to the osteitis is important.

P3-285

A case of chronic myeloproliferative disorder with erythema nodosum and renal dysfunction.

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Conflict of interest: None

Patients with chronic myeloproliferative disorder (JAK2V617F) develop renal dysfunction or pleuritis have been reported. We experienced the patient of chronic myeloproliferative disorder with erythema nodosum, renal dysfunction, pleuritis and pericarditis. The patient was 57 years old woman who was diagnosed with polycythemia vera in 1988. The patient had been treated with busulfan for about 2 years in another hospital and dropped out. The patient visited to our hospital in 1993 because of following up of polycythemia vera. In 2005, The patient had erythema nodosum and in 2008 deterioration of renal function was observed. In June, 2011 the patient was being treated with 5mg of prednonisolone for erythema nodosum, but the patient began to skip taking predonisolone. The patient was transferred to our hospital on 26th, 2011, because of pleuritis and pericarditis. The character of pleurisy was exudative. On admission, JAK2V617F mutation was detected and the patient was treated with antibiotics and prednisolone 5 mg/day for two weeks, and improvement of pleuritis and pericarditis was observed. However, the evidence of bacterial infection was not observed..

P3-286

Scleritis, Hypopigmentation, Dermatitis and Multiple Sclerosis-Like Neurologic Feature (Manaviat-Owlia syndrome)

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Conflict of interest: None

[Objectives] Aggregation of some sign and symptoms from different organ system are important issues in medicine. Scleritis, vitiligo, poliosis, dermatitis and multiple sclerosis-like neurologic feature are features with common immunologic base. Poliosis or loss of normal pigmentation of hair is also frequently associated with known immunologic syndromes such as Vogt-Koyanagi-Harada (VKH). [Methods] Herein we describe a 23 years-old man with possible new syndrome of scleritis, hypopigmentation, dermatitis and multiple sclerosis-like neurologic manifestations. We

search Medline and Google Scholar for similar entity but no matched aggregation was found. [Results] This could be the first report of constellation of scleritis, vitiligo, poliosis and MS-like presentation in a patient. So, if other observations proved similar presentation, it could be considered as a new and independent entity. (Manaviat-Owlia syndrome)

P3-287

Two cases of the pseudothrombophlebitis syndrome caused by synovial rupture of the knee

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Conflict of interest: None

[Introduction] Synovial rupture of the knee occurs in patients with RA. As its symptom is similar to thrombophlebitis, it belongs to the pseudothrombophlebitis syndrome. We report here two cases diagnosed the pseudothrombophlebitis syndrome caused by synovial rupture of the knee. [Case 1] A 73 y-old man presented acute pain and swelling of the calf with high levels of D-dimer and CRP. He was diagnosed thrombophlebitis and had been treated with warfarin but the symptom became worse. The CT and MR images showed hematoma between calf muscles. He underwent removal of the hematoma and the symptom disappeared immediately after surgery. [Case 2] A 55 y-old woman presented acute pain and swelling of the calf with a high fever and multiarthralgia. The blood analysis showed higher levels of WBC with an increase in neutrophils and the serum ferritin level showed abnormally high. The serology showed both RF and ANA were negative. She was diagnosed adult Still disease and the symptom was improved with 30 mg of PSL. [Conclusion] Previous reports have shown that 2-6% of patients diagnosed thrombophlebitis was in fact the pseudothrombophlebitis syndrome. Not only in RA but also in non-inflammatory diseases, the pseudothrombophlebitis syndrome caused by synovial rupture should be considered.

Luncheon Seminar

LS1

All-Case Surveillance for Abatacept - Interim Report

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Conflict of interest: Yes

It has been reported that activation of T cells plays an important role in the disease process formation of rheumatoid arthritis and that the costimulation pathway from antigen-presenting cells is essential to modulation of the T cell activation. Abatacept is a therapeutic agent which has a novel mechanism of action to modulate T cell activation by inhibiting the costimulation pathway between antigen-presenting cells and T cells, and was launched in the market here in Japan in September 2010 under the approval condition that a drug use results survey (all-case surveillance) be conducted. As for progress of the all-case surveillance, a goal number of enrolled patients (4000 cases) were accomplished by June 2011, and case enrollment alone is currently under way. A sum total of about 5600 cases have been enrolled by the end of October 2011. In this seminar, we review results of tallying/summarization of data on safety and efficacy from the first 1000 cases enrolled in this all-case surveillance as the latest evidence regarding abatacept in Japan, and discuss the profile of the drug in the actual setting of clinical practice in Japanese patients on the ground of overseas data and clinical results gained at this department.

LS2

Clinical application of tacrolimus (TAC) for the treatment of rheumatoid arthritis (RA)

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Conflict of interest: Yes

TAC, an oral macrolide calicneurin (CaN) inhibitor, is an immunosuppressive agent by suppressing T cell activation. TAC diminishes the ability of CaN to dephosphorylate and translocate the NFAT that initiates gene transcription for the synthesis of IL-2. As well as the inhibition of T cell activation, TAC inhibits the production of TNFa, IL-1b, and IL-6, which play crucial roles in the pathogenesis of RA. Six years has past since TAC (prograf®) was approved for RA. The efficacy of TAC for RA was studied in Japan and Western countries. In the phase II Japanese trial, the ACR 50 response was 27.5% and 22.6% for the overall TAC group and for the patients inadequate response to MTX, respectively. In the trial for aged RA patients (> 65 years old), the 18.5% of patients of TAC group (1.5mg/day) achieved ACR 50 response. In the 52-week multicenter double-blind, randomized placebo-controlled trial for RA patients inadequate response to previous DMARDs therapy, the patients of TAC group showed significantly more good response by EULAR criteria than placebo group (55.7% vs 20.0%). The mean change in the total Sharp and erosion scores were lower in the TAC group, but the difference was not significant. The randomized, double-blind US phase III trial was done to evaluate the efficacy of TAC+ MTX when compare to MTX alone in patients with a partial response to MTX. The combination of TAC 3mg/day + MTX was more effective and retarded the progression of structural damage. 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. MTX is considered to be the anchor drug and should be used first. TAC might be used as an alternative 1st line DMARDs when MTX contraindications are present. Furthermore, when MTX therapy does not at-

tain a state of low disease activity or remission, the addition of TAC is a considerable choice to achieve the goal.

LS3

Safety management of biologic use in modern rheumatoid arthritis treatment era

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Conflict of interest: None

Over the past 10 years, treatment algorism of rheumatoid arthritis (RA) has made remarkable progress. Updated recommendations for achieving optimal therapeutic outcomes in RA include a state of clinical remission as the primary target for treatment, and frequent adjustment of drug therapy until completion of the desired treatment target. Introduction of biologics plays an essential role in this revolution. Eight years have passed since approval of the first biologic agent infliximab in Japan, and a total of six biologics are currently available: abatacept, adalimumab, etanercept, golimumab, infliximab, and tocilizumab. A recent estimate for frequency of biologic use in Japanese patients with RA exceeds 20%. In these circumstances, the most important safety concern with the biologic therapies remains the increased risk of infection. Physicians should exercise caution when considering the use of biologic therapies in patients with RA. Tips on how to minimize serious infection include (i) screening programs of latent infection of potential pathogenic microorganisms, including *Mycobacterium tuberculosis*, *hepatitis B virus*, and *Pneumocystis jiroveci*, prior to biologic treatment; (ii) preventive use of anti-tuberculosis and anti-pneumocystis drugs when applicable and inoculation of vaccines; (iii) monitoring of reactivation of latent infection during the treatment; and (iv) prompt introduction of treatment at onset of acute lung injury. Evaluation of risk factors for serious infection identified by postmarketing surveillance is also useful. Biologics should be avoided if the risk of serious infection overwhelms potential benefits. Finally, longer follow-up may be necessary to determine the association between biologic therapy and malignancy. In summary, adequate safety management is crucial to maximize the benefits of biologic treatment in patients with RA.

LS4

Musculoskeletal imaging for early diagnosis of rheumatoid diseases

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Conflict of interest: Yes

Introduction of biologic agents (Bio) over the past decade has changed the treatment strategies for rheumatoid arthritis (RA). As the functional prognosis of the affected joints may be improved by early therapeutic intervention before structural change of the joints and functional disability, classification of early RA from other diseases has been recognized to be more important than ever. The 2010 ACR/EULASR classification criteria for RA have been developed to identify the patients at the risk of persistent and/or erosive arthritis. Differential diagnosis should be done with basic information of the patient such as disease history, clinical findings and laboratory data, and the high resolution imaging modalities such as magnetic resonance imaging (MRI) or ultrasonography (US) provide additional evidences of joint inflammation. The major implication of US has been well recognized with the paradigm shift of pharmacological treatment for RA. US can visualize the joint swelling (synovial hyperplasia or joint fluid) or tenosynovitis that could not be assessed by palpation, and can improve the quality of early diagnosis of RA. US has been a reliable technique that detects more erosions than conventional radiography, especially in early RA. Physician utilize the US in a daily practice as a supplementary imaging technique for decision making in the step up of or step down of medication, and indication of intraarticular injection of corticosteroid or orthopaedic surgery, as well as in judgment of disease remission or discontinuation of the drugs. Real-time visualization of the underlying structure of symptomatic joint is very persuasive for patients. In early diagnosis of RA, MRI might have a diagnostic advantage over US, detecting synovitis, bone marrow edema and erosion including pre-erosion. However, these findings are not specific for RA. It would be important to utilize MRI or US at adequate timing, with knowledge of pitfalls of these imaging modalities.

LS5

Update on the treatment of rheumatoid arthritis with etanercept: focus on efficacy, safety, dosing, and health economics

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Anti-TNF agents, including etanercept, have revolutionized the treatment of rheumatoid arthritis (RA) and other inflammatory arthropathies, and have become well-established in the daily management of patients with these diseases. Studies in recent years have added to our understanding of the optimal use of such agents. Here, new insight on etanercept (Enbrel) will be reviewed with a focus on several areas of importance to the practicing physician: 1) The demonstration of long-term efficacy and an overall favorable safety profile in large practice-based registries including the Swedish ARTIS registry. This includes new data on the efficacy of a second biologic after failure of the first biologic. 2) Demonstration of differential safety aspects with various biologics that help in identifying optimal treatments for the individual patient. 3) Data from recent studies suggesting that etanercept dosages can be modified based on the patients' clinical course. This includes data from the recent PRESERVE trial that suggest that a 36-week course of etanercept in moderately active RA can induce low disease activity and even remission in a significant proportion of patients, and that these improvements can be maintained in a minority of patients with methotrexate alone and in a much larger proportion with continued etanercept. Importantly, the latter biologic was very effective at the usual dose but also at the reduced dose of 25 mg once weekly, providing a proof-of-principle for the concept of induction-maintenance therapy in certain subsets of patient with RA. 4) Recent data providing information on the health-economic benefits of anti-TNF therapy in RA. Data from our registry have shown that patients with RA who are treated with anti-TNF agents increase their work-force participation, yielding important societal benefits in addition to the clinical benefits for the individual. It can be concluded that while etanercept and other biologic agents have become well-established in rheumatology, we are still learning more about the optimal use of these important therapeutics.

LS6-1

Characteristics of fracture in patients with rheumatoid arthritis

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Conflict of interest: Yes

It is well known that halting the progression of structural damage is a critically important goal of therapy given its effect on pa-

tient function and quality of life. However, full prevention of radiographic damage and/or clinical disease progression is not necessarily easy especially in patients with comorbidity or drug resistance. So, it is important to focus our consideration into the appropriate type and timing of drug therapy for clinical and structural remission of arthritis. On the other hand, disability due to fracture occurred in patients with RA tend to be overshadowed by the obvious clinical signs or symptoms of joint destruction, although secondary osteoporosis is well recognized in RA. Furthermore, many osteoporotic fractures occur at sites other than the spine and proximal femur in patients with RA, while it is not well recognized because of the difficulty in diagnosis of insufficiency fracture. Insufficiency fractures are defined as the fracture produced by normal or physiological stress applied to bone with deficient elastic resistance (Pentecost RL et al. JAMA 187, 111, 1964). It is difficult to detect them in clinical practice since they are often undetectable by plain radiography at the onset of pain. RA is the one of the common underlining diseases of patients with insufficiency fractures and the most of the fractures in patients with RA resulted in ambulatory dysfunction. So, prevention of fractures is important to maintain their mobility. Furthermore, both joint erosions and osteoporosis in RA share a common cellular pathway which involves stimulation of the osteoclast and inhibition of osteoblastic bone formation. So, the optimal management approach for patients with RA takes into consideration the appropriate type and timing of both of anti-rheumatic drugs and anti-osteoporotic drugs. Early identification and treatment against both of arthritis and osteoporosis can reduce disease progression and loss of function in patients with RA.

LS6-2

Treatment for bone fragility in rheumatoid arthritis

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Conflict of interest: Yes

Rheumatoid arthritis (RA) is a chronic systemic inflammatory disorder with an unknown etiology characterized by the invasive synovial hyperplasia leading to the progressive joint destruction. Radiographic studies have shown that the bone erosion in RA begins at the early stage of the disease, and gradually exacerbates. Bone erosion results in the severe deformity of the affected joints and impairs the normal activity and the quality of life of the RA patients, and hereby, preventing marked bone destruction is one of the most challenging issues in RA treatment. Proliferating synovium produces an elevated amount of proinflammatory cytokines such as interleukin-1β, 6 and TNF-α, and matrix-degenerating enzymes matrix metalloproteinases and cathepsins, which are involved in the bone and cartilage destruction. In addition, generalized bone loss observed in RA patients, in particular who are treated with steroid, are susceptible to fragility fractures. Bone erosion usually begins at the interface of the bone and the proliferating synovium, and bone-resorbing osteoclasts can be observed at the erosive synovium/bone interfaces in RA joints. Osteoclasts, primary cells responsible for bone resorption, are involved in the bone destruction in RA, and recent progress in the molecular biology and biochemistry has elucidated the cricical role of receptor activator of nuclear factor kappa B ligand(RANKL) in osteoclast development. In this seminar, I would like to introduce the role of osteoclasts in the joint destruction in RA, and the critical involvement of SFCs on the osteoclast differentiation in RA. In addition, the effectiveness of the treatment targeting osteoclasts will be discussed.

LS7

***Pneumocystis* pneumonia in patients with rheumatic diseases**

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Conflict of interest: None

While the incidence of *Pneumocystis* pneumonia (PCP) in human immunodeficiency virus-infected patients (HIV PCP) has been reduced by the introduction of chemoprophylaxis and intensive anti-retroviral treatment, the number of patients with non-HIV PCP is increasing along with implementation of more aggressive immunosuppressive therapy or chemotherapy for rheumatic diseases, malignancy, and organ transplantation. Post-marketing surveillance programs of TNF antagonists revealed that treatment of rheumatoid arthritis (RA) patients with TNF antagonists increased incidence of PCP in Japan compared to Western countries. We conducted a multicenter, case-control study using 51 and 250 RA patients who did and did not develop PCP during treatment with TNF antagonists, respectively, and identified several risk factors for development of PCP. Despite the intensive researches of non-HIV PCP, there remain several unsolved issues for the management of the infectious disease. First, there is no consensus for diagnosis of PCP in the absence of microscopic detection of the pathogen. Second, treatment of PCP with trimethoprim-sulfamethoxazole (TMP-SMX) is often prematurely terminated because of adverse drug reactions. Third, limited data are available for the frequency of mutation of dihydropteroate synthase gene in Japanese PCP patients. Fourth, previous reports demonstrated colonization of the pathogen in healthy individuals, patients with rheumatic diseases, and patients with pulmonary diseases, but more evidence is required to establish association of colonization with development of PCP. Fifth, optimal chemoprophylaxis protocol for Japanese patients with rheumatic diseases has not been established. In addition to TMP-SMX and pentamidine isetionate that are the main stay of treatment for PCP in Japan, atovaquone is now under investigation for approval. This lecture will cover recent advances in non-HIV PCP including new treatment option in Japan.

LS8

Pharmacotherapy for Rheumatoid Arthritis Primarily Using Non-biological Disease-modifying Antirheumatic Drugs

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Conflict of interest: Yes

The current mainstream treatment for rheumatoid arthritis (RA) consists of methotrexate (MTX) as an anchor drug, followed by disease-modifying antirheumatic drugs (DMARDs) in poor responders. In Japan, MTX up to 8 mg/week is administered only in patients refractory to other antirheumatic agents. MTX 16 mg/week was approved in February 2011, and MTX could be prescribed at the beginning of treatment when the patient has poor prognostic factors such as anti-cyclic citrullinated peptide antibody. Moreover, MTX therapy is initiated at an early stage after introduction of the 2010 ACR/EULAR classification criteria. Thus, the number of patients with complete remission without using biological DMARDs has increased. However, 417 deaths have been reported in Japan where the causal relationship with MTX cannot be excluded; thus, the prevention, early detection, and control of drug-related adverse events are important. MTX should be avoided in hepatitis B virus (HBV) or HCV carriers. Recently, serious de novo hepatitis due to immunosuppression is reported in patients positive for anti-HBs or anti-HBc antibody; therefore, HBV-DNA level should be monitored monthly in these patients. MTX dose should be reduced or MTX administration should be avoided in el-

derly patients and those with renal impairment or pulmonary complications. Combination of mizoribine (MZR) pulse therapy and low-dose tacrolimus (TAC) with MTX is effective in poor responders in whom the MTX dose cannot be increased. In addition, MZR and TAC are effective in patients who cannot be given MTX. MZR administered orally once-a-day is effective in increasing blood drug levels. Monitoring blood TAC levels is effective in not only predicting adverse effects but also augmenting treatment efficacy, and the TAC dose should be determined while monitoring blood levels and clinical manifestations.

LS9-1

The management of pulmonary arterial hypertension complicated with systemic lupus erythematosus and mixed connective tissue diseases

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Conflict of interest: Yes

Pulmonary arterial hypertension (PAH) is a life-threatening complication in connective tissue diseases (CTD), such as systemic sclerosis (SSc), mixed connective tissue disease (MCTD), systemic lupus erythematosus (SLE). Considering a low prevalence of idiopathic PAH (approximately 0.0002%), CTD is recognized as a major underlying disease of PAH as well as HIV infection, portal hypertension, congenital heart diseases, schistosomiasis and chronic hemolytic anemia. CTD-associated PAH (CTD-PAH) is classified in the subgroup of "PAH associated with identified diseases" in the Dana Point clinical classification of pulmonary hypertension. Evidence-based treatment algorithm on PAH was proposed at Dana Point 4th pulmonary hypertension world meeting in 2008. This algorithm consists mainly of how to use vasodilators (e.g. prostacyclins, endothelin receptor antagonists and phosphodiesterase 5 inhibitors). CTD-PAH is not excluded from the algorithm. However, it remains controversial whether immunosuppressive therapy is useful for CTD-PAH due to little clinical evidence. Inflammatory cells infiltrates composed of macrophages and lymphocytes have been detected in plexiform lesions, and antinuclear antibodies, rheumatoid factor, IgG, and complement have been identified in pulmonary vessel walls from patients with CTD-PAH. These findings indicate immunopathological mechanism in the development of PAH in CTD and suggest the efficacy of immunosuppressive agents. The Dana Point treatment algorithm does not refer immunosuppressive therapy. Here we report five cases of CTD-PAH treated with glucocorticosteroids and discuss the management of CTD-PAH with immunosuppressive agents.

LS9-2

Connective Tissue Disease, systemic sclerosis in particular, associated Pulmonary Arterial Hypertension

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Conflict of interest: None

Pulmonary hypertension is one of the most life-threatening manifestations in connective tissue diseases. Pulmonary hypertension in patients with connective tissue diseases can be multi-factorial. 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. 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. 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. As opposed to systemic sclerosis with which selective vasodilatoion therapy with PDE5 inhibitor and endothelin receptor antagonist is initiated upon the diagnosis of pulmonary arterial hypertension, immunosuppressive treatment with glucocorticoid and cyclophosphamide can be the first intervention for pulmonary hypertension in non-scleroderma connective tissue diseases, such as systemic lupus erythematosus and mixed connective tissue disease. However, in real world majority of lupus patients with pulmonary hypertension requires at least either PDE5 inhibitor or endothelin receptor antagonist, possibly due to irreversible remodeling in lung tissue. To improve survival rate of connective tissue disease patients with pulmonary arterial hypertension, institution of systematic screening and diagnostic protocol is crucial.

LS10

Long-term Management of Patients with Sjogren's Syndrome: Cooperative Community Healthcare and Improved Patient Follow-up

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Conflict of interest: None

Sjogren's syndrome is a systemic rheumatic disease characterized by chronic inflammation of exocrine glands whose etiology remains unknown. Patients have varied manifestations in addition to dryness of eyes and mouth. The number of patients in Japan may be greater than that reported by the Ministry of Health, Labour and Welfare (cir. 79,000) since it is estimated overseas that the number of patients is similar to or greater than that of patients with rheumatoid arthritis. Early diagnosis is critical for improving quality of life of potential patients with Sjogren's syndrome. This paper presents our approach to early diagnosis and early treatment of Sjogren's syndrome whose awareness is still low. Key components of the treatment of Sjogren's syndrome are patient education, multidisciplinary total management through regular consultation and lifestyle guidance. Dry mouth symptoms are treated with cevimeline, pilocarpine hydrochloride and artificial saliva. Symptoms of dryness of both mouth end eyes, which are often associated with Sjogren's syndrome, should be treated. Pilocarpine hydrochloride, which has been marketed since 1994 and indicated for dryness of both mouth and eye overseas, has been approved in Japan only for improvement of oral dryness in patients with Sjogren's syndrome since 2007 and there is limited evidence in Japanese patients. This paper reports the positioning of pilocarpine hydrochloride with its treatment results at our hospital and literature review. Long-term management of patients with Sjogren's syndrome obviously requires steroid therapy and use of immunosuppressants according to organ complications and it is also essential to provide local treatment for ocular and oral symptoms. The future challenges in constructing a treatment system for Sjogren's syndrome include establishment of total management based on cooperation between primary care physicians and community hospitals and active involvement and support by governmental authorities.

LS11-1

Advances in measures for preventing infections — an important point when using biological anti-rheumatic drugs in the clinic

Motohiro Oribe

Oribe Clinic Of Rheumatology And Internal Medicine

Conflict of interest: Yes

With the appearance of biological agents for the treatment of rheumatoid arthritis (RA), the effects of RA have improved remarkably. Accordingly, the targets of RA treatment have now changed from the conventional alleviation and improvement of symptoms to achievement of clinical, structural, and functional remissions and maintenance of these effects. The benefits of these biological agents are now available not only to RA patients in university hospitals and regional core hospitals, but also to RA patients in local clinics. However, it has been noted that accompanying the dramatic effects of these biological agents, the incidence of infections, especially serious infections, is higher than the incidence of infections under conventional treatment. These results indicate that countermeasures against infections are important to maximize the efficacy and safety of biological DMARDs. It is also essential to have a hospital referral system if infections become serious in the clinics. Oribe Rheumatism and Internal Medicine Clinic is a medical institute that functions both as a general practice and as a RA specialist facility. About 500 RA patients have been treated with biological agents in this hospital. In order to administer biological products safely and to help prevent infections and aid in early discovery of infections, we conduct an educational program for patients and their families to instruct them in the importance of a clean lifestyle, oral care, and infection prevention in the home. We have also established an integrated hospital referral system for patients with infections. I will introduce the basic structure of the hospital referral system and discuss the effective methods for ensuring patient safety when using biological products in a clinical setting.

LS11-2

Rotation-type collaboration between regional core hospitals and local clinics in the treatment of rheumatoid arthritis — Maximizing collaboration by building relations of trust

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Centor for Rheumatic Diseases

Conflict of interest: None

Since rheumatoid arthritis (RA) is a chronic disease, treatment strategies require a long-term outlook. This situation has not changed with the recent introduction of the so-called biological agents. With the appearance of biological agents the targets of RA treatment have changed from conventional alleviation and improvement of symptoms to achievement of clinical, structural, and functional remissions and the maintenance of these effects. However, the use of these biological agents necessitates precautions such as ongoing monitoring for adverse reactions such as serious infections. Sasebo Chuo Hospital is a core hospital in the northern part of Nagasaki Prefecture that actively promotes collaboration between our hospital and other hospitals or clinics in remote areas, including referrals for RA treatment, and has made efforts to establish a rotation-type system of collaboration. In the treatment of RA, this collaboration is based on three basic concepts: (1) unification of RA diagnosis and treatment, (2) cooperation in diagnosis and treatment through educational program for the staff in the local clinics, and (3) promotion of RA treatment by local physicians and establishment of a local collaboration system among local clinics and hospitals that not only makes referrals in one direction but also makes reverse referrals when the therapeutic results become stable. The most important factor in the success of such a rotation-type system of therapeutic collaboration is a basic understanding of the advantages of such collaboration by the patients themselves. I will introduce the actual rotation-type collaboration system established by Sasebo Chuo Hospital for RA treatment and discuss the requirements to establish this system.

LS12

Recent progress and future perspective of the treatment with TNF inhibitors in rheumatoid arthritis

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TNF inhibitors have dramatically changed the treatment of Rheumatoid Arthritis over the past 14 years. They have allowed patients to achieve superior disease control with respect to clinical efficacy, including signs and symptoms, improved patient function and reduce radiographic progression, compared to traditional oral DMARDs, such as methotrexate (MTX), sulfasalazine and leflunomide. This presentation will review, from a historical perspective, the efficacy of chimeric and humanized monoclonal antibodies to TNF, in patients who are MTX naïve, have failed MTX or have failed a first, second or third TNF inhibitor. In 2012, there are several other clinically important questions for both the physician and patients which include: (1) whether when switching to a second TNF inhibitor, after one fails, is it possible to switch from a humanized monoclonal antibody or a fusion protein to a chimeric monoclonal antibody to TNF, (2) if a patient responds to the combination of a TNF inhibitor and MTX, can the dose of MTX be reduced and clinical efficacy maintained, and, (3) if a patient responds to the combination of a TNF inhibitor and MTX, can the dose of the TNF inhibitor be reduced or stopped (and if the patient flares, can the TNF inhibitor be re-introduced with re-capture of clinical response). Although not all these questions have been answered fully, there have been several studies reported over the past few years with infliximab, golimumab, etanercept, adalimumab and certolizumab, which have begun to answer these questions. This presentation will review the data available in 2012, which have been presented to answer to answer these questions, and what data is still missing.

LS13

Tocilizumab: a new step in rheumatoid arthritis treatment

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Conflict of interest: Yes

Rheumatoid Arthritis (RA) is a chronic systemic inflammatory disease characterized with progressive destruction of joints. Methotrexate (MTX) remains the most commonly used therapy and, to date, the introduction of biologic agents, such as TNF alpha inhibitors, represented an advance in the treatment of RA. However, there are still patients with no or inadequate response, patients in whom responsiveness to treatment is lost over time, and patients in whom safety issues may develop. Thus, patients may benefit from treatment with newer biologic agents with a different mechanism of action. Tocilizumab (TCZ) is a monoclonal antibody which inhibits the interleukin-6 receptor. This paper summarizes the key efficacy and toxicity findings from the major clinical trials including our data. TCZ works quickly and effectively in RA either as monotherapy or in combination with other agents in early disease, DMARD inadequate responders, established disease and after anti-TNF failure. The toxicity profile is manageable but includes infections, increases in serum cholesterol, transient decreases in neutrophil count and abnormal liver function tests. Otherwise, the perioperative mechanisms of TCZ are also currently under investigation. Unfortunately, very few studies about the clinical features of TCZ-treated RA patients following joint surgery have been reported. Therefore, more data are required to fully evaluate

the influence of TCZ on post-operative complications. To evaluate the perioperative changes and the complications in surgical intervention for RA patients, a multicenter TOPP study (TOPP: TOcilizumab in Perioperative Period) was organized, that analyzed the perioperative features and complications of surgical operations under TCZ in twenty-five hospitals. In summary, there is sufficient evidence to make TCZ a first line biologic therapy for RA especially for those who are unable to take MTX or who fail anti-TNF therapy.

LS14

COX-2 specific inhibitor in treatment of rheumatoid arthritis-Efficacy and safety in Japanese patients with rheumatoid arthritis-

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Conflict of interest: Yes

COX-2 specific inhibitors have shown marked risk reduction for GI ulcers and ulcer complications, which is most common adverse reactions to traditional NSAIDs. However, their effects on pre-existing NSAIDs-induced GI lesions have not been well examined. The aim of this study is to prospectively investigate the effects of COX-2 specific inhibitor (celecoxib:CEL) after switching from NSAIDs on the GI tract in RA patients with endoscopically identified GI mucosal injury. We investigated GI tract injury and disease activity in RA patients who had been treated with NSAIDs using upper GI endoscopy and DAS28 pre and post switching to CEL. Sixteen weeks after switching to CEL, LANZA score and the total number of GI erosions/redness were significantly reduced and further, DAS28 (ESR4 and CRP4) were significantly improved. Furthermore CEL has been reported to suppress osteoclastogenesis in vitro, reduce bone resorption in ovariectomized mice. However, the effects of COX-2 specific inhibitor on bone metabolism have not been demonstrated in clinical setting. Urinary type I collagen cross-linked N-telopeptide (uNTX), serum bone alkaline phosphatase (BAP) were examined pre and post switching to CEL. The average uNTX was significantly reduced in female patients post switching to CEL. There was a significant reduction in uNTX in postmenopausal females. However, uNTX was not significantly altered in premenopausal females or males. We revealed that NSAIDs-induced GI complications are still clinically significant in RA patients receiving long-term NSAIDs therapy. These results demonstrated that preexisting NSAID-induced upper GI injury is improved after switching to CEL without reducing analgesic efficacy, suggesting the usefulness of switching to CEL for patients with RA. Furthermore, the data demonstrated that CEL significantly reduces uNTX, a bone resorption marker, in postmenopausal patients with RA who switched from traditional NSAIDs to CEL, suggesting that CEL may suppress bone resorption.

LS15

Treatments of osteoporosis with bone anabolic agent and rheumatoid arthritis

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Conflict of interest: None

Recently teriparatide [rhPTH(1-34)], a bone anabolic drug has been approved in Japan, and osteoporosis treatments entered a new era. While bisphosphonates remain the standard treatment for osteoporosis, atypical femoral fractures and osteonecrosis of the jaw have emerged as potential complications of long-term bisphosphonate therapy. Concerns of oversuppression of bone turnover can be addressed with a drug holiday depending on the patient's fracture risk. An anabolic agent such as teriparatide is a powerful tool for the prevention of fragility fractures and should be reserved for patients at high risk for fracture. Osteoporosis occurs more frequently in patients with rheumatoid arthritis (RA), than in otherwise healthy individuals. Multiple factors are known to be involved, including glucocorticoid treatment, inflammatory cytokines, decreased physical activity, menopause, and various glandular imbalances, while RA itself is known to significantly increase the fracture risk. Careful management should be taken into consideration especially in glucocorticoid-treated RA patients in addition to tight control of RA disease activity. Teriparatide has been approved for the treatment of glucocorticoid-induced osteoporosis both in Europe and US, and suggested as one of the recommended treatment options in American College of Rheumatology 2010 Recommendation update. In this session, the teriparatide treatment will also be discussed with regard to the bone microarchitecture and the strength.

LS16

A practical approach to drug free remission.

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Conflict of interest: None

It is generally accepted that, since rheumatoid arthritis (RA) is a chronic disease, treatment needs to be chronic as well. In the past, patients who discontinued medication would develop a disease flare. Only if the disease had died out could patients discontinue medication, by which time the symptoms were no longer a result of active inflammation but of joint destruction and deformities. As a benefit of early initiation of antirheumatic drugs and frequent targeted treatment adjustments, patients now achieve and maintain low disease activity and remission much earlier in the disease course. Based on the FINRA-Co, RRR and BeSt studies, is has become clear that many patients who have prolonged low disease activity can taper and discontinue medication for a long period of time. In daily practice, discontinuation of medication is often more difficult, in particular in patients with longer disease duration. It is unclear whether this depends on different disease aspects or on different expectations. Patients in daily practice may need to have had longer and lower disease activity before it is possible, and they feel safe to try, to discontinue treatment. Imaging of joints may provide additional information before a decision is made to stop medication. A financial incentive to stop treatments may help, but may be counterproductive if patients discontinue too early, and flare. It is important to provide a plan for systematic follow up and targeted treatment adjustments. Data from the BeSt study show that with timely reintroduction of the discontinued drugs, remission is regained quickly in the vast majority of patients. To achieve drug free remission for more patients, we may need to treat earlier and aim at remission as soon as possible, then taper and discontinue medication as long as remission persists. Moreover, we need to inform our patients that drug free remission will be our target of treatment.

LS17

Pulmonary hypertension in association with other cardiopulmonary complications in patients with systemic sclerosis

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Conflict of interest: None

Prognosis of connective tissue diseases has been markedly improved by introduction of molecular-targeting drugs and progress of supportive therapies, but pulmonary hypertension (PH), cardiomyopathy, and interstitial lung disease (ILD) still remain intractable. These conditions are often seen in patients with systemic sclerosis (SSc), mixed connective tissue disease, or polymyositis/dermatomyositis. The survival of patients with PAH has significantly improved by use of molecular-targeting PAH drugs, and 3-year survival rate in recent cohorts is >80% in patients with idiopathic PAH or PAH-associated SLE. However, long-term survival is disappointedly low even in recent cohorts of SSc patients with PAH: 3-year survival rate of 39-64%. This malignant nature of PAH-SSc can be explained by several reasons. First, pulmonary vascular pathology of PAH-SSc is quite unique in terms of prominent concentric intimal fibrosis without apparent cellular proliferation in the media and intima, leading to a poor response to PAH drugs that primarily target smooth muscle cells. Second, subclinical myocardial fibrosis makes a negative impact on hemodynamics in SSc patients with PAH. In fact, hemodynamic features of PAH-SSc include a low cardiac output relative to pulmonary arterial pressure. Finally, it has been reported that, in patients with PAH-SSc, the survival rate is significantly worse in patients with coexistent ILD than in those without. This is probably due to lack of effective treatment to SSc-associated ILD, and restrictions on the PAH drug use. Namely, PAH drugs that induce dilation of pulmonary arteries potentially cause deterioration in gas exchange by increasing ventilation/perfusion mismatch. These cardiopulmonary complications together contribute to inadequate responses to current treatment regimens in patients with PAH-SSc. Therefore, multidisciplinary management approach is necessary to improve the survival in patients with PAH-SSc.

LS18

Sjögren's syndrome in childhood

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Conflict of interest: None

Sjögren's syndrome (SS) is a systemic autoimmune disease with sicca complex. Although it has been believed to be an adult-onset disease until recently, it is now no doubt that quite a few children have SS. Most of children with SS have no dryness, what is called subclinical SS. Their chief complaints are mainly nonspecific such as fatigue, low grade fever, sore muscle, joint pain and headache. They are defined as SS by positive biopsies and anti-Ro. The reason why SS has been believed to be adult-onset is that dryness may not be recognized until glands are badly destroyed. It may be possible to prevent the "clinical" SS by early diagnosis and treatment before they recognize dryness. Therefore, it is crucial that pediatricians diagnose SS. It is important for pediatricians to be aware of nonspecific complaints. A working group has recently been booted up by the Pediatric Rheumatology Association of Japan to establish criteria for childhood SS.

LS19

Management and Prevention of NSAIDs Ulcers

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Conflict of interest: Yes

The discovery of *Helicobacter pylori* (*H. pylori*) is undoubtedly considered one of the biggest topics of the 20th century in the field of digestive diseases, because it was shown that peptic ulcers were caused by an infectious disease. With the development of improved diagnostic and therapeutic methods, as well as improved public health, the incidence of peptic ulcer was expected to rapidly decrease. However, instead of simply decreasing, attention has shifted to ulcers with a new etiology: non-steroidal anti-inflammatory drugs (NSAIDs) ulcers. *H. pylori* infection and NSAIDs independently induce serious gastrointestinal ulcers. Among them, NSAIDs are likely to induce bleeding, significantly increasing the risk of peptic ulcer and its complications, sometimes with poor prognosis. In addition, NSAIDs are known to cause mucosal injuries not only in the upper GI tract, but throughout the entire tract, including the small and large intestines. It is very important for rheumatologists to have a correct view and sufficient knowledge on the mechanism of NSAIDs ulcer development, and its management and prevention. In this seminar, I would like to present basic and current knowledge on NSAIDs ulcers. I hope this seminar will help encourage rheumatologists to use this useful drug more effectively and safely.

LS20

Diagnosis and Treatment Strategy of CTD-PAH Based on the Disease's Particularity

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Conflict of interest: Yes

Pulmonary arterial hypertension (PAH) associated with connective tissue diseases (CTD) (CTD-PAH) is known to have poorer prognosis than other causes of PAH. On the other hand, CTD-PAH can be detected in early stage without showing any symptom of PAH. In principle, we perform the right heart catheter on all the patients with scleroderma (SSc) because SSc-PAH has extremely poor prognosis among CTD-PAH. It is reported that patients with SSc-PAH showed more severe decrease in cardiac output with elevation of pulmonary artery pressure (PAP) than patients with idiopathic PAH. Our results revealed that cardiac output in patients with SSc started to decrease from the stage of borderline PAH (ie mean PAP≧21mmHg). Therefore, we consider borderline PAH in patients with CTD (especially SSc) as an indication for treatment of PAH. On the other hand, there are some problems to treat CTD-PAH. One of the critical issues is that there are many patients with CTD-PAH who are difficult to receive intravenous epoprostenol therapy because of their disease's particularity such as difficulty in preparation of drug due to deformed extremities, presence of coexisting lung fibrosis or increased risk of infection accompanied with immunosuppressant therapy. However, a lot of new oral PAH specific agents were developed recently and marked improvement of hemodynamics were obtained with oral agent combination therapy in many PAH patients. I will show some case presentations from troublesome experience to successful case and discuss the treatment strategy for CTD-PAH based on the disease's particularity.

LS21

Advances in MR imaging of osteoarthritis and cartilage

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Conflict of interest: None

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. Delayed gadolinium-enhanced MR imaging of cartilage (dGEMRIC) has been developed as a sensitive and specific method for monitoring glycosaminoglycan (GAG) in articular cartilage. GAG is a major solid constituent of articular cartilage and is critical to mechanical function. GAG is abundant within healthy cartilage, however, its concentration starts decreasing from early stage of osteoarthritis (OA). Thus, dGEMRIC could be a useful and non-invasive method of assessing the quality of articular cartilage. In the meanwhile, T2 mapping is an MR imaging technique that can evaluate the cartilage matrix status, such as collagen integrity and hydration within cartilage. It is known that T2 of articular cartilage increases with the loss of collagen matrix integrity and water content. Thus, T2 mapping can be an ideal marker of assessing the quality of cartilage. 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. As the decrease of GAG concentration and the increase of water concentration associated with cartilage degeneration elongate T1ρ, T1ρ mapping can be a useful marker of assessing the quality of cartilage. We have been monitoring cartilage images of the patients with OA as well as the patients who underwent cartilage repair techniques to predict long-term outcome and find out tailor made strategy for the prevention of cartilage degeneration. It has been shown that deterioration of cartilage is observed from the early stage of rheumatoid arthritis and it affects prognosis of joints. Thus quantitative MR imaging techniques can be ideal markers for monitoring disease activity and joint damage also in rheumatoid arthritis.

LS22

Recent progression for basic analysis on SAA and therapeutic for RA have resulted in the prevention and the improvement of AA amyloidosis

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Conflict of interest: Yes

In case of a patient with rheumatoid arthritis (RA) with long suffering, who showes renal disorder, proteinuria or / and diarrhea, we should suspect the presense of AA amyloidosis with RA. We have to recognize difficulty in prevention and treatment of RA-combined diseases, such as interstitial pneumonitis (IP) and AA amyloidosis, even if signs and symptoms of RA can be improved by the recent progressive treatment. AA amyloidsis is thought to be a progressive and fatal disease at almost 6% of RA patients with the continuous deposition of AA amyloid fibril on systemic organs, especially kidney, thyroid and intestine. Therefore, it is expected to have an effective and curable medicine and treatment for AA amyloidosis. 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, Tosilizumab 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, and We present a part of results to you, today.

LS23

Osteoporosis treatment by novel active vitamin D_3 analogue

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Conflict of interest: Yes

Vitamin D3 plays a pivotal role in the regulation of bone metabolism as well as calcium homeostasis, and the metabolic activation of vitamin D3 is essential for its biological function. It has been reported that vitamin D insufficiency and deficiency are common in the elderly. 1alpha-Hydroxyvitamin D3 [alfacalcidol] is an active form of vitamin D3 which have been widely used in Japan to treat a variety of metabolic bone diseases such as renal osteodystrophy, rickets/osteomalacia and osteoporosis. It exerts bone-protective effects independently of its Ca-related effects. Alfacalcidol was reported to increase bone mass in ovariectomized osteopenic rats by suppressing bone turnover. In postmenopausal osteoporosis, the administration of alfacalcidol resulted in an increase in trabecular bone mineral density and a significant reduction in the incidence of vertebral fractures. Compared to plain vitamin D, alfacalcidol exerts higher bone-protective effects, thus allowing the doses to be minimized and lowering the risk of adverse effects, including hypercalcemia. In addition, a new active vitamin D compound with greater anti-osteoporotic activity, eldecalcitol, was recently developed and its clinical efficacy was exhibited. Eldecalcitol was more efficacious than alfacalcidol in preventing vertebral and wrist fractures in osteoporotic patients with vitamin D sufficiency, with a safety profile similar to alfacalcidol.

LS24

Risk of infection in patients with rheumatoid arthritis and a significance of 23-valent pneumococcal polysaccharide vaccine

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Conflict of interest: Yes

The life expectancy is shortened and infection is the leading cause of death in patients with rheumatic arthritis (RA). Pneumonia is the major cause of death. Factors increasing the risk of infection include comorbid illnesses and treatment with prednisolone in RA patients. The introduction of biologic therapies may further increase the risk of infection among these patients. On the other hand, pneumonia is the fourth leading cause of death in Japan. Death rate due to pneumonia is apparently high in adults older than 80 years of age. *Streptococcus pneumoniae* accounts for 20 to 40 % of the etiology of community-acquired pneumonia (CAP) in adults and non-bacteremic pneumonia is common in CAP in adults. Recently, severe pneumococcal infections have been reported in RA patients under treatment with anti-TNF therapy. The 23-valent pneumococcal polysaccharide vaccine (PPV23) covers more than 80% of causative pathogen responsible for invasive diseases and non-bacteremic pneumonia in Japan. Although this vaccine was found to be protective against invasive diseases in immunocompetent adults, the evidence of its efficacy against all-cause pneumonia remained inconclusive. However, the recent studies demonstrated the protective efficacies against pneumococcal pneu-

monia and the reducing effect of medical cost for all-cause of pneumonia in the elderly people in Japan. Until now, PPV23 is subsidized for elderly people by approximately 40% of the local governments in Japan, and the routine immunization of PPV23 is currently expected for this population. The Japanese Respiratory Society guidelines recommend the immunization of both influenza vaccine and PPV23 for elderly people. The guideline of Japanese College of Rheumatology for anti-TNF therapy against RA strongly recommends the immunization with influenza vaccine, but only suggests a consideration of vaccination with PPV23 for elderly people. The future role of PPV23 in the management of RA will be discussed.

LS25-1

Treatment strategies for rheumatoid arthritis: T-cell targeted therapy

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Conflict of interest: None

Rheumatoid arthritis (RA) is a chronic progressive inflammatory disease mainly affecting the synovial membrane of joints and is characterized by lymphocyte activation, synovial proliferation, and bone/cartilage destruction. In 2010, ACR/EULAR proposed rheumatoid arthritis classification criteria to classify patients with progressive arthritis and introduce methotrexate-based therapy in early stage disease. It also issued a new definition of RA remission, leading to higher remission rates, a treatment goal. With early therapeutic intervention using biologics, RA treatment with clinical, structural, and functional remission has become a reality. In Japan, abatacept (ABT), an inhibitor of T-cell activation, is available in addition to five cytokine inhibitors of TNF-α or IL-6. Unlike conventional approaches, ABT targets upper-stream T-cell activation to normalize abnormal immune response and is thus expected to have a clinical effect different from that of cytokine inhibitors. Between October 2010 and October 2011, ABT was administered to 64 patients at our department, 87.5% of whom continued ABT therapy for 24 weeks. In ABT patients treated at our department, the remission rate at Week 24 based on DAS28-ESR was 18.8%, while in SDAI assessment, 25% achieved remission indicating a higher remission rate based on SDAI, which is generally considered a stricter index. This finding may be attributable to a marked decrease in tender and swollen joint counts, SDAI components, and this improvement in subjective findings resulted in better SDAI scores. Although treatment was only 24 weeks, 83.3% of patients achieved structural remission, showing that ABT is comparable to TNF inhibitors in efficacy including inhibition of joint destruction. In the lecture, I will report the clinical results of ABT use in Japan together with the latest overseas findings and discuss where ABT fits into RA treatment based on its pharmaceutical properties.

LS25-2

6month real life results of abatacept in patients with rheumatoid arthritis using TBC database

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Conflict of interest: None

ABT was launched in Japan in September 2010, and has been used to treat RA patients for more than one year. ABT is the only biologic other than anti-cytokine agents. How to use ABT effectively may lead to satisfaction of patients. The ABT use-results survey, beginning at launch, gathered data only for 6 months. Therefore, data after 6 months will only be available from clinical practice. In addition, drug use-results surveys focus on the occurrence of adverse drug reactions, and the efficacy data from the surveillances are often insufficient for solving the issues arising in clinical practice. Accordingly, we, a multi-center collaborative research group including 14 orthopedic hospitals affiliated with Nagoya University (Tsurumai Biologics Communication, TBC), analyzed 153 cases treated with ABT after marketing. The study cohort consisted of 67 biologic-naive subjects and 86 biologic-experienced subjects, with a mean age of 63.3 years (range: 28 to 81) and a mean disease duration of 11.4 years (range: 1 month to 54 years). The probability of remaining on treatment after 12 months using the Kaplan-Meier method was 85.0%, favorably higher than those for other biologics examined by TBC. The pharmacological properties of ABT that have been recognized gradually in clinical practice are different from anti-cytokine agents in various ways. In this seminar, the speaker will discuss efficacy and safety in patients administered ABT for 12 months and introduce the vital facts and critical issues in decision in routine use of ABT. The contents are as follows: (i) Evaluation time points and indices of effect (ii) Effects of ABT in biologic-naive and biologic-experienced patients (effects by type of previous biologics) (iii) Influence of concomitant use of methotrexate The seminar will also review the appropriate use of ABT and its clinical positioning.

LS26

Pharmacological pain management for rheumatoid arthritis

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Conflict of interest: None

Though significant advances in the management of rheumatoid arthritis (RA) over the last decade, which may lead complete remission of RA, studies show that even in people with relatively controlled RA more than three quarters report significant pain in their joints. Even elderly RA survivors may suffer from their joint pain due to aging. Most people experience a chronic, fluctuating disease course, which if uncontrolled may lead to decrease of ADL and QOL of RA patients. Relief of pain and improvement of functional status are essential components of effective therapy. Currently, RA pain can be managed with various drugs including selective and non-selective NSAIDs, acetaminophen, tramadol, weak and strong opioids, and others. Physician have to adopt a safety strategy using less toxic and less interactive analgesics, considering cardiovascular risk, GI risk, renal adverse events, and hepatotoxicity in RA patients. Pharmacotherapies of pain management in RA patients are focused below. # Sites of action of steroids and COX inhibitors in arachidonate metabolism # COX-1 inhibition and COX-2 inhibition # Selective and non-selective NSAIDs and acetaminophen # The role of opioid analgesics, the safety of long-term opioid use # Safe and effective opioid therapy for chronic noncancer pain and selection of patients

LS27

Importance of early therapeutic intervention in patients with rheumatoid arthritis

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Conflict of interest: Yes

Rheumatoid arthritis (RA) is a systemic inflammatory disease that causes joint destruction and functional disability. The concept

of "window of opportunity" has been proposed recently since joint destruction of RA rapidly progresses within the first 2 years. From this point of view, 2010 RA classification criteria is developed to purify the patients who will progress later erosive and persistent arthritis at high risk from early arthritis patients. Thus, early recognition as well as the treatment toward these patients are really warranted recently. Clinical application of imaging technique such as MRI and US for the diagnosis and therapeutic decision has also become to be popular. Therapeutic options in patients with RA are rapidly spreading. Inflammatory cytokines such as TNF and IL-6, T cells and B cells are critically involved in the pathogenesis of RA that facilitate the development of biologic agents for the treatment of RA. For example, as for TNF inhibitors, four kinds of biologics including infliximab, etanercept, adalimumab and golimumab have been approved in Japan. PEGylated anti-TNF agent, certolizumab pegol, is now in the clinical trial in Japan. Clinical efficacy as well as the inhibition of joint destruction have been approved by each clinical trial among all of the biologic agents including tocilizumab and abatacept. Therapeutic recommendation of these biologic agents with synthetic disease-modifying antirheumatic drugs (DMARDs), especially methotrexate (MTX), has been published, and in addition, its efficacy in the real-world is being established. However, these medications are better effective in early RA as compared with long-standing RA (established RA). In patients with early RA, clinical remission is a realistic goal when treat-to-target (T2T) strategy is applied. In this seminar, I am going to show the evidence of advantage in early RA to achieve in clinical remission and avoid joint destruction and functional disability.

LS28

New Evolution in RA treatment in Japan

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Conflict of interest: Yes

Recent remarkable progress of treatment for rheumatoid arthritis (RA) has considerably improved the prognosis of RA. To provide such benefits to as many patients as possible, standardization of the tight disease control is quite important. Treat to Target: T2T is an approach, by which patients with definitive rheumatoid arthritis undergo the tight control toward the treatment target, and thus a very important process to prevent future joint destruction. In daily practices, it is necessary to set the target and communicate with the patients using specific numerical values based on a Composite measure, and it is said such practices are current RA global standards. On the other hand, this Composite measure must serve as an indicator that can help reach optimal therapeutic outcomes in RA. The new definitions of remission published by ACR and EULAR in 2011 recommend Composite measures such as SDAI and CDAI as indicators that meet the above requirement. To practice the tight control, efficient use of MTX based on benefit vs. risk assessment is quite important. If the T2T approach is applied to daily practices, the dose of MTX would be increased to the upper limit within the first three months of the treatment, and at this time point, modifications of the treatment might be considered based on the response determined as a composite measure. Especially, in patients with highly active rheumatoid arthritis, such rapid escalation of the MTX dose may considerably contribute to prevention of future joint destruction. Even if the effect of MTX at 3 months is not sufficient, subsequent addition of biological products may lead to additive or synergistic effects of both products. Of patients with highly active rheumatoid arthritis, a certain proportion of patients may well need combination treatment of MTX + biologic from the beginning. The EULAR recommendations published in 2010 suggest this treatment strategy in the Statement 14. The HOPEFUL study conducted in Japan is a post-marketing clinical trial of adalimumab, which was designed to evaluate the effects of MTX + adalimumab treatment in MTX-naive patients with highly active rheumatoid arthritis. In this speech, I review a new treatment strategy with adalimumab that can lead the era of the tight control.

LS29

Front-line in the management of gout and hyperuricemia

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Conflict of interest: Yes

Although gout had been recognized as a disease associated with extravagant life, gout has recently become a common disease in daily practice. Hyperuricemia has been well recognized as a predisposing condition for gout, and many patients with hyperuricemia visit doctors. From global perspective, history of gout is relatively short in Japan, however standard treatment of gout and hyperuricemia has been well inplemented in Japan, and cases such as refractory gout is very uncommon. It is our honor to know that this is the consequence of successful intervention for hyperuricemia according to the guideline established in 2002. On the other hand, in western countries, management of hyperuricemia has been historically rather neglected and sufficient management for gout has not been well implemented in daily practice. As the result, 'refractory gout' or 'difficult gout' has become a serious issue in daily practice. In ACR2011, management guideline for gout was reported, and it was quite impressive for me to see audience filled up the congress hall. A new anti-hyperuricemic drug, febuxostat has been on market in 2011, we have many therapeutic options for the management of gout and hyperuricemia in daily practice. On the other hand, there are many misunderstandings or pit-halls in the management of gout in daily practice. Since gout is a representative rheumatic disease with acute monoarthritis, rheumatologists should have the skills for the management of gout patients properly. It may not be common that gout is highlighted in Japan College of Rheumatology (JCR), but I would like to ask all members in JCR to have the accurate knowledge in the management of gout and hyperuricemia. In this luncheon seminar, I would like to introduce how to manage gout and hyperuricemia from basic to front-line perspective.

LS30-1

Slit diaphragm dysfunction causes proteinuria

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Conflict of interest: None

Glomerular visceral epithelial cell (podocyte) is highly differentiated cells, which form multiple interdigitating foot processes. The foot processes cover the outer side of the glomerular basement membrane. The neighboring foot processes derived from different cell bodies were connected by a continuous membrane-like structure called slit diaphragm or slit membrane. Our group showed that the anti-slit diaphragm antibody caused massive proteinuria by a single intravenous injection into rats, which indicated the significance of the slit diaphragm for retaining the plasma proteins. Some studies with the experimental models and the biopsy materials suggested that the slit diaphragm dysfunction is involved in the development of proteinuria in several kinds of glomerular diseases including IgA nephropathy and lupus nephritis. Recently, we intended to identify the molecules whose expressions were altered in proteinuric states. We found that the expression of synaptic vesicle protein 2B, and the receptors for angiotensin II was clearly altered in proteinuric states resulted from podocyte dysfunction, and

we reported that these molecules could be a novel therapeutic target for proteinuria. In this presentation, first, we review the early studies of our group that have investigated the pathogenesis of the slit diaphragm dysfunction. Then, we introduce the nature and the proposal functions of the molecules we recently identified as molecules which are involved in the development of proteinuria.

LS30-2

Clarification of the pathology of lupus nephritis from the kidney histology and advances in treatment

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Conflict of interest: Yes

Lupus nephritis (LN) is a disease in which immune deposits can be identified histologically in the glomeruli. Antigen-antibody complexes formed by DNA and anti-DNA antibodies are initially deposited in the mesangium or the subendothelial spaces of the loop walls in the form of IgG, IgA, or IgM (type I). Activation of the classic pathway deposition of complement (C1q, C4, and C3) occur. Subsequently, there is infiltration of inflammatory cells, such as neutrophils and mononuclear cells, which undergo activation. Then a change occurs in the mesangial cells or endothelial cells that bring about intratubular proliferation (types II, III, and IV). Complement-fixing IgG3 has an important among the various IgGs. With deposition of IgG3, complement is activated and induces subsequent cascades, resulting in changes of the glomerular structure that cause proteinuria and hematuria. There is also type V lupus nephritis, in which complement is mainly deposited beneath the epithelial cells, but the significance of this type is yet to be clarified. Glomerular lesions mainly occur, but occasionally arteriolar lesions are dominant. Concomitant use of IVCY enhances the response of patients resistant to steroid therapy, and can achieve reduction of the steroid dose. The new calcineurin inhibitors have demonstrated marked efficacy and also allow dose reduction of steroids. When lupus nephritis (mainly type V) fails to respond to CyA, the effect of Prograf is attracting attention. Prograf is a calcineurin inhibitor that blocks binding between FKBP12 and TRPC6, suggesting that it may influence type V LN via this unique mechanism of action that CyA does not have.

LS31

Status of PDE5 inhibitors for pulmonary arterial hypertension associated with systemic sclerosis

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Conflict of interest: Yes

Pulmonary arterial hypertension (PAH) is the complication with systemic sclerosis, previously difficult to be treated. Several pathways associated with the development of PAH have been recently revealed. The important mediators of those pathways were endothelin-1, nitric oxide and prostanoids. The novel drugs for PAH involved in the three pathways are available to be used in Japan. In particular, an efficacy of phosphodiesterase 5 inhibitors (PDE5I) for the treatment of PAH has been confirmed in Japan. In this luncheon seminar, I would like to talk about the key points of the usage of PDE5I for the treatment of systemic sclerosis-related PAH.

LS32

Intraarticular Injection Therapy of Hyaluronan for Osteoarthritis of the Knee Joints

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Conflict of interest: Yes

Intraarticular injection therapy of hyaluronic acid (HA) has history of usage more than 20 years as conservative treatment of knee osteoarthritis (OA), however its clinical evidence is poor. This therapy is logical since both molecular weight and concentration of HA in OA synovial fluid is lower than normal. Friction between cartilages in human joint is reduced effectively by intraarticular injection of HA. These results indicated that HA has significant rheological effect. HA has *in vitro* action to inhibit apoptosis of chondrocytes, inhibit MMP production, increase type II collagen and aggrecan production, and these effects are neutralized by adding antibody against CD 44 which is a major HA receptor. These findings suggest that HA is an agent which has metabolic effects on chondrocytes. It is a very important point clinically what kind of OA patients HA is effective. Generally speaking, HA is effective for early ~ advanced stage of OA without much of synovial fluid. Availability of HA for knee OA is affirmed by most meta-analysis, but it is also reported that there are significant scatter in effectiveness by molecular weight of HA and evaluation methods. In guideline of OARSI, it was reported that HA injection therapy may be useful for knee OA patients, and HA has longer duration of effectiveness than adrenocorticosteroid injection. In Japan, 3 types of HA with different mean molecular weight can be used recently. However, few studies have compared clinical effects of HA with different molecular weight, and the difference of clinical effectiveness still remains unclear. It is not yet demonstrated whether HA has a true anti-OA effect, however results of animal OA models have shown that HA are the most promising in the drugs which are clinically available now. HA injection therapy is one of the useful therapies to reduce pain and increase ADL for elderly patients with many complications.

LS33

Most recent knowledge concerning the efficacy and safety of methotrexate for the treatment of rheumatoid arthritis

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Conflict of interest: Yes

Methotrexate (MTX) is known to be effective for treatment of rheumatoid arthritis (RA). Since the data from clinical trials have indicated that MTX suppresses pain and inflammation as well as progression of joint damage, it is now considered to be the standard drug for treatment of RA. Combination disease-modifying anti-rheumatic drugs (DMARDs) therapy may be used after MTX monotherapy in patients with persistently disease activity. The use of MTX in combination with other DMARDs may still represent a valuable therapeutic option in patients who fail to DMARD monotherapy. Therefore, MTX has been the anchor treatment in RA, and is especially used in combination with biologic agents to enhance efficacy in patients at risk for rapid radiographic progression. MTX courses show some of the longest continuation rates reported in clinical medicine, due to both effectiveness and safety. The safety profile of MTX indicates that it is among the safest of any mediation used for the treatment of arthritis. Though MTX has already been approved for treatment of RA in Japan, the maximum dosage had indicated only 8 mg/week until 2010. However, the 16 mg/week as maximum dosage has been able to be prescribed from 2011. Seto Y, et al. reported both efficacy and safety of use of MTX in Japanese RA patients at dosages over 8 mg/week using the IORRA cohort database (Seto Y, et al. Mod Rheumatol. 2011(epub)). Despite its widespread use and the frequent need of elective orthopaedic surgical procedures in patients with RA, some confu-

sion exists concerning the use of MTX in the perioperative period. Currently available data do not suggest a need to discontinue MTX because of surgery. At least, disease activity should be better controlled when MTX is not interrupted from weekly administration. Better information on the effectiveness and safety of weekly-low dose MTX should be communicated to all health professionals involved in the management of RA patients.

LS34

Diagnosis and treatment of pulmonary NTM infection with respect to biological agent.

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Conflict of interest: None

TNF is an essential cytokine that confine tuberculous lesion with granuloma formation. Thus administration of TNF-blocker may lead a danger of spreading mycobacteria. In Japan, about 15 times TB cases the general population out of early 5000 Infliximab treated were reported. But attentions related nontuberculous mycobacterial (NTM) disease have been focused in recent years. Winthrop collected 105 NTM cases with TNF-blocker treatment. These data reveal 9 death cases and 54% cases of extra pulmonary lesions. The estimated prevalence of this disease in Japan since 2007 is over 5.7 and it seems highest level internationally. Nowadays, more than 150 nomenclatures are registered as NTM species. In Japan, *Mycobacterium avium* complex dominate (about 80%) over other species, and the upward trend of the nodular bronchiectatic type lung disease in elderly woman has been noticeable. Most difficult problems are that there are no bactericidal drugs or combination chemotherapies, and in vitro susceptibility dose not match the clinical efficacy, so the drug selection for the present species only depends on the clinical experiences accumulated for each species. Thus, different treatment protocol is required for each species. The appropriate chemotherapy may become a status of certain improvement, but it needs a long period often exceed one or two years. If the lesion is localized, surgical resection is an effective procedure. This disease frequently overlap population group predilection of RA. From these issues, corresponding to NTM with TNF-blocker is much more difficult than that of Tuberculsosis. Administration of biologic agents, such as in the case of *M. abscessus* disease or underlying the state, such as COPD, generally seems to be contraindication. In the treatment of bacterial species relatively low degree of difficulty, administration of some biologic agents may be acceptable.

LS35

State of art for treatments of rheumatoid foot

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Conflict of interest: Yes

Paradigm shift was occurred in treatments for rheumatoid arthritis (RA), since biologics were introduced in our country. Although feet were frequently affected by RA, fortunately biologics effect very well for small joints in the toes. Paradigm shift was also observed in orthopedic treatment. New ways of thinking for treatments of rheumatoid foot will be demonstrated in this lecture by dividing to forefoot and hindfoot. Concerning the forefoot lesion, synovitis causes slackening of joint capsule around the metatarsophalangeal (MTP) joints, leading to several deformities. Procedures sacrificing the joints, like arthrodesis or resection arthroplasty, were selected for severe forefoot deformities. It is thought that recurrence of the deformities might be unavoidable, if synovitis could not be controlled. Therefore previously positive treatments have not been indicated for mild deformities. It was proved that pathomechanism of hallux valgus in RA are the same as common hallux valgus. Osteotomies as we select for common hallux valgus should be indicated for the feet with well controlled RA. Less invasive procedures should be indicated before deformities progressed. As for the hindfoot lesion, opportunities of treatment for severe deformities are decreasing. However, monoarthritis of the ankle resisting biologics was sometimes observed. Combined therapy with internal treatment and arthroscopic synovectomy is well effective in some patients. On the other hand, life time became longer and number of patients confined to their beds was decreased. Osteoarthritic changes were observed in aged patients. Neglected foot deformities should be treated using modern medicine. In addition, osteoporosis is an important problem. Fragile fracture of the talus is very difficult to treat. Newly developed devises, like external fixator and unique implant may solve these problems.

LS36

Therapeutic strategy of pulmonary hypertension (PH) secondary to connective tissue diseases (CTDs)

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Conflict of interest: None

Possibility of early detection, efficacy of immunosuppressive therapies and existence of various etiologies are three peculiarities of PH secondary to CTDs. Accordingly, PH screening and early intervention, appropriate immunosuppressive therapy and etiologically specific treatment are required to treat PH secondary to CTDs. Such etiology-based therapies comprise the following strategies. 1) Pulmonary arterial hypertension (PAH) Pulmonary vasodilators are used. These selectively act through either the prostaglandin, endothelin or nitric oxide pathway; however, it remains to be clarified which pathway constitutes the first-line therapy. If initial treatment is insufficient, proactive administration of drugs targeting an alternative pathway is required. If CTD activity is observed, immunosuppressive therapy is often selected; however, long-term PAH control is often difficult to achieve with this option and careful observation is required. 2) PH associated with left heart disease CTDs are often accompanied by left-heart dysfunction. For related PH complications, optimal treatment of left heart disease should be prioritized over administration of pulmonary vasodilators. 3) PH associated with interstitial lung disease Long-term oxygen administration or treatment of interstitial pneumonia are indicated as pulmonary vasodilators can exacerbate the ventilation-perfusion ratio imbalance. In cases of PH disproportional to degree of lung disease severity, pulmonary vasodilators may be indicated as for PAH. 4) PH secondary to chronic pulmonary thromboembolism Thromboendarterectomy constitutes the first-line therapy for PH secondary to chronic pulmonary thromboembolism, although balloon pulmonary aterioplasty is also increasingly performed. Pulmonary vasodilators are indicated for patients in whom these options are contraindicated, such as those with postoperative residual PH, recurrent PH or requiring preoperative hemodynamic improvement.

Evening Seminar

ES1-1

Reactivation of Hepatitis B virus in Patients Receiving Immunosuppressive or Anticancer Agents

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Conflict of interest: Yes

Hepatitis B virus (HBV) prevails among populations in eastern Asia. Thus, more than 20% of populations aged greater than 50 years old have been transiently infected by HBV in Japan, and they show positive serum anti-HBc and/or HBs despite that serum HBs-antigen is undetectable. In such patients, serum HBV-DNA may become detectable following immunosuppressive or anticancer therapies (HBV reactivation) leading to development of liver damage (*de novo* HBV hepatitis), since covalently closed circular DNA (cccDNA) of HBV inevitably remains in hepatitis even in those receiving transient HBV infection. To prevent severe liver damage due to HBV reactivation, serum HBV-DNA should be monitored every month in patients with history of transient HBV infection according to the guideline published under the aegis of the Ministry of Health, Welfare and Labour, when they are given immunosuppressive or anticancer agents. The usefulness of this guideline was validated, and the following results were obtained. (1) Serum HBV-DNA was detectable about in 2% of patients with transient HBV infection, in whom serum HBs-antigen was negative. (2) HBV reactivation developed about in 5% of such patients following immunosuppressive or anticancer therapies without rituximab. (3) HBV reactivation occurred even in those receiving monotherapy with methotrexate or glucocorticoid. (4) *De novo* HBV hepatitis could be prevented when antiviral therapy with entecavir was done immediately after serum HBV-DNA levels increased up to 2.1 Log copy/mL. These data suggested that the guideline is useful to prevent liver damage due to HBV reactivation in patients receiving immunosuppressive or anticancer therapies. However, the guideline is required to further be validated considering medical expense especially in patients with rheumatic diseases, since serum HBV-DNA measurement should repeatedly be done for a long time.

ES1-2

Hepatitis B Reactivation during Rheumatoid Arthritis Care and Countermeasures: From the Standpoint of Rheumatologist

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Conflict of interest: None

HBV reactivation and de novo hepatitis B have been reported among liver transplant recipients from HBV surface antigen (HBsAg)- negative and HBs antibody (HBsAb) and/or HBc antibody (HBcAb)-positive donors or patients with HBV infection + malignant lymphoma treated with rituximab. These are often fulminant/fatal due to covalently closed circular DNA (cccDNA) remaining in the liver cells after HBs/cAb formation. At the gene level, these cases are viewed as equivalent to HBsAg-positive carriers. Two MHLW study groups on liver disease prepared Guidelines on HB after Immunosuppression/Chemotherapy, and its revised version is now under prospective evaluation by the MHLW study group for elucidation of HBV reactivation by immunosuppressive/antitumor drugs and establishment of countermeasures. At this seminar, I shall outline interim results in the rheumatology field obtained by this study group, and describe major precautions to prevent HB during immunosuppressive therapy (including biologics), in line with "Proposals on immunosuppressive therapy for HBV-infected rheumatic disease patients," revised in 2011 autumn jointly by JCR and Japan Society of Hepatology. Basic precautions: Before immunosuppressive therapy, 1) check for HBV infection; 2) if HBsAg-positive (HBV carrier), measure DNA and start on nucleic acid analogs (in consultation with a hepatologist), and then start immunosuppressants. If HBsAg-negative, measure HBs/cAb. 3) If either is positive (excluding HBsAb-positive cases after HBV vaccination), measure HBV-DNA (deemed carrier if over the cutoff level). 4) If DNA-negative, start immunosuppressive therapy (continue DNA monitoring monthly). If DNA titer increases during care, immediately consult hepatologist and start on nucleic acid analogs. Immunosuppressive therapy should not be ceased suddenly to avoid the risk of fulminant hepatitis. Nucleic acid analogs need to be used for about 12 months after the end of immunosuppressive therapy.

ES1-3

Rheumatoid arthritis treatment outcomes in patients with hepatitis B reactivation

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Conflict of interest: None

OBJECTIVE The purpose of this study was to investigate the clinical course of RA and hepatitis B in 10 RA patients with previous HBV infection whose HBV-DNA status changed from negative to positive. METHODS At initial HBV DNA testing (baseline, BL), when the HBV-DNA levels became positive (reactivation time point, RP), and at the final evaluation (endpoint, EP), disease activity score 28 (DAS28), modified total Sharp score (mTSS), and modified Heath Assessment Questionnaire (mHAQ) score were determined. Subjects were followed up from RP to EP. RESULTS Subjects included 6 females (60%), with a mean age of 65.3 years, mean disease duration of 83.6 months, and mean observation period of 27 months. The following treatments were given after HBV DNA levels became detectable: concomitant use of entecavir in 81%; DMARDs in 45%; immunosuppressive drugs in 40%; glucocorticoids in 54% (mean PSL equivalent dose: 11 mg/day [MAX dose]); MTX in 81% (mean dose: 7.7 mg/week); folic acid in 100%; biologics in 73%. At BL, RP, and EP, the DAS28 scores were 3.08 ± 1.57, 2.91 ± 1.19, and 2.48 ± 0.46, respectively, indicating no significant difference between time points. However, the clinical remission rate (DAS28 < 2.6) at EP was 55%. The mTSS results were 8.9 ± 12.9, 1.6 ± 3.6, and –0.2 ± 3.0, respectively, showing statistically significant difference between BL and RP (P = 0.008). The mHAQ scores were 0.16 ± 0.23, 0.10 ± 0.18, and 0.11 ± 0.25, respectively, showing no statistically significant difference between them, although the HAQ remission rate (HAQ ≤ 0.5) was 91% at EP. The alanine aminotransferase levels were 23 ± 12, 19 ± 7, and 17 ± 7 IU/L, respectively, revealing no significant difference between the time points. At EP, all subjects tested negative for HBV DNA. CONCLUSION Our results showed that RA patients with resolved HBV infection who became positive for HVB DNA could be managed successfully with entecavir while monitoring HBV-DNA. Liver function was well preserved.

ES2-1

Attaining Remission in Rheumatoid Arthritis: Prediction and Preservation

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Remission is the optimal therapeutic outcome in rheumatoid arthritis (RA), because it is associated with maximal reversal of

disability *and* halt of progression of joint damage. With the availability of many new therapies, it should be easier in in previous times to achieve this state. Importantly, to attain the best clinical, functional, and structural results in *all* patients achieving this state, several aspects need to be considered. Firstly, remission must be defined stringently; if the definition is not stringent enough, a significant number of patients who are thought to be in remission by such non-stringent criteria will experience impaired physical function and progression of irreversible joint damage. To this end, ACR and EULAR have recently defined stringent remission criteria which have meanwhile been validated repeatedly. Secondly, while attaining remission is a primary aim, sustaining this best achievable state is of great importance. This can be done by the help of regular evaluation of disease activity, whereby self-assessment of joint counts by the patients may be a helpful way to avoid frequent clinic visits. In line with the treat-to-target recommendations, remission or at least low disease activity as an alternative goal should be aimed for by timely switching of therapy, as long as the treatment target is not attained. Aside from the actual disease activity predictors of bad outcome may guide these treatment decisions. Taken together, with the use of the new criteria and adhering to various recommendations, remission has not only become an achievable goal for a large proportion of RA patients, but will also be associated with an excellent outcome for the future of RA patients.

ES2-2

Best practice in the treatment of rheumatoid arthritis based on logic and evidence

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Conflict of interest: Yes

The revolution in RA treatment began in late 1990's with the use of biological DMARDs in clinical settings in the US and Europe. In the same year when infliximab was approved in the west in 1999, MTX became available for the treatment of RA in Japan, and four years later, infliximab was approved. From that day forth, dramatic improvements have been obtained in the QOL of RA patients undergoing the treatment, now with the possibility of maintaining remission after discontinuing infliximab. The universal goal of RA treatment has become clinical remission in all patients with revisions of classification criteria and treatment recommendations. On the other hand, the efficacy of biologics is not uniform and the proportion of patients achieving remission is about 50% at best. In other words, the remaining 50% cannot achieve remission no matter which biologics they use. In searching for ways to lessen the patients with primary and secondary failure to infliximab, we looked for answers as to why this drug was inadequate for some patients in our own institution and the RISING study. These studies demonstrated the concomitant medication, Fcγ receptor polymorphism, the trough level of infliximab and the circulating TNFα level in blood, vary in individual patient, which accounts, in part, for the different efficacy of infliximab. By integrating these information, we could optimize the amount and interval of infliximab. In sub-analysis of RISING study, the inhibition of either TNFα or IL-6 or both were observed by MTX plus infliximab. Interestingly, clinical remission rate was highest in the patient population, when the two cytokines were inhibited. These are new approach toward personalizing strategies of RA treatment to realize the concept of Treat-to-Target in individual patient. It enables us to possibly introduce each patient to remission faster than the previous experience-based strategy. Following this, a new study ("RRRR study") has started to practice tight-control based on circulating TNF level aiming for biologic-free remission. I believe the mission of rheumatologists today is to show clearly the treatment path toward clinical remission as a primary goal in individual patient, followed by biologic–free, drug-free and cure in RA.

ES3-1

Current Management of RA

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Conflict of interest: None

The outcome of patients with rheumatoid arthritis (RA) has improved dramatically in the last few years. This improvement has been driven by a number of elements that have included updated management principles; first of diagnosing and treating RA at the earliest opportunity before damage has occurred, and second, treating to a pre-defined target, which is ideally remission. (This has been the aim of therapy for some years but only recently encapsulated formally in international recommendations). Important additional factors have been the more effective use of existing therapies, and importantly the availability of new improved therapies including biologic therapies. Biologic treatments not only induce higher remission rates, but have a specific effect on structural damage virtually halting all radiological progression. Initial studies confirmed the efficacy of TNF blockers in patients who had failed all conventional disease-modifying anti-rheumatic drugs (DMARDs). Patients with incomplete response to methotrexate (MTX). The next study randomised controlled trials again showed significant benefits over the additional placebo. In the last few years several studies have sought to refine the optimal use of TNF blockers and examined the use of combination TNF blockers and MTX in patients who were MTX naive. These all showed superiority of the combination versus MTX monotherapy both clinically and particularly for structural damage. However, there remains a debate about whether randomised control trials with rigid protocols are the optimal way to inform management, or whether practical management approaches in the form of strategy trials offer greater guidance. Patients who fail TNF blockers now have a number of options including B-cell depletion, alternative TNF blockers, TNF co-stimulation blockade, blockade of IL-6R with tocilizumab. The RADIATE study showed the advantage of using a different mode of action and high level of effectiveness of IL-6 blockade in this population. The importance of remission will also be discussed.

ES3-2

Treatment of rheumatoid arthritis in clinical practice — Maximizing the efficacy and safety of tocilizumab—

Naoki Ishiguro
Department of Orthopedic Surgery Nagoya University, School of Medicine

Conflict of interest: Yes

Rheumatoid arthritis (RA) is an autoimmune disease of unknown etiology. Immunological abnormalities via T cells and associated cytokines, such as TNF-α, IL-6, and IL-1, play important roles in the pathophysiology and onset of RA. Anti-cytokine treatment has led to a paradigm shift in the treatment of RA, and the goals of RA treatment have changed from merely alleviating and improving symptoms to achieving clinical, structural, and functional remission, as well as the maintenance of these effects. The various studies to investigate the new therapeutic strategies have been started and various evidences have been conducted for preserving joint function by active treatment, maintaining quality of life by early diagnosis. Among anti-cytokine treatments, the humanized anti-human IL-6 receptor antibody tocilizumab (TCZ) has a completely different mechanism of action than that of anti-TNF

agents. Clinical studies of TCZ, completed for 601 RA patients in Japan and more than 4,000 world-wide, showed that TCZ has good efficacy in patients who have inadequate response to synthetic DMARDs or anti-TNF treatment and who are naïve to MTX. TCZ was approved in Japan as an anti-rheumatic drug in 2008, and subsequently approved in Europe in 2009 and in the United States in 2010; TCZ is now used in more than 100 countries worldwide. I will present the most recent information obtained from the all-case postmarketing surveillance (PMS) of 7901 patients in Japan, including the factors contributing to efficacy and safety, and I will present data obtained from investigator-initiated studies including our own research. I will also discuss the proper method of using TCZ for maximizing the efficacy and safety.

ES4-1

T2T for biologics?

Tatsuya Koike
Department of Rheumatosurgery, Osaka City University Medical School, Osaka, Japan

Conflict of interest: Yes

In rheumatoid arthritis (RA), joint damage and physical disability are the major adverse outcomes associated with reduction in quality of life and premature mortality. Aiming at therapeutic targets has reduced the risk of organ failure in many diseases such as diabetes or hypertension. Such targets have not been defined for RA. And so, recommendations on treating RA to target (T2T) based on both evidence and expert opinion were provided from an international task force (T2T Steering Committee) in 2010. This statement includes 4 overarching principles and 10 recommendations. However, the evidence level of individual recommendation is not high at all. Furthermore there was no statement on the use of biologics. We should review that T2T recommendations do not advise about use of biologics. Previous studies such as BeST, FINRACo, and TEAR showed excellence of the combination therapy with DMARDs (Disease-modifying antirheumatic drugs). The most important point is to achieve lower disease activity during the initial treatment. For that purpose, we must assess disease activity of RA reliably with for example composite measures and consider the use of biologics which have enabled the attainment of unprecedented outcomes. In this talk, I would like to describe the concept and problems of T2T recommendations.

ES4-2

Treat to target for rheumatoid arthritis in daily practice.

Satoshi Ito
Division of Rheumatology, Niigata Rheumatic Center

Conflict of interest: Yes

In the past, treatment target has not been defined for rheumatoid arthritis (RA). Introduction of the Treat to Target (T2T) for RA by strictly defining remission as the target with use of composite measures i.e. DAS28 is expected to lead to paradigmatic changes and prevent joint destruction and functional impairment. The T2T concept needs to be shared and appreciated not only by rheumatologists but also by co-medicals such as nurses, pharmacists and rehabilitation stuffs. But most important of all is that patients construe the T2T notion, understand composite measures and acknowledge necessary therapeutic changes. In our center because we introduced e-medical charts with composite measure calculation functions, patients are aware of their disease activity. It is surprising to learn patients with moderate disease activity satisfied with their treatment on my outside duty where no such electronic system is available. Although it requires extra time, it is worth to accommodate it in routine care. Rheumatologists can earn good communication by sharing the information on targets and means to achieve them with patients. It becomes easier to convince patients of needs for treatment reinforcement. Moreover, patients participate in disease management by asking questions like "What is my DAS28 score today?" Since February 2011 Japanese rheumatologists can start methotrexate (MTX) first line and use up to 16 mg/week in patients with poor prognostic factors. In addition, introduction of the new classification criteria for RA by ACR/EULAR would facilitate early institution of MTX. These changes along with T2T may increase the proportions of patients who achieve remission. It is well expected that concomitant use of MTX at an adequate dose would further improve effects of biologics such as adalimumab. In our center, we are experiencing much higher efficacy of adalimumab than ever with higher doses of MTX, e.g. early remission induction and its sustainability.

ES4-3

How to achieve Treat-to-Target goals in clinical practice

Toshihiko Hidaka, Yayoi Hashiba, Hiroshi Kuroda
Insutitution of Rheumatology, Zenjinkai Shimin-no-Mori Hospital, Miyazaki, Japan

Conflict of interest: None

Over the last decade, there have been remarkable advances in the treatment of rheumatoid arthritis (RA). Once, RA treatment just focused on managing clinical signs and symptoms. Improved diagnostic techniques have allowed for early diagnosis/treatment of RA. Through tight control towards a treatment goal (Treat-to-Target or T2T), remission of the disease has become a reality. For this aim, it is essential to effectively combine disease-modifying antirheumatic drugs (DMARDs) considering methoterxate as the anchor drug and biological agents. First, it is critical to use DMARDs anchored by MTX as steadily as possible. If the disease still remains active after treatment with DMARDs, biological agents should be introduced to control disease activity as early as possible. Careful use of biological agents is also a key feature for the treatment success. For this purpose, measures to (1) improve the safety and (2) increase remission rate need to be taken. (1) To improve the safety, it is required to i) assess risk prior to introduction, followed by preventive measures for adverse reactions based on the findings, and ii) monitor closely and deal with unexpected events at an early stage, as appropriate, are required. On the other hand, (2) to increase the remission rate, biological agents should be introduced i) in combination with a sufficient dose of MTX, ii) under such a condition that minimizes or suppresses disease activity as much as possible, iii) at an early stage of the disease course, iv) while functional impairment is still mild, if any. In this seminar, we would like to present details of the T2T practice focusing on biological therapy in real-life clinical settings.

ES5

The Annual Meeting of the Society for Surgery of the Rheumatoid Hand

Shigeki Momohara[1,2]
[1]Department of Orthopaedic Surgery, Institute of Rheumatology, Tokyo Women's Medical University, [2]Representative Organizer of The Annual Meeting of the Society for Surgery of the Rheumatoid Hand

Conflict of interest: Yes

In this edition of the Society for Surgery of the Rheumatoid Hand, we shall focus on extensor tendon rupture, which has a particularly high incidence, among all rheumatic hand disorders. We shall feature case study reports from 3 doctors, in which the pathophysiology and therapy options for extensor tendon rupture would

be discussed The pannel discussion shall feature 4 doctors who are facilitators of this research committee, in which they shall discuss the pathophysiology, prognosis factors, pathological variations, differential diagnosis, reconstruction (tendon graft, migration) and aftercare related to extensor tendon rupture. The ensuing general discussion will focus on reconstruction in the case of extensor tendon rupture on multiple fingers, its clinical practice and aftercare leading on to the topic of therapy in the era of biologic agents. Also, the session will feature a lecture by Dr. Ishiguro, in which he will be discussing the Ishiguro method of reconstruction and aftercare for treating extensor tendon rupture.

ES6-1

Treatment strategies for patients with early rheumatoid arthritis

Yasuo Niki
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Conflict of interest: None

Early aggressive treatment toward clinical remission is perceived strategy for treatment of early rheumatoid arthritis (RA) based on the concept of a limited 'window of opportunity' early in the disease process, whereby higher remission rates and longer remission maintenance may be achieved. According to the current ACR recommendations, anti-TNF agent in combination with MTX or dual- / triple-DMARD combinations are recommended in early RA with high disease activity and features of both a poor prognosis and an absence of cost-related barrier. Particularly for the patients with periarticular bony erosion, anti-TNF therapy should be employed by virtue of inhibitory effects of osteoclast differentiation. Comparative analysis of early RA versus established RA may provide the key for decision-making of therapeutic strategies in early RA. We examined 30 patients each in early and established RA groups treated with 54-week infliximab and MTX, and assessed temporal course of disease activity measures, serum cartilage markers and cytokine profiles.. Although CRP, MMP-3, DAS28 and delta TSS were improved to similar degrees in both groups, HAQ-DI was not improved in the established RA group. Level of serum C2C/CPII, an indicator of type II collagen synthesis/degradation, was shifted toward CII synthesis at week 54 in the early RA. Strikingly, C2C/CPII levels were universally improved in early RA, regardless of CRP levels or EULAR response grade. HAQ-DI and C2C/CPII might reflect inherent structural joint damage rather than systemic inflammation, and were not improved in established RA, even though anti-TNF therapy was employed. Consequently, early aggressive treatment, including anti-TNF therapy should be started in the early phase, while the regenerative capacity of articular cartilage is maintained or before irreversible structural joint damage occurs.

ES6-2

Key points for the diagnosis of early rheumatoid arthritis

Keishi Fujio
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Conflict of interest: Yes

Rheumatoid arthritis (RA) is an autoimmune disease characterized by persistent polyarthritis, and its progression causes bone erosion and destruction of joints, cartilages, and bones. Because early treatment of RA is important for remission induction as a goal of RA treatment, how to diagnose early-stage RA is an important challenge also for RA treatment strategies. In early-stage RA, since there are patients with few clinical findings and imaging findings characteristic of RA, such as those with a small number of inflamed joints, those with negative anti-CCP antibodies and rheumatoid factors, and those with undefined bone change by X-rays, there are many cases presenting difficulties in RA diagnosis. Cautions for clinical application of the New 2010 ACR/EULAR Classification Criteria for RA have so far been discussed also at RA scientific meetings. However, how to narrow down patients for the criteria before scoring and how to make an exclusive diagnosis of arthritis due to other diseases such as collagen disorder except RA are important. Moreover, there are various issues in arthritis diagnosis such as: What types of joint findings should be taken?; Should RF and anti-CCP antibodies equivalently be evaluated?; How is the sensitivity of the criteria for rheumatoid arthritis with negative serum factors?; and How should the criteria be combined with ultrasonographic and MRI image evaluations?. In this part, we examine points about the usefulness of the New ACR-EULAR Classification Criteria and those about how the criteria should be applied in daily medical practice on the basis of questions.

ES6-3

Treatment to target: strategy and practice, a view of internal medicine

Naoto Tamura
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Conflict of interest: None

Rheumatoid arthritis is a chronic inflammatory disease characterized by destructive arthritis. The joint destruction, which may consequently cause irreversible functional disability, progresses particularly within first 1-2 years of the onset, and it is difficult to improve quality of life of patients once it advances. Further, sustained disease activity may induce various systemic manifestations. Therefore, it is necessary to settle down the inflammation with efficacious drugs as early as possible; hence, early diagnosis and intervention are getting more critical in the management of RA. It has been recommended that treatment to target (T2T) by measuring disease activity with appropriate composite measures and adjusting therapy accordingly. Indeed, practice of T2T allows patients achieving the remission state earlier and more frequently. T2T strategy and new remission criteria proposed by ACR/EULAR markedly clarified the management of RA. The dose escalation of methotrexate, a gold standard drug for RA, was recently approved in Japan, and has become more important in RA treatment. More DMARDs including biologics are also getting available. However, on the other hand, it is challenging to practice T2T accurately in daily clinic. And it is not standardized how to increase the dose of MTX. Moreover, the best second DMARD is still uncertain. ACR recommended the therapy determined due to the disease activity, the disease duration, and the presence of poor prognostic factors, but it is not always corresponded with the actual use of DMARDs in Japan. Therefore, we have to choose the therapy targeting remission due to the background, including complications, of individual patient to reduce disease activity as possible. In this talk, I would like to discuss the treatment of RA targeting remission.

ES6-4

Treatment strategies for achievement of treatment goals (remission and low disease activity) and their actual status ¾ from the orthopedists' perspective

Tetsuya Tomita
Department of Orthopaedic Biomaterial Science, Osaka University Graduate School of Medicine

Conflict of interest: Yes

In recent years, diagnoses and drugs surrounding rheumatoid

arthritis (RA) treatment have remarkably progressed, and with their progression the new classification criteria for RA have been proposed. The purpose of the New 2010 ACR/EULAR RA Classification Criteria is to early identify patients having bone erosion with a chronic course from those with undiagnosed new-onset inflammatory arthritis and prevent RA conditions meeting the 1987 ACR RA Classification Criteria by initiating treatment with DMARDs centering on MTX as early as possible and preventing joint destruction. In Japan, public knowledge-based application of MTX in 2010 has made the drug available as a first-line choice and has allowed doses up to 16 mg/week for patients with poor-prognosis RA. MTX can be positively used for patients with obviously poor- prognosis RA, and concomitant use of biological drugs is recommended as needed. Application of the new classification criteria first requires ability to make an accurate differential diagnosis of a disease that can explain synovitis. However, it must be understood that the criteria can be applied only with a medical history, clinical findings, and laboratory data, and the criteria focus on small joints and serum reactions. Careful medical examinations of local swollen joints are required, and the medical examinations depending on serum reactions are likely to fall into a pitfall. Although the T2T Recommendations in the field of RA are widely understood and its concept is spreading, one of the most unimplemented items in actual clinical practice is that "The use of validated composite measures of disease activity, which include joint assessments, is needed in routine clinical practice to guide treatment decisions.", which provides a glimpse into the actual state that strategies for RA is still determined only by laboratory data. In actual clinical practice, the time has come that the ability to respond flexibly to individual cases is required.

ES7-1

Smoldering inflammation in local finger joint despite achieving low disease activity with biological agent treatment: Detailed observation of synovial vascularity with power Doppler sonography

Jun Fukae
Hokkaido Medical Center for Rheumatic Diseases

Conflict of interest: None

Treatment of rheumatoid arthritis (RA) dramatically developed in last decade leading to have deeper remission or curative potential, however, clinical study of biological agent therapy revealed some problems. One of the problems was presence of patients with joint damage progression despite having clinical improvement with biological agent: rapid radiological progression (RRP). Analysis of RRP was performed, then revealed that there was difficulty in screening the group in early stage. We have studied detailed change of synovial vascularity by power Doppler sonography (PDUS) and its relation of structural destruction in each finger joint. We found that synovial vascularity reflected therapeutic response of anti-rheumatic therapies in local finger joint. Analysis of RA in clinical remission state revealed that there were asymptomatic or symptom-limited joints with poor prognosis. These joint inflammation or so-called sub-clinical synovitis could be detected only with imaging techniques such as PDUS. Most of the previous reports about sub-clinical synovitis were in the field of DMARDs therapies. We observed detailed change of synovial vascularity in RA patients newly treated with biological agents and found that remaining synovial vascularity despite having clinical improvement showed poor prognosis. Patient with such smoldering inflammatory joints might be therapeutic resistant group: RRP. Furthermore, our data suggested that the smoldering inflammation might be altered inflammation different from acute inflammation. A sign of remaining synovial vascularity positive in clinical improvement phase indicates poor prognosis of local joint. Using synovial vascularity as predictable marker for RRP may be useful. Clinical study is necessary to establish clinical significance of synovial vascularity and therapeutic approach for smoldering inflammation.

ES7-2

Clinical application of musculoskeletal ultrasonography

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Conflict of interest: Yes

Importance of early intervention and achieving remission as treatment goal has become evident in management of patients with rheumatoid arthritis (RA), as proposed in new classification criteria and new definitions of remission. Although the role of new imaging modality such as musculoskeletal ultrasonography (US) and MRI is not clear in these criteria, recent US data imply the value of US application in clinical practice, such as data in early arthritis, and predictive value of power Doppler US findings associated with structural damage and/or clinical flare. US is more sensitive than clinical examination that can help diagnosing patients without typical RA signs and symptoms, and going through lists of differential diagnosis by detecting subclinical synovitis and sometimes by presenting disease-specific findings. Though new definitions of remission predict favorable structural and functional outcome in group of patients, there may present imaging residual joint inflammation which imply unfavorable outcome in individual patient even when one achieve stringent clinical remission. US application in clinic is also useful in terms of sharing the condition of disease and decision making with patients and improving clinical examination skill of physicians. Though standardization of US technique and establishment of global scoring system are mandatory for further promotion and academic research, US scan on even a single joint, in addition to careful clinical examination, may help decision-making in clinical practice.

ES7-3

Global progress in the methods for evaluating synovitis and its application for the management of rheumatoid arthritis

Kei Ikeda
Department of Allergy and Clinical Immunology, Chiba University Hospital

Conflict of interest: Yes

In the evaluation of synovitis with ultrasound, gray-scale synovial hypertrophy and Doppler flow signals are assessed for each joint region, and the findings are often graded with the semi-quantitative scoring system proposed by OMERACT ultrasound taskforce for data analysis. This scoring system is based on the one Szkudlarek et al reported although both gray-scale (GS) synovitis score and power Doppler (PD) signal score have been modified. OMERACT ultrasound taskforce has been working on the composite scoring system integrating GS and PD scores, the recommended joint regions to be assessed, and the scoring system for teno-synovitis. The clinical use of ultrasound for evaluating synovitis has been rigorously studied, especially for its application in diagnosis and evaluation for disease activity of rheumatoid arthritis (RA). We performed ultrasound in 117 cases referred to our hospital for possible diagnosis of RA and defined joint involvement as having GS synovitis and/or PD signal. As a result, approximately 20% of these cases were differently classified with 2010 ACR/EULAR RA classification criteria. Interestingly, combined ultrasound use increased not only sensitivity, but also specificity of RA classification, by excluding false positive cases. Although there have been many reports on the use of ultrasound in the evaluation for disease activity of RA, the control study aimed at showing the benefit of ultrasound-guided therapy was lacking. Targeted Ultra-

sound Initiative (TUI), which was founded by Emery et al in Leeds University for promotion, education, and research of ultrasound in rheumatic diseases, conducts an international multi-center randomized control study to compare ordinary treat-to-target therapy and ultrasound-guided therapy in early RA patients who achieved low disease activity with methotrexate therapy. In this study, the impact of ultrasound-guidance on the clinical outcome of RA will become clear.

ES8

The Riumachi Frontier (RA Frontier) 2012

Nobuyuki Miyasaka[1,2]
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Conflict of interest: Yes

Riumachi Frontier (RA Frontier) is an academic group consisting of specialists involved in the diagnosis and treatment of RA, formed in 2002, with Dr. Michael Weinblatt of the US as one of the trustee members. Over the last nine years since its formation, with the sincere cooperation and guidance of a large number of RA specialists, the group has succeeded in organizing a variety of activities like annual academic lectures, public educational lectures, publication of the group journal named "Frontier Communication" etc. After the approval of Rheumatrex in 1999, 10 years after it was approved in the US, RA treatment in Japan took a giant step forward with the advent of biologic agents in 2003. It is poised to take another huge leap with the impending approval of increased dosage of MTX. At present, with a choice of 6 biologic agents to choose from, the choice of therapy is entrusted with the RA specialist. While new treatment guidelines aimed at the standardization of RA treatment are being established in US and Europe, further investigation is essential in several topics like early diagnosis of RA, criteria for treatment initiation, identification of ideal therapy, criteria for measuring disease activity, monitoring of side effects etc. In Japan as well, there is a crying need to establish and promote the usage of practical treatment targets for enabling the early diagnosis of RA, monitoring of disease activity and the management of risks associated with side effects. The purpose of this meeting is to engage in active discussion based on a variety of issues in the clinical practice of RA treatment, and develop agreeable solutions.

ES9-1

Is there an alternative shortcut for the prevention of joint damage in rheumatoid arthritis?

Tatsuya Koike
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Conflict of interest: Yes

Rheumatoid arthritis (RA) is a systemic autoimmune disease characterized by persistent synovitis and destruction of joints. RA cannot be cured at present time, so the main treatment goals are to slow or stop the progression of RA, to relieve symptoms, and improve function. We aim to lower the level of disease activity, put RA into remission if possible, minimize joint damage, and enhance physical function and quality of life for patients. Today remission is an achievable goal in many RA patients in clinical practice and less joint damage and better physical function have been unequivocally shown to be a consequence of the early institution of disease-modifying antirheumatic drugs (DMARDs) when compared with their delayed start. For that purpose, use of biologic agents might be powerful option for the treatment of RA. However, biologic agents also have faults; expensiveness of agents and risks such as serious infection. To reduce the cost and lower the risk, low dose of biologics has been administered without evidence in the real world practice. We conducted a randomized prospective study to compare the effect of low dose Etanercept (ETN 25 mg/w) and standard dose of ENT (50 mg/w) on the prevention of joint destruction and clinical efficacy (PRECEPT study). Finally we found that low dose ETN was not inferior to standard dose ETN on clinical manifestations but inferior on prevention of joint damage. On the other hand, GO-FORTH study conducted in Japan demonstrated that golimumab (GLM) with MTX (Methotrexate) was safe and effective in Japanese active RA patients despite MTX therapy. Surprisingly in Japan both dosages of GLM 50 mg/M and 100 mg/M were approved and then we Japanese physicians must provide the evidence about the use of both dose. I would like to discuss the difference of the effects in both doses from existing data.

ES9-2

RA treatement targeted to unrestricted daily life

Hideto Kameda
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Conflict of interest: Yes

Biological agents against tumor necrosis factor (TNF) with concomitant methotrexate (MTX) may induce remission of synovitis by rheumatoid arthritis (RA), and the suspension of joint destruction, or even the repair of it. Consequently, these therapies dramatically improve the physical function of RA patients. In order to maximize the benefit of patients from the progress in therapeutic agents, precise evaluation of joint diseases and its appropriate interpretation are mandatory. In addition, it is important to determine the therapeutic strategy for each patient based on one's comorbidities, problems, and future design of life, with referring to available guidelines for RA treatment. Due to a dynamic variability of immune and inflammatory states of the patients, the dosing adjustment of MTX and anti-TNF biological agents at the right timing is critical to the success in RA treatment. Thus, the management of RA patients requires continuous therapeutic decisions about MTX initial dosing and subsequent dose escalation, the timing of the addition of anti-TNF biologics and the choice of agents and their dosing regimen. The sub-analyses of the RISING study implicated the key to the discrimination of patients requiring dose escalation of infliximab from others. Furthermore, the determination of the right patients and the right timing for the introduction of golimumab 100 mg/day with concomitant MTX, which has been approved only in Japan, should be examined by us and delivered worldwide. The ultimate goal led by the best therapy is to maximize the quality of life of the patients. To achieve that goal, all the medical stuffs should care RA patients together in order to maximize their physical function and social activity, with minimal joint pain, fatigue, economical disadvantages, and co-morbidities.

Hands-on Seminar

HS1

Evaluation of synovitis with musculoskeletal ultrasonography utilizing the JCR guideline for ultrasound image acquisition for RA

Kei Ikeda
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Conflict of interest: None

In 2011, Japanese College of Rheumatology (JCR) rheumatoid arthritis (RA) ultrasound standardization committee published a guideline for ultrasound image aquisition for RA. The primary objective of this guideline is to standardize the image acquisition procedure, the first step in the process of standardizing the use of ultrasound in clinical practice and research for RA. The guideline focuses on the synovial pathology among various lesions ultrasound can detect in RA patients. The guideline encompasses DAS44 joints and hip joint and systematically provides anatomical drawings, normal images, and images of active synovitis for each joint region. Few other guidelines and textbooks for ultrasound published in European nations focus on RA or synovitis, making this guideline very distinctive. This guideline does not provide methods for interpreting acquired images as proposed scoring systems are still controversial even for local assessment. The standardization of image acquisition methods with this guideline can help with the standardization process of determining synovitis severity. In this seminar, the proper methods of image acquisition for each joint region according to the JCR guideline for ultrasound image aquisition for RA will be presented and the interpretation of synovitis and its application will be discussed.

HS2

Various approaches in using Japan College of Rheumatology Joint Ultrasonography guideline: Medical and orthopedic viewpoints

Akihiro Narita[1], Isao Matsushita[2]
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Conflict of interest: None

Joint ultrasonography is useful device to detect joint structural abnormality such as synovitis or bone destruction in rheumatoid arthritis. Futhermore, the joint power Doppler ultrasonography is able to detect and evaluate abnormal vascularization in synovitis that correlate inflammatory level and have potential to predict structual destruction. We will present various approaches in using Japan College of Rheumatology Joint Ultrasonography guideline in the session. From the viewpoint of medical practice, we give explanations about tips of joint ultrasonography with gray scale mode and power Dopplar mode in imaging small joint or evaluation of their abnormal vascularization to use with daily practice. From the viewpoint of orthopedic practice, focusing on large joint such as shoulder, elbow and knee those destruction directly result in deterioration of patients daily activities. To observe large joints, several scanning are need to understend global image, we present tips in scanning techniques of each joint.

Annual Course Lecture

ACL1

The diagnosis and the latest treatment of collagen diseases.

Masaya Mukai
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Conflict of interest: None

While the new classification criteria for RA has recently been applied in Japan, the purpose of this criteria is to administer MTX to RA as soon as possible. However, the differential diagnosis of RA is so important when a patient with arthritis is presented. Because many collagen diseases other than RA will be satisfied with the criteria unless differential diagnosed at first step, they will be treated with the unnecessary or maybe harmful drug, MTX without necessary treatment of steroid for the serious symptoms. It is important not to diagnose collagen diseases only depend on laboratory data, especially autoantibodies. As it is commonly known for generalists not to diagnose the patient with both arthralgia and positive rheumatoid factor (RF) as RA, we cannot diagnose the patient with anti-nuclear antibody (ANA) as collagen diseases. While, 20-40% of normal female and 10-20% of normal male show positive result of ANA in titer of around 1:40. It is very important for clinicians to make a differential diagnosis for such patients from collagen diseases carefully. We have to diagnose the patients as collagen diseases by the laboratory data including autoantibodies mainly depending on their suitable symptoms and physical findings. For the treatment, some biologics such as rituximab are tried for SLE patients with serious symptoms such as central nervous system lupus and showed good results. As remittent high dose of intravenous cyclophosphamide is so effective for many severe clinical features, it was permitted for many collagen diseases last year in Japan. Other immunosuppressive agents showed steroid tapering effect. The prognosis of pulmonary hypertension has been markedly improved by the endothelin receptor antagonist and the phosphodiesterase-5 inhibitor adding on the prostanoid agents in very recently. However the treatment of collagen diseases has not been revolutionarily progressed in RA, it has been recently improved step by step.

ACL2

Early diagnosis of rheumatoid arthritis: 2010 RA classification criteria and imaging

Atsushi Kawakami
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Conflict of interest: Yes

2010 rheumatoid arthritis (RA) classification criteria is developed to purify the patients who will progress later erosive and persistent arthritis at high risk from early arthritis patients. In this issue, RA is recognized as highly erosive and persistent arthritis unless proper medication is introduced. This criteria is formed from the early arthritis cohort at western countries. Clinical definition of RA in this issue is the use of methotrexate (MTX) within the first 12 months. The items or factors in this scoring system have been characterized to associate with the arthritis patients who must be treated with MTX early considered as highly erosive and persistent potential. If the patients are scored as greater than 6 according to this criteria, they are classified as RA. Immediate introduction of disease-modifying anti-rheumatic drugs (DMARDs) is recommended to the patients classified as RA. Recently, the role of MTX is increasing as first-line DMARDs. Thus, 2010 RA classification criteria is really important that may involve in the treatment

decision. However, we have to pay attention to the use of this criteria in some points. Before the application of 2010 RA classification criteria, we have to notice that the apparent non-RA patients with arthritis such as osteoarthritis, Sjögren's syndrome, systemic lupus erythematosus, polymyalgia rheumatica and psoriatic arthritis are excluded, and 2010 RA classification criteria scoring system is applied in the patients who are not best explained by another diseases. Therefore, the knowledge of differential diagnosis of RA is essential to use this criteria. In addition to this criteria, MRI and/or US are verified to be useful to qualify the joint injury in early arthritis patients including our previous and recent observations. Essential points of early diagnosis of RA will be shown in this lecture.

ACL3

Pathogeneses and pathogenic immune responses of rheumatoid arthritis

Kazuhiko Yamamoto
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Conflict of interest: Yes

Rheumatoid arthritis (RA) is a complex disorder with genotypes, environmental factors, and accidental events. Several studies implicate genetic factors are crucial in RA. The association with HLA–DRB1 alleles that contain a common amino acid motif termed the shared epitope (SE) has been confirmed in patients who are positive for anti-citrullinated peptide antibodies (ACPA). Citrullination is a modification of arginine residues catalyzed by peptidylarginine deiminase (PAD) enzymes. This post-translational modification has the potential to change the structure, antigenicity, and function of proteins. The presence of ACPA in patients with RA has been reported to be observed before development of clinical sign. Large case-control studies have demonstrated that cigarette smoking is a risk factor for ACPA positive RA. Smoking can trigger specific immune reactions against citrullinated proteins possibly by inducing PAD enzymes in the lung. RA also appears to be associated with periodontal diseases. The major bacteria, *Porphyromonas gingivalis,* expresses a PAD enzyme which is capable of promoting citrullination of bacterial as well as mammalian proteins. In such individuals an accidental infection or trauma could temporally induce PAD enzymes in the joints followed by citrullination of proteins in the joints. It is possible that immune responses to citrullinated proteins can then directed into joints and chronic inflammation can be maintained by the interaction of citrullinated proteins in the joints and ACPA. This hypothesis needs further investigation in order to learn precise mechanisms of RA.

ACL4

Pregnancy in autoimmune rheumatic diseases

Yohko Murakawa
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Conflict of interest: Yes

Rheumatic diseases occur preferentially in women, often during the childbearing years. The female preponderance has raised the confirmed conviction that sex hormones play an important role in both disease development and course. In the present lecture, effects of pregnancy on disease activities, effects of diseases on pregnancy, and fatal and neonatal effects of drugs will be reviewed. Improvement of disease activity of RA during pregnancy are often observed, however, improvement may occur more frequently in the absence of anti-CCP and RF. Patients with low disease activity (LDA) usually maintain LDA during pregnancy, while only half of patients with moderate-high RA disease activity before conception improve disease activity during pregnancy. Therefore it is important to control RA disease activity before pregnancy especially in early RA. Effects of drugs on outcome of pregnancy and fatal or neonatal toxicity are important during pregnancy and lactation. Several drugs such as MTX, cyclophosphamide, and bosentan have fetal toxicities. In contrast, some drugs even immunosuppressive one can be used safer during pregnancy. Data of safety of biologics have also accumulated. In contrast to RA, SLE often remains active or even flares during pregnancy. Pregnancy loss is increased when there is proteinuria, anti-phospholipid antibody, or thrombocytepnia. Transplacental transfer of maternal anti-SSA/SSB antibodies can induce neonatal lupus syndrome, either skin rash or congenital heart block. Furthermore, pregnant patients with pulmonary hypertension may need termination of pregnancy because of risks of continuing pregnancy.

ACL5

The treatment of rheumatoid arthritis by biologics in Japan

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Conflict of interest: Yes

Rheumatoid arthritis (RA) is a representative autoimmune disease characterized by chronic and destructive inflammatory synovitis that causes severe disability and mortality. Although DMARD such as methotrexate (MTX) has been used as the cornerstone of RA treatment, their efficacy for the joint destruction has not been well accepted. However, biological products targeting TNF and IL-6 have promoted revolution of the treatment. Accordingly, four TNF-inhibitors, infliximab, etanercept, adalimumab and golimumab, an IL-6 receptor inhibitor tocilizumab and a T-cell costimulatory signal inhibitor abatacept are domestically commercialized. For instance, the combinational application of TNF-inhibitors and MTX has brought about a paradigm shift in the management of RA and the treatment target of RA has evolved to induction of clinical remission and maintenance of the remission, which could lead to long-term structural remission and functional remission, from just the release of polyarthlargia. In addition to clinical examinations, post-marketing nation-wide surveillance, multi-central retrospective studies and post-marketing clinical studies have been intensively performed in each biologics and a large amount of clinical evidence has been accumulated. Furthermore, after the maintenance of remission biological-free remission can be achieved in some patients. However, we have to pay special attentions that rheumatologists also have to treat, manage and prevent patients from disadvantage timely and appropriately when and/or before adverse events due to the use of biologics are occurred. Thus, we have to realize that whole body management of patients is prerequisite when we use biologics for the treatment of RA.

ACL6

Joint surgery in rheumatoid arthritis

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Conflict of interest: Yes

The treatment of rheumatoid arthritis (RA) has improved dramatically with the advent of the latest generation of disease-modifying antirheumatic drugs. Despite these advances, in some patients inflammation is not diminished sufficiently to prevent irreversible musculoskeletal damage, thereby necessitating surgical intervention to reduce pain and improve function. We have previously reported that there has been a decline in the use of synovec-

tomy surgery for RA, and the declining use of orthopedic surgery in our institute appears to be primarily influenced by increased treatment with methotrexate (MTX) and biologics (1, 2). Meanwhile, a recent multicenter study (CORE study) that included our institute revealed that the total number of RA-associated surgeries has actually not decreased, and that the numbers have been relatively stable from 1998 to 2008 (3). Although the number of synovectomies has definitely declined, the numbers of upper limb surgeries and foot arthroplasties have increased. When disease activity is increased in joints undergoing damage and destruction in established RA patients, surgical intervention should be considered as a therapeutic option (2, 3). Otherwise, the disease duration of patients who underwent any type of surgery increased (4). The reason for the observed increase in disease duration at time of RA-associated surgery may be related to the suppression of disease activity that has resulted from use of MTX and biological agents. Together, these studies suggest that RA treatment consisting of both medical treatment and orthopedic joint surgery may lead to a greater improvement in patient quality of life. 1. Momohara S, et al. Ann Rheum Dis. 68(2): 291-292, 2009 2. Momohara S, et al. Ann Rheum Dis. 69(1): 312-313, 2010 3. Momohara S, et al. Mod Rheumatol. 21(4): 337-42, 2011 4. Momohara S, et al. Rheumatol Int. 2011 (e-pub).

ACL7

Proper distribution of rheumatology specialists and a good co-operation system between central hospitals and private clinics for a better rheumatology practice and patients' safety in Japan

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Conflict of interest: Yes

Since the advent of methotrexate as an approved drug for the treatment of rheumatoid arthritis (RA) in 1999, in Japan, the treatment-effectiveness improved remarkably. The addition of infliximab as a first biological DMARD to methotrexate in 2003 made the difference epoch-making. Catch-phrases such as: early treatment: window of opportunity: tight control: and treat to target are being propagated nation-wide. However, these phrases are matters of course in any medical fields. This means that the rheumatologists have not been able to practice these ordinary things due to a lack of good drugs. The introduction of biological DMARDs also made a big change in clinical practice; it made time- and energy-consuming. This produced a problem, especially in rural districts where there are only a handful of rheumatologists. Concentration of patients to a central hospital made the load of the rheumatologist to a degree where he/she could not give a good rheumatology practice universally in the district. To solve this issue, a rheumatologist needs to build up a close connection with private practitioners in the same district. We have made such a co-operation system since 2003, a half year and two and a half years before infliximab and etanercept hit the Japan's market, respectively. To facilitate hospital-clinic co-operation, we made several agreements at the outset. First, we made the roles of hospital and clinics clearly. We should be complementary to each other. Second, initial RA treatment should be done at a hospital. Only patients who become better and stable after initial treatment are to be transferred to clinics. Third, a central hospital is prepared, 24 hours a day, 7 days a week, for an emergency of patients who are transferred to clinics. Lastly, private practitioners are advised to honor the treatment modality patients choose. The most important thing for the system to keep going was found to be good human relations between doctors in a hospital and clinics.

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